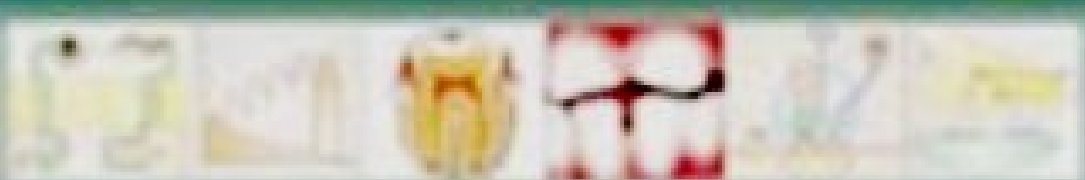
Essentials of Pharmacology for Dentistry

KD Tripathi



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Preface

With phenomenal growth of information on mechanism of action and clinical application of drugs as well as rapid introduction of new drugs, pharmacology, the science of drugs (medicines), has become increasingly important to all health professionals who prescribe/administer drugs. Practice of dentistry utilizes drugs as primary treatment modality as well as facilitator of dental procedures. Dentists may have to manage a medical emergency arising in their clinic. Moreover, many dental patients could be receiving other medication that may have orodental implications, or may interact with drugs prescribed by the dentist. As such, a broad knowledge of pharmacology with emphasis on certain aspects is needed by the dentist.

This book is divided into three sections. The first describes the general pharmacological principles with which all professionals involved in drug therapy must be conversant. The second on systemic pharmacology presents a brief account of drugs acting on various organ systems and used in the treatment of common disorders. Each chapter is systematically organised. The opening sentence defines the class of drugs, followed by their classification. The 'prototype' approach is followed by describing the representative drug of the class. Wherever applicable, the implications in dentistry are highlighted, such as drugs and diseases affecting postextraction haemostasis, dental procedures in patients on corticosteroid therapy or in diabetics, oral complications of cancer chemotherapy, conscious sedation in dentistry, etc. Management of medical emergencies like anaphylactic shock, seizures, angina, or asthmatic attack during dental treatment is outlined.

The third section mainly elaborates drugs which the dentists prescribe or administer themselves; but for the sake of continuity also includes other antimicrobials that they are unlikely to prescribe. The allocation of topics in sections two and three does not indicate water-tight distinction, which is impossible, but has been done with a view to focus attention on drugs that have greater relevance in dentistry. To mention a few, the application of analgesics and NSAIDs in dental pain, dental anaesthesia, role of each class of antimicrobials in orodental infections, prophylaxis of postextraction infection and endocarditis in patients at special risk, choice of antiseptics and antibiotics for control of dental plaque and periodontal disease are emphasized. A chapter on drug interactions has been included, highlighting those that may be encountered in dentistry. Leading trade names and dosage forms of drugs generally prescribed by dentists are mentioned distinctively. Thus, the book is oriented to provide essential pharmacological knowledge and understanding, and cater to the specific needs of dental students and practitioners.

I am indebted to my colleagues in pharmacology and dentistry for conceptual and clinical inputs that helped in orienting the book. The motivational influence of Shri J.P. Vij, CEO, Jaypee Brothers, was the main impetus for this book. The meticulous preparation of the manuscript and illustrations by Ms Sunita Katla, Mr Manoj Pahuja and Mr KK Raman is highly appreciated. The editorial support and cooperation of my wife is sincerely acknowledged.

5th June, 2005 **KD Tripathi**

Contents

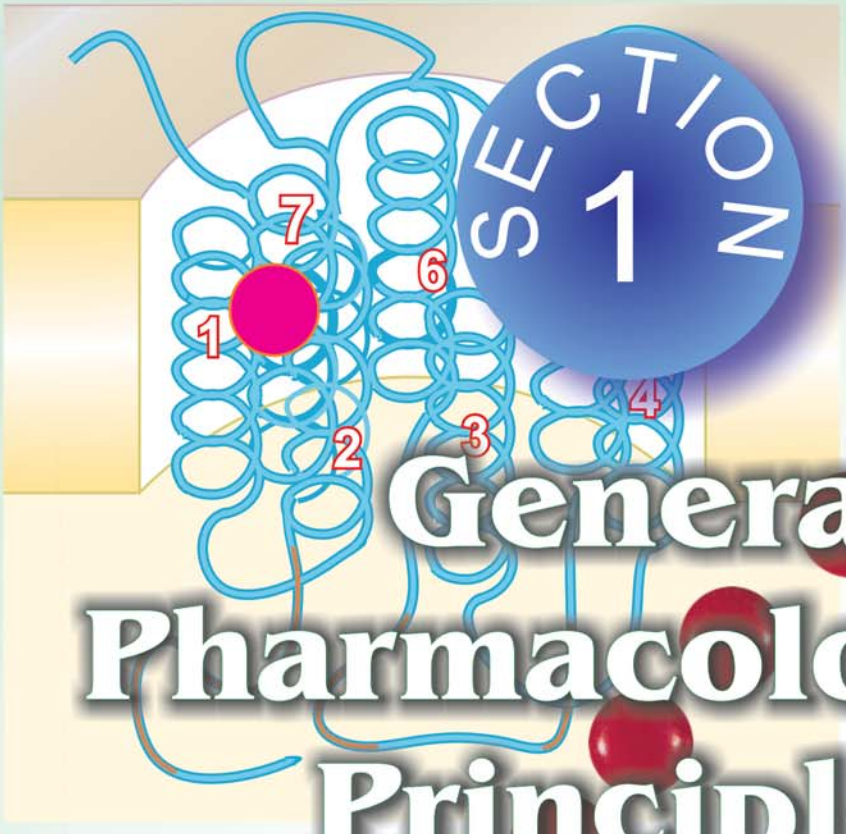
List of Abbreviations

A-I/II/III	Angiotensin I/II/III
AA	Amino acid
AB	Antibody
AC	Adenylyl cyclase
ACE	Angiotensin II converting enzyme
ACh	Acetylcholine
AChE	Acetylcholinesterase
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
ADH	Antidiuretic hormone
ADP	Adenosine diphosphate
Adr	Adrenaline
AF	Atrial fibrillation
AFl	Atrial flutter
AG	Antigen
AIDS	Acquired immunodeficiency syndrome
AIP	Aldosterone induced protein
ALA	Alanine
AMA	Antimicrobial agent
AMB	Amphotericin B
amp	Ampoule
AMP	Adenosine monophosphate
ANC	Acid neutralizing capacity
ANS	Autonomic nervous system
AP	Action potential
APD	Action potential duration
aPTT	Activated partial thromboplastin time
ARC	AIDS related complex
5-ASA	5-Amino salicyclic acid
Asc LH	Ascending limb of Loop of Henle
AT-III	Antithrombin III
ATP	Adenosine triphosphate
ATPase	Adenosine triphosphatase
A-V	Atrioventricular
AVP	Arginine vasopressin
AZT	Zidovudine
B_{12}	Vitamin B_{12}
BCNU	Bischloroethyl nitrosourea (Carmustine)
BD	Twice daily
BHP	Benign hypertrophy of prostate
BMD	Bone mineral density
BMR	Basal metabolic rate
BP	Blood pressure
BPN	Bisphosphonate
BSA	Body surface area
BuChE	Butyryl cholinesterase
BW	Body weight
BZD	Benzodiazepine
C-10	Decamethonium
CA	Catecholamine
CaBP	Calcium binding protein
CAD	Coronary artery disease
CAM	Calmodulin
cAMP	3', 5' Cyclic adenosine monophosphate
cap	Capsule
CAse	Carbonic anhydrase
CBS	Colloidal bismuth subcitrate
CCB	Calcium channel blocker
CD	Collecting duct
cGMP	3', 5' Cyclic guanosine monophosphate
CGRP	Calcitonin gene-related peptide
CH	Cholesterol
ChE	Cholinesterase
CHE	Cholesterol ester
CHF	Congestive heart failure
CI	Cardiac index
CL	Clearance
CLcr	Creatinine clearance
Clo	Clofazimine
CMI	Cell-mediated immunity
CMV	Cytomegalovirus
CNS	Central nervous system
c.o.	Cardiac output
CoEn-A	Coenzyme-A^r
COMT	Catechol-O-methyl transferase
COX	Cyclooxygenase
CPS	Complex partial seizures
CPZ	Chlorpromazine
CRF	Corticotropin releasing factor
CSF	Cerebrospinal fluid
CTZ	Chemoreceptor trigger zone
CVS	Cardiovascular system
CWD	Cell wall deficient
CYP450	Cytochrome P450
DA	Dopamine
DA-B_{12}	Deoxyadenosyl cobalamin
DAG	Diacyl glycerol
DCI	Dichloroisoproternol
dDAVP	Desmopressin
DDS	Diamino diphenyl sulfone (Dapsone)
DHE	Dihydroergotamine

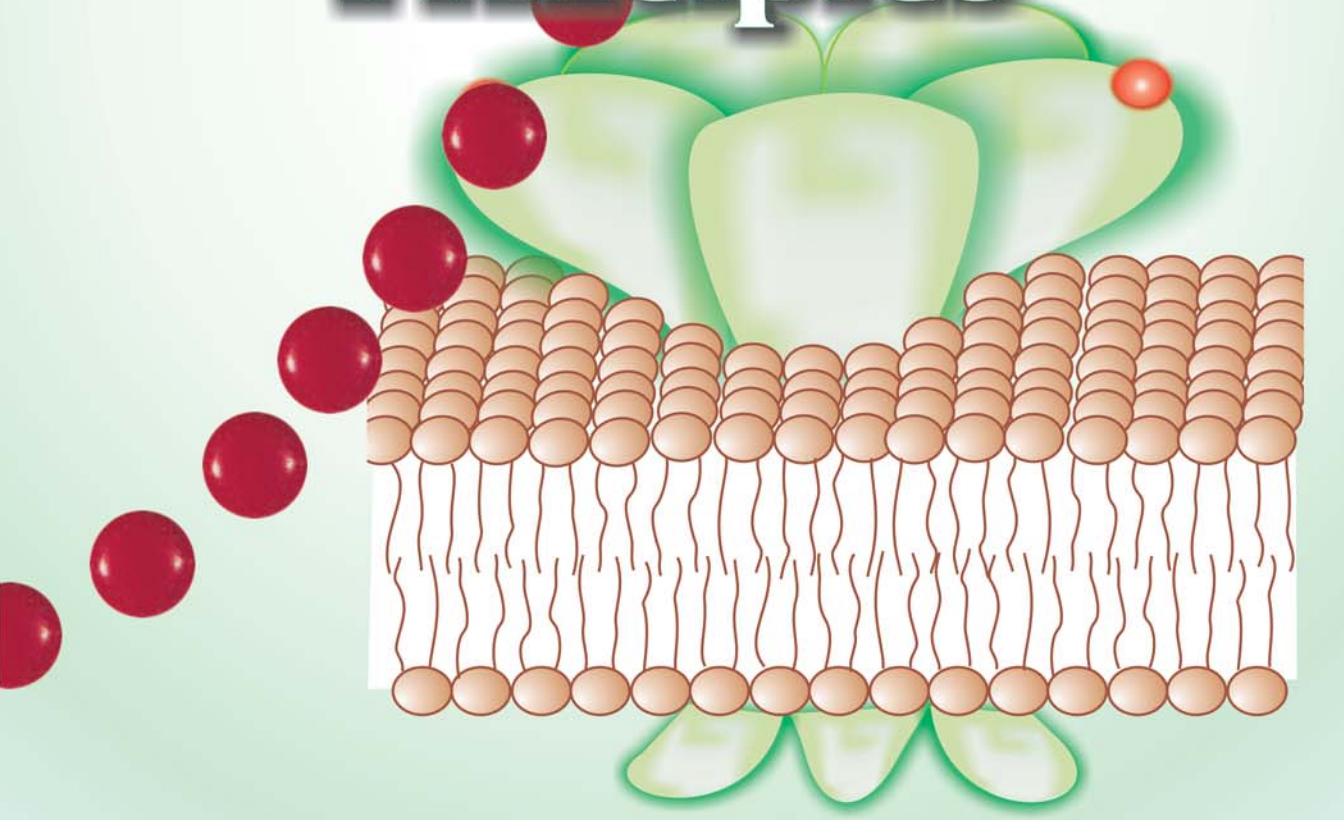
DHFA	Dihydro folic acid
DHFRase	Dihydrofolate reductase
DHP	Dihydropyridine
DI	Diabetes insipidus
DIT	Diiodotyrosine
dl	Decilitre
DLE	Disseminated lupus erythematosus
DMARD	Disease modifying antirheumatic drug
DMPA	Depot medroxyprogesterone acetate
DMPP	Dimethyl phenyl piperazinium
DNA	Deoxyribose nucleic acid
DOCA	Desoxy corticosterone acetate
dopa	Dihydroxyphenyl alanine
DOSS	Dioctyl sulfosuccinate
DOTS	Directly observed treatment short course
DRC	Dose-response curve
DT	Distal tubule
d-TC	d-Tubocurarine
E	Ethambutol
EACA	Epsilon amino caproic acid
e.c.f.	Extracellular fluid
ECG	Electrocardiogram
EDTA	Ethylene diamine tetraacetic acid
EEG	Electroencephalogram
β-END	β-Endorphin
EPEC	Enteropathogenic *E. coli*
EPO	Erythropoietin
ERP	Effective refractory period
EPSP	Excitatory postsynaptic potential
ER	Estrogen receptor
ES	Extrasystole
ESR	Erythrocyte sedimentation rate
ETEC	Enterotoxigenic *E. coli*
Etm	Ethionamide
FA	Folic acid
5-FC	5-Flucytosine
FEV_1	Forced expiratory volume in 1 second
FFA	Free fatty acid
FQ	Fluoroquinolone
FSH	Follicle stimulating hormone
5-FU	5-Fluorouracil
GABA	Gamma amino butyric acid
GC	Guanylyl cyclase
GDP	Guanosine diphosphate
GERD	Gastroesophageal reflux disease
g.f.r.	Glomerular filtration rate
GH	Growth hormone
g.i.t.	Gastrointestinal tract
GITS	Gastrointestinal therapeutic system
GLUT	Glucose transporter
GnRH	Gonadotropin releasing hormone
G-6-PD	Glucose-6-phosphate dehydrogenase
GTCS	Generalised tonic-clonic seizures
GTN	Glyceryl trinitrate
GTP	Guanosine triphosphate
H	Isoniazid (Isonicotinic acid hydrazide)
HAART	Highly active antiretroviral therapy
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HDL	High density lipoprotein
5-HIAA	5-Hydroxyindole acetic acid
HETE	Hydroxyeicosa tetraenoic acid
HIV	Human immunodeficiency virus
HMG-CoA	Hydroxymethyl glutaryl coenzyme A
HPA axis	Hypothalamo-pituitary-adrenal axis
HPETE	Hydroperoxy eicosatetraenoic acid
hr	Hour
HR	Heart rate
HRT	Hormone replacement therapy
5-HT	5-Hydroxytryptamine
5-HTP	5-Hydroxytryptophan
HVA	Homovanillic acid
ICSH	Interstitial cell stimulating hormone
IDL	Intermediate density lipoprotein
IGF	Insulin-like growth factor
IL	Interleukin
ILEU	Isoleucine
i.m.	Intramuscular
INH	Isonicotinic acid hydrazide
INR	International normalized ratio
i.o.t.	Intraocular tension
IP_3	Inositol trisphosphate
IPSP	Inhibitory postsynaptic potential
Iso	Isoprenaline
IU	International unit
i.v.	Intravenous
KTZ	Ketoconazole
LA	Local anaesthetic
LDL	Low density lipoprotein
LES	Lower esophageal sphincter
leu-ENK	Leucine enkephalin
LH	Luteinizing hormone
liq	Liquid
LMW	Low molecular weight
LOX	Lipoxygenase
LSD	Lysergic acid diethylamide
LT	Leukotriene
MAC	Minimal alveolar concentration
MAC	*Mycobacterium avium* complex
MAO	Monoamine oxidase
MAPKinase	Mitogen activated protein kinase
max	Maximum
MBC	Minimum bactericidal concentration
MBL	Multibacillary leprosy
MDI	Manic depressive illness
MDR	Multidrug resistant
MDT	Multidrug therapy (of leprosy)
met-ENK	Methionine enkephalin
mEq	milliequivalent

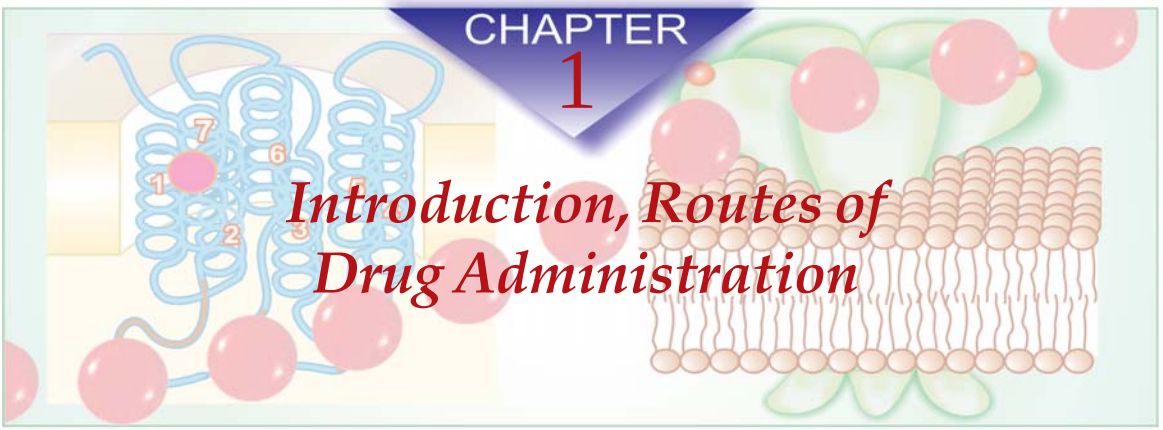
Mf	Microfilariae
MHC	Major histocompatibility complex
MI	Myocardial infarction
MIC	Minimal inhibitory concentration
min	Minimum
MIT	Monoiodo tyrosine
MLCK	Myosin light chain kinase
6-MP	6-Mercaptopurine
MRSA	Methicillin resistant *Staphylococcus aureus*
Mtx	Methotrexate
MW	Molecular weight
NA	Noradrenaline
NABQI	N-acetyl-p-benzoquinoneimine
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NAG	N-acetyl glucosamine
NAM	N-acetyl muramic acid
NANC	Nonadrenergic noncholinergic
NaSSA	Noradrenergic and specific serotonergic antidepressant
NEE	Norethindrone enanthate
NFAT	Nuclear factor of activated T-cell
NLEP	National leprosy eradication programme
NMDA	N-methyl-D-aspartate
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NPY	Neuropeptide-Y
NR	Nicotinic receptor
N-REM	Non rapid eye movement (sleep)
NRTI	Nucleoside reverse transcriptase inhibitor
NSAID	Nonsteroidal antiinflammatory drug
NTS	Nucleus tractus solitarius
OC	Oral contraceptive
OCD	Obsessive-compulsive disorder
OD	Once daily
ORS	Oral rehydration salt (solution)
ORT	Oral rehydration therapy
PABA	Paraamino benzoic acid
PAE	Post antibiotic effect
2-PAM	Pralidoxime
PAF	Platelet activating factor
PAS	Paraamino salicylic acid
PBPs	Penicillin binding proteins
PBL	Paucibacillary leprosy
PD	Parkinsons's disease
PF	Purkinje fibre
PG	Prostaglandin
PGI_2	Prostacyclin
PI	Protease inhibitor
PIP_2	Phosphatidyl inositol-4, 5-bisphosphate
PKA	Protein kinase: cAMP dependent
PKC	Protein kinase C
PL_A	Phospholipase A
PL_C	Phospholipase C
PnG	Penicillin G
POMC	Pro-opio melanocortin
PP	Partial pressure
PPARγ	Paroxysome proliferator-activated receptor γ
PPH	Postpartum haemorrhage
PPI	Proton pump inhibitor
ppm	Part per million
PPNG	Penicillinase producing *N. gonorrhoeae*
Prl	Prolactin
PSVT	Paroxysmal supra-ventricular tachycardia
PT	Proximal tubule
PTCA	Percutaneous transluminal coronary angioplasty
PTH	Parathyroid hormone
PTP	Post-tetanic potentiation
QID	Four times a day
R	Rifampin (Rifampicin)
RAS	Renin-angiotensin system
RBP	Retinol binding protein
REM	Rapid eye movement (sleep)
RIMA	Reversible inhibitor of MAO-A
rINN	Recommended international nonproprietary name
RMP	Resting membrane potential
RNA	Ribonucleic acid
RNTCP	Revised National Tuberculosis Control Programme
RP	Refractory period
RTF	Resistance transfer factor
S	Streptomycin
SA	Sinoatrial (node)
SAARD	Slow acting antirheumatic drug
SABE	Subacute bacterial endocarditis
s.c.	Subcutaneous
SCh	Succinylcholine
SERM	Selective estrogen receptor modulator
SGA	Second generation antihistaminic
s.l.	Sublingual
SLE	Systemic lupus erythematosus
SMON	Subacute myelo-optic neuropathy
SNRI	Serotonin and noradrenaline reuptake inhibitor
s.o.s.	as required
SPS	Simple partial seizures
SR	Sustained release
SRS-A	Slow reacting substance of anaphylaxis
SSRIs	Selective serotonin reuptake inhibitors
susp	Suspension
SWS	Slow wave sleep
syr	Syrup
t½	Half-life
T_3	Triiodothyronine

T_4	Thyroxine
tab	Tablet
TB	Tubercle bacilli
TCAs	Tricyclic antidepressants
TDS	Three times a day
TG	Triglyceride
6-TG	6-Thioguanine
THC	Tetrahydrocannabinol
THFA	Tetrahydro folic acid
THR	Threonine
TIAs	Transient ischaemic attacks
TNF-α	Tumour necrosis factor α
t.p.r.	Total peripheral resistance
t-PA	Tissue plasminogen activator
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
TTS	Transdermal therapeutic system
TX	Thromboxane
U	Unit
UDP	Uridine diphosphate
UFH	Unfractionated heparin
V	Volume of distribution
VAL	Valine
VF	Ventricular fibrillation
Vit	Vitamin
VLDL	- Very low density lipoprotein
VMA	Vanillyl mandelic acid
VRE	Vancomycin resistant enterococci
VRSA	Vancomycin resistant *Staphylococcus aureus*
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White syndrome
Z	Pyrazinamide
ZE syndrome	Zollinger-Ellison syndrome



General Pharmacological Principles





CHAPTER 1

Introduction, Routes of Drug Administration

INTRODUCTION

Pharmacology

Pharmacology is the science of drugs (Greek: *Pharmacon*—drug; *logos*—discourse in). In a broad sense, it deals with interaction of exogenously administered chemical molecules (drugs) with living systems. It encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use for medicinal purposes.

In the context of dental practice, a broad understanding of pharmacology with emphasis on certain aspects is imperative because:

- Dentists have to prescribe/use drugs, albeit from a limited range, for the treatment of dental conditions.
- Many dental patients concurrently suffer from other medical conditions, e.g. diabetes, hypertension, arthritis, etc. for which they may be taking drugs that may have dental implications or may interact with drugs prescribed by the dentist.
- The dentist may have to deal with a medical emergency arising on the dental chair.

For thousands of years most drugs were crude natural products of unknown composition and limited efficacy. Only the overt effects of these substances on the body were known, that too rather imprecisely; but how the same were produced was entirely unknown. Over the past 100 years or so, drugs have been purified, chemically characterized and a vast variety of highly potent and selective new drugs have been developed. The mechanism of action including molecular target of many drugs has been elucidated. This has been possible due to prolific growth of pharmacology which forms the backbone of rational therapeutics.

The two main divisions of pharmacology are pharmacodynamics and pharmacokinetics.

Pharmacodynamics (Greek: *dynamis*—power)—What the drug does to the body.

This includes physiological and biochemical effects of drugs and their mechanism of action at organ system/subcellular/macromolecular levels, e.g. adrenaline → interaction with adrenoceptors → G-protein mediated stimulation of cell membrane bound adenylyl cyclase → increased intracellular cyclic 3′,5′AMP → cardiac stimulation, hepatic glycogenolysis and hyperglycaemia, etc.

Pharmacokinetics (Greek: *Kinesis*—movement)—What the body does to the drug.

This refers to movement of the drug in and alteration of the drug by the body; includes absorption, distribution, binding/localization/storage, biotransformation and excretion of the drug, e.g. paracetamol is rapidly and almost completely absorbed orally attaining peak blood levels at 30-60 min; 25% bound to plasma proteins, widely and almost uniformly distributed in the

body (volume of distribution ~ 1 L/kg); extensively metabolized in the liver, primarily by glucuronide and sulfate conjugation into inactive metabolites which are excreted in urine; has a plasma half-life (t½) of 2–3 hours and a clearance value of 5 ml/kg/min.

Drug (French: *Drogue*—a dry herb) It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/cure of a disease. The WHO (1966) has given a more comprehensive definition—"Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."

The term 'drugs' is being also used to mean addictive/abused substances. However, this restricted and derogatory sense usage is unfortunate degradation of a time honoured term, and 'drug' should refer to a substance that has some therapeutic application.

Some other important aspects of pharmacology are:

Pharmacotherapeutics It is the application of pharmacological information together with knowledge of the disease for its prevention, mitigation or cure. Selection of the most appropriate drug, dosage and duration of treatment are a part of pharmacotherapeutics.

Clinical pharmacology It is the scientific study of drugs in man. It includes pharmacodynamic and pharmacokinetic investigation in healthy volunteers and in patients; evaluation of efficacy and safety of drugs and comparative trials with other forms of treatment; surveillance of patterns of drug use, adverse effects, etc.

The aim of clinical pharmacology is to generate data for optimum use of drugs.

Chemotherapy It is the treatment of systemic infection/malignancy with specific drugs that have selective toxicity for the infecting organism/malignant cell with no/minimal effects on the host cells.

Drugs, in general, can thus be divided into:

Pharmacodynamic agents These are designed to have pharmacodynamic effects in the recipient.

Chemotherapeutic agents These are designed to inhibit/kill invading parasite/malignant cell and have no/minimal pharmacodynamic effects in the recipient.

Pharmacy It is the art and science of compounding and dispensing drugs or preparing suitable dosage forms for administration of drugs to man or animals. It includes collection, identification, purification, isolation, synthesis, standardization and quality control of medicinal substances. The large scale manufacture of drugs is called *Pharmaceutics*. It is primarily a technological science.

Toxicology It is the study of poisonous effect of drugs and other chemicals (household, environmental pollutant, industrial, agricultural, homicidal) with emphasis on detection, prevention and treatment of poisonings. It also includes the study of adverse effects of drugs, since the same substance can be a drug or a poison, depending on the dose.

Drug nomenclature

A drug generally has three categories of names:

(a) *Chemical name* It describes the substance chemically, e.g. 1-(Isopropylamino)-3-(1-naphthyloxy) propan-2-o1 for propranolol. This is cumbersome and not suitable for use in prescribing. A *code name*, e.g. RO 15-1788 (later named flumazenil) may be assigned by the manufacturer for convenience and simplicity before an approved name is coined.

(b) *Nonproprietary name* It is the name accepted by a competent scientific body, e.g. the United States Adopted Name (USAN) or the British Approved Name (BAN). The nonproprietary names of newer drugs are kept uniform by an agreement to use the 'recommended International Nonproprietary Name (rINN)' only. However,

many older drugs have more than one nonproprietary names, e.g. meperidine (USA) and pethidine (UK, India) for the same drug. Until the drug is included in a pharmacopoeia, the nonproprietary name may also be called the *approved name*. After its appearance in the official publication, it becomes the *official name*.

In common parlance, the term *generic name* is used in place of nonproprietary name. Etymologically this is incorrect: 'generic' should be applied to the chemical or pharmacological group (or genus) of the compound, e.g. aminoglycoside antibiotics, tricyclic antidepressants, etc.; but has become synonymous with nonproprietary name due to wide usage and official acceptance.

(c) *Proprietary (Brand) name* It is the name assigned by the manufacturer(s) and is his property or trade mark. One drug may have multiple proprietary names, e.g. ALTOL, ATCARDIL, ATECOR, ATEN, BETACARD, LONOL, TENOLOL, TENORMIN for atenolol from different manufacturers. Brand names are designed to be catchy, short, easy to remember and often suggestive, e.g. LOPRESOR suggesting drug for lowering blood pressure. Brand names generally differ in different countries, e.g. timolol maleate eyedrops are marketed as TIMOPTIC in the USA but as GLUCOMOL in India. Even the same manufacturer may market the same drug under different brand names in different countries. In addition, combined formulations have their own multiple brand names. This is responsible for much confusion in drug nomenclature.

There are many arguments for using the nonproprietary name in prescribing: uniformity, convenience, economy and better comprehension (propranolol, sotalol, timolol, pindolol, metoprolol, acebutolol, atenolol are all β blockers, but their brand names have no such similarity). However, when it is important to ensure consistency of the product in terms of quality and bioavailability, etc. and especially when official control over quality of manufactured products is not rigorous, it is better to prescribe by the dependable brand name.

ROUTES OF DRUG ADMINISTRATION

Most drugs can be administered by a variety of routes. The choice of appropriate route in a given situation depends both on drug as well as patient-related factors. Mostly common sense considerations, feasibility and convenience dictate the route to be used.

Factors governing choice of route

1. Physical and chemical properties of the drug (solid/liquid/gas; solubility, stability, pH, irritancy).
2. Site of desired action—localized and approachable or generalized and not approachable.
3. Rate and extent of absorption of the drug from different routes.
4. Effect of digestive juices and first pass metabolism on the drug.
5. Rapidity with which the response is desired (routine treatment or emergency).
6. Accuracy of dosage required (i.v. and inhalational can provide fine tuning).
7. Condition of the patient (unconscious, vomiting).

Routes can be broadly divided into those for (*a*) local action and (*b*) systemic action.

LOCAL ROUTES

These routes can only be used for localized lesions at accessible sites and for drugs whose systemic absorption from these sites is minimal, slow or absent. Thus, high concentrations are attained at the desired site without exposing the rest of the body. Systemic side effects or toxicity are consequently absent or minimal. For drugs (in suitable dosage forms) that are absorbed from these sites/routes, the same can serve as a systemic route of administration. The local routes are:

1. Topical This refers to external application of the drug to the surface for localized action. It is often more convenient and efficient mode of delivering the drug to skin, oropharyngeal/nasal

mucosa, eyes, ear canal, anal canal, vagina, etc. Nonabsorbable drugs given orally for action on g.i. mucosa (sucralfate, neomycin), inhalation of drugs for action on bronchial mucosa (cromolyn sodium) and irrigating solutions/jellys (povidone iodine, lignocaine) applied to urethra are other forms of topical medication. In dental practice antiseptics, astringents, haemostatics are often applied as paints, toothpastes, mouthwashes, gargles or lozenges.

2. Deeper tissues Certain deep areas can be approached by using a syringe and needle, but the drug should be such that systemic absorption is slow, e.g. infiltration around a nerve or intrathecal injection (lignocaine, amphotericin B), intraarticular injection (hydrocortisone acetate), retrobulbar injection (hydrocortisone acetate).

3. Arterial supply Close intra-arterial injection is used for contrast media in angiography; anticancer drugs can be infused in femoral or brachial artery to localize the effect for limb malignancies.

SYSTEMIC ROUTES

The drug administered through systemic routes is intended to be absorbed into bloodstream and distributed all over, including the site of action, through circulation (*see* Fig. 1.1).

1. Oral

Oral ingestion is the oldest and commonest mode of drug administration. It is safer, more convenient, does not need assistance, noninvasive, often painless, the medicament need not be sterile and so is cheaper. Both solid dosage forms (powders, tablets, capsules, spansules, dragees, moulded tablets, gastrointestinal therapeutic systems—GITs) and liquid dosage forms (elixirs, syrups, emulsions, mixtures) can be given orally.

2. Sublingual (s.l.) or buccal

The tablet or pellet containing the drug is placed under the tongue or crushed in the mouth and spread over the buccal mucosa. Only lipid-soluble and non-irritating drugs can be so administered.

Limitations of oral route of administration

- Action is slower and thus not suitable for emergencies.
- Unpalatable drugs (chloramphenicol) are difficult to administer; drug may be filled in capsules to circumvent this.
- May cause nausea and vomiting (emetine).
- Cannot be used for uncooperative/unconscious/vomiting patient.
- Certain drugs are not absorbed (streptomycin).
- Others are destroyed by digestive juices (penicillin G, insulin) or in liver (glyceryl trinitrate, testosterone, lignocaine) by high first pass metabolism.

Absorption is relatively rapid—action can be produced in minutes. Though it is somewhat inconvenient, one can spit the drug after the desired effect has been obtained. The chief advantage is that liver is bypassed and drugs with high first pass metabolism can be absorbed directly into systemic circulation. Drugs given sublingually are—glyceryl trinitrate, buprenorphine, desamino-oxytocin.

3. Rectal

Certain irritant and unpleasant drugs can be put into rectum as suppositories or retention enema for systemic effect. This route can also be used when the patient is having recurrent vomiting. However, it is rather inconvenient and embarrassing; absorption is slower, irregular and often unpredictable (diazepam solution is dependably absorbed from rectum in children). Drug absorbed into external haemorrhoidal veins (about 50%) bypasses liver, but not that absorbed into internal haemorrhoidal veins. Rectal inflammation can result from irritant drugs. Aminophylline, indomethacin, diazepam, ergotamine and a few other drugs are sometimes given rectally.

4. Cutaneous

Highly lipid-soluble drugs can be applied over the skin for slow and prolonged absorption. The

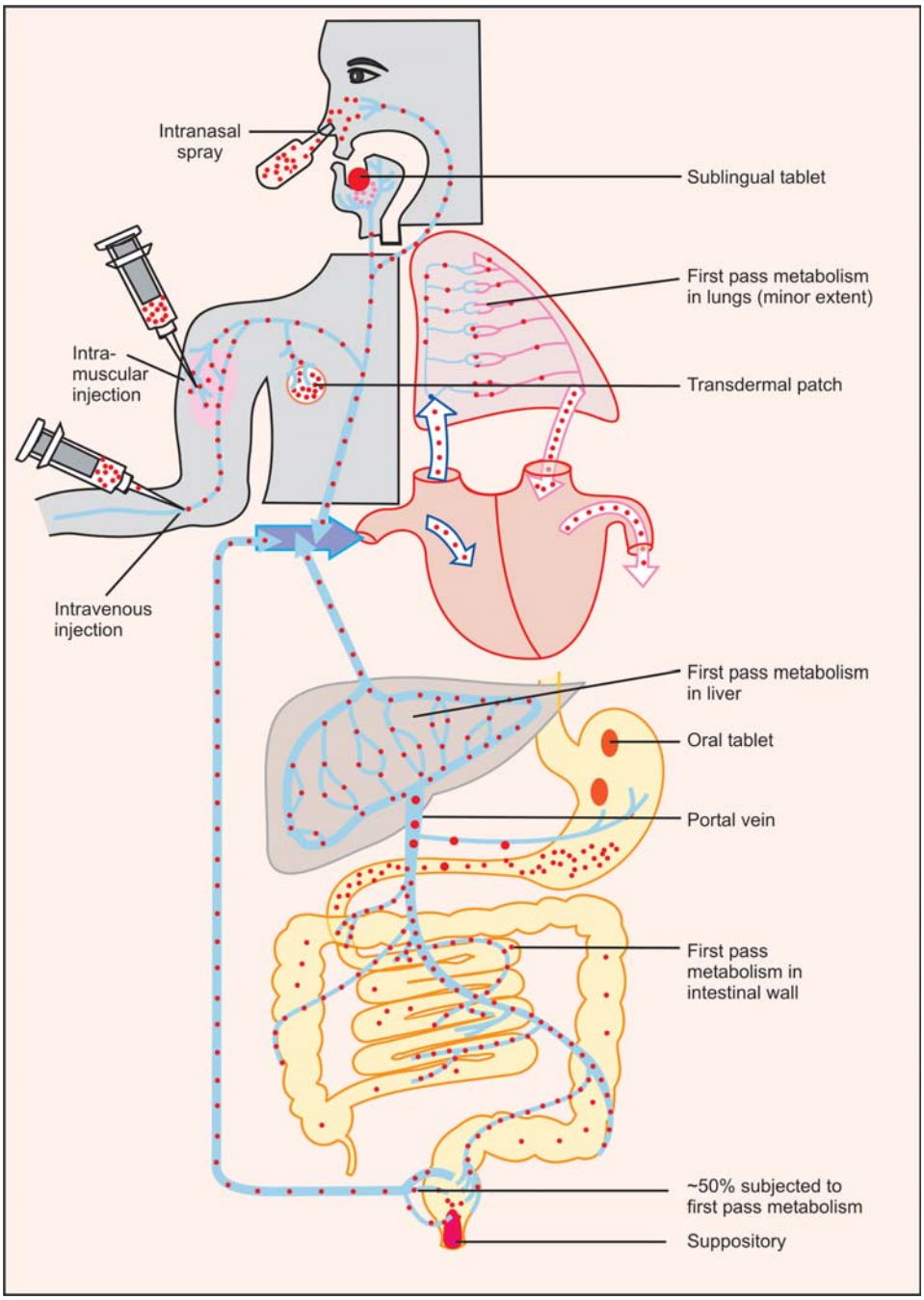


Fig. 1.1: Vascular pathway of drugs absorbed from various systemic routes of administration and sites of first pass metabolism

Note: All drug administered orally is subjected to first pass metabolism in intestinal wall and liver, while approximately half of that absorbed from rectum passes through liver. Drug entering from any systemic route is exposed to first pass metabolism in lungs, but its extent is minor for most drugs.

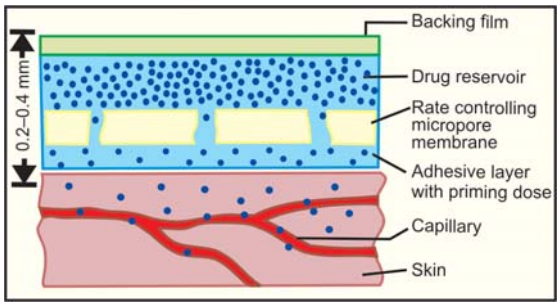


Fig. 1.2: Cross section of a transdermal drug delivery system

liver is also bypassed. The drug can be incorporated in an ointment and applied over specified area of skin.

Transdermal therapeutic systems These are devices in the form of adhesive patches of various shapes and sizes (5–20 cm^2) which deliver the contained drug at a constant rate into systemic circulation *via* the stratum corneum (Fig. 1.2). The drug (in solution or bound to a polymer) is held in a reservoir between an occlusive backing film and a rate controlling micropore membrane, the undersurface of which is smeared with an adhesive impregnated with priming dose of the drug that is protected by another film to be peeled off just before application. The drug is delivered at the skin surface by diffusion for percutaneous absorption into circulation. The micropore membrane is such that rate of drug delivery to skin surface is less than the slowest rate of absorption from skin. This offsets any variation in the rate of absorption according to the properties of different sites. As such, drug is delivered at constant and predictable rate irrespective of site of application: usually chest, abdomen, upper arm, lower back, buttock or mastoid region are utilized.

Transdermal patches of glyceryl trinitrate, fentanyl, nicotine and estradiol are available in India, while those of isosorbide dinitrate, hyoscine, and clonidine are available in other countries. These have been designed to last for 1 to 7 days in case of different drugs and are becoming increasingly popular, because they provide smooth plasma concentrations of the drug without fluctuations; minimize interindividual variations (drug is subjected to little first pass metabolism) and side effects. They are also more convenient—many patients prefer transdermal patches to oral tablets of the same drug; patient compliance is better. Local irritation and erythema occurs in some, but is generally mild; can be minimized by changing the site of application each time by rotation. Discontinuation has been necessary in 2 to 7% cases.

5. Inhalation

Volatile liquids and gases are given by inhalation for systemic action, e.g. general anaesthetics. Absorption takes place from the vast surface of alveoli—action is very rapid. When administration is discontinued, the drug diffuses back and is rapidly eliminated in expired air. Thus, controlled administration is possible with moment-to-moment adjustment. Irritant vapours (ether) cause inflammation of respiratory tract and increase secretion.

6. Nasal

The mucous membrane of the nose can readily absorb many drugs; digestive juices and liver are bypassed. However, only certain drugs like GnRH agonists and desmopressin applied as a spray or nebulized solution have been used by this route. This route is being tried for some other peptide drugs like insulin.

7. Parenteral

(*Par*—beyond, *enteral*—intestinal)

This refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa. The limitations of oral administration are circumvented. Drug action is faster and surer (valuable in emergencies). Gastric irritation and vomiting are not provoked. Parenteral route can be employed even in unconscious, uncooperative or vomiting patient. There are no chances of interference by food or digestive juices. Liver is bypassed.

Disadvantages of parenteral routes are—the preparation has to be sterilized and is costlier, the technique is invasive and painful, assistance of

another person is mostly needed (though self-injection is possible, e.g. insulin by diabetics), there are chances of local tissue injury and in general it is more risky. The important parenteral routes are:

(i) Subcutaneous (s.c.) The drug is deposited in the loose subcutaneous tissue which is richly supplied by nerves (irritant drugs cannot be injected) but is less vascular (absorption is slower). Self-injection is possible because deep penetration is not needed. This route should be avoided in shock patients who are vasoconstricted—absorption will be delayed. Repository (depot) preparations—oily solutions or aqueous suspensions can be injected for prolonged action. Some special forms of this route are:

(a) *Dermojet* In this method needle is not used; a high velocity jet of drug solution is projected from a microfine orifice using a gun-like implement. The solution passes through the superficial layers and gets deposited in the subcutaneous tissue. It is essentially painless and suited for mass inoculations.

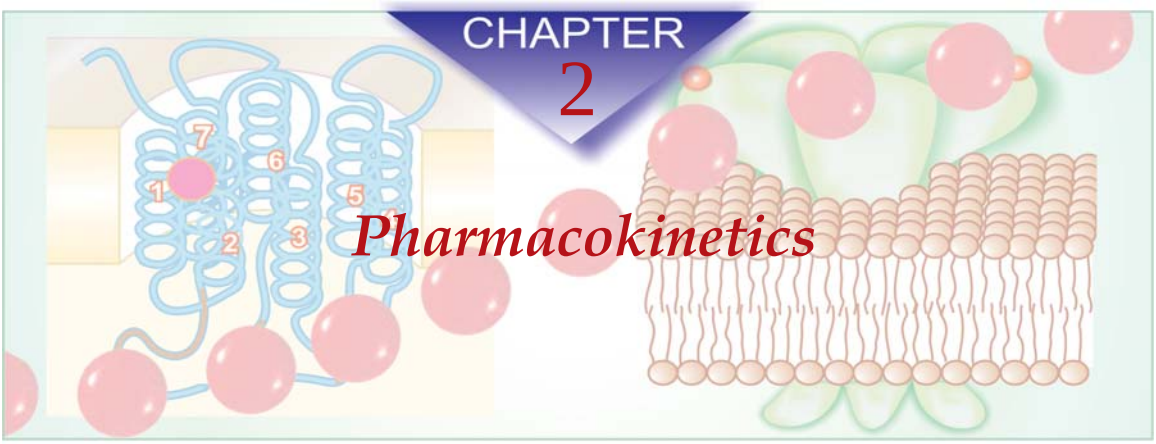
(b) *Pellet implantation* The drug as solid pellet is introduced with a trochar and cannula. This provides sustained release of the drug over weeks and months, e.g. DOCA, testosterone.

(c) *Sialistic (nonbiodegradable) and biodegradable implants* Crystalline drug is packed in tubes/capsules made of suitable materials and implanted under the skin. Slow and uniform leaching of the drug occurs over months providing constant blood levels. The nonbiodegradable implant has to be removed later on but not the biodegradable one. This has been tried for hormones and contraceptives (e.g. NORPLANT).

(ii) Intramuscular (i.m.) The drug is injected in one of the large skeletal muscles—deltoid, triceps, gluteus maximus, rectus femoris, etc. Muscle is less richly supplied with sensory nerves (mild irritants can be injected) and is more vascular (absorption is faster). It is less painful, but self-injection is often impracticable—deep penetration is needed. Depot preparations can be injected by this route.

(iii) Intravenous (i.v.) The drug is injected as a bolus (Greek: *bolos*-lump) or infused slowly over hours in one of the superficial veins. The drug directly reaches into the bloodstream and effects are produced immediately (great value in emergency). The intima of veins is insensitive and drug gets diluted with blood, therefore, even highly irritant drugs can be injected i.v., but hazards are—thrombophlebitis of the injected vein and necrosis of adjoining tissues if extravasation occurs. These complications can be minimized by diluting the drug or injecting it into a running i.v. line. Only aqueous solutions (not suspensions) can be injected i.v. and there are no depot preparations for this route. The dose of the drug required is smallest (bioavailability is 100%) and even large volumes can be infused. One big advantage with this route is—in case response is accurately measurable (e.g. BP) and the drug short acting (e.g. sodium nitroprusside), titration of the dose with the response is possible. However, this is the most risky route—vital organs like heart, brain, etc. get exposed to high concentrations of the drug.

(iv) Intradermal injection The drug is injected into the skin raising a bleb (e.g. BCG vaccine, sensitivity testing) or *scarring/multiple puncture* of the epidermis through a drop of the drug is done. This route is employed for specific purposes only.



Pharmacokinetics is the quantitative study of drug movement in, through and out of the body. The overall scheme of pharmacokinetic processes is depicted in Fig. 2.1. Intensity of response is related to concentration of the drug at the site of action, which in turn is dependent on its pharmacokinetic properties. Pharmacokinetic considerations, therefore, determine the route(s) of administration, dose, latency of onset, time of peak action, duration of action—frequency of administration of a drug.

All pharmacokinetic processes involve transport of the drug across biological membranes.

Biological membrane This is a bilayer (about 100 Å thick) of phospholipid and cholesterol molecules, the polar groups of these are oriented at the two surfaces and the nonpolar hydrocarbon chains are embedded in the matrix, with adsorbed extrinsic and intrinsic protein molecules (Fig. 2.2). The proteins are able to freely float through the membrane and some of the intrinsic ones, which extend through the full thickness of the membrane, surround fine aqueous pores. Paracellular spaces or channels also exist between certain epithelial/endothelial cells. Other proteins have enzymatic or carrier properties.

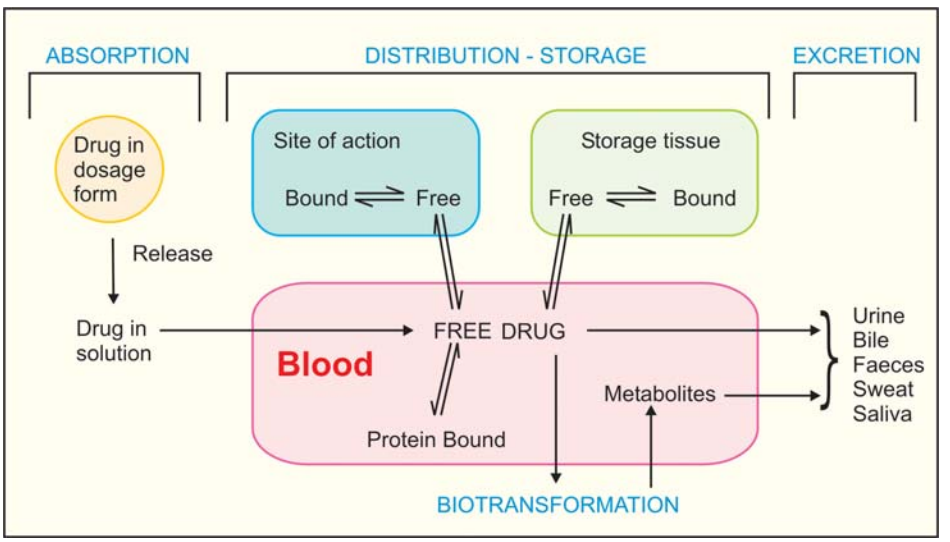


Fig. 2.1: Schematic depiction of pharmacokinetic processes

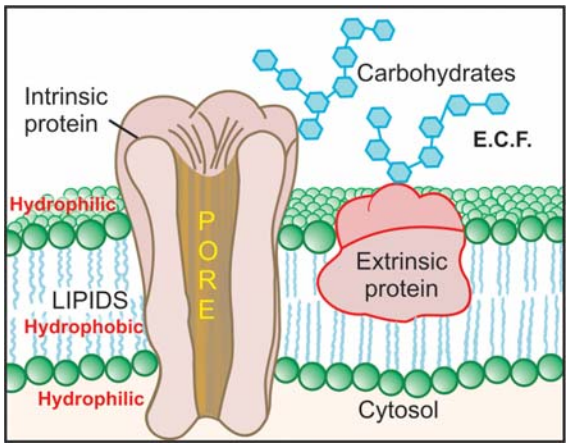


Fig. 2.2: Illustration of the organisation of biological membrane

Drugs are transported across the membranes by:
(a) Passive diffusion and filtration.
(b) Specialized transport.

Passive diffusion

The drug diffuses across the membrane in the direction of its concentration gradient, the membrane playing no active role in the process. This is the most important mechanism for majority of drugs; drugs are foreign substances and specialized mechanisms are developed by the body for normal metabolites only.

Lipid-soluble drugs diffuse by dissolving in the lipoidal matrix of the membrane, the rate of transport being proportional to lipid : water partition coefficient of the drug. A more lipid-soluble drug attains higher concentration in the membrane and diffuses quickly. Also, greater the difference in the concentration of the drug on two sides of the membrane, faster is its diffusion.

Influence of pH Most drugs are weak electrolytes, i.e. their ionization is pH dependent (contrast strong electrolytes which are nearly completely ionized at acidic as well as alkaline pH). The ionization of a weak acid HA is given by the equation:

$$pH = pKa + \log \frac{[A^-]}{[HA]} \qquad ...(1)$$

pKa is the negative logarithm of acidic dissociation constant of the weak electrolyte. If the concentration of ionized drug $[A^-]$ is equal to the concentration of unionized drug [HA], then—

$$\frac{[A^-]}{[HA]} = 1$$

since log 1 is 0, under this condition

$$pH = pKa \qquad ...(2)$$

Thus, *pKa* is numerically equal to the pH at which the drug is 50% ionized.
If pH is increased by 1, then—

$$\log [A^-]/[HA] = 1 \quad \text{or} \quad [A^-]/[HA] = 10$$

Similarly, if pH is reduced by 1, then—

$$[A^-]/[HA] = 1/10$$

Thus, weakly acidic drugs, which form salts with cations, e.g. *sod.* phenobarbitone, *sod.* sulfadiazine, *pot.* penicillin-V, etc. ionize more at alkaline pH and 1 scale change in pH causes 10-fold change in ionization.

Weakly basic drugs, which form salts with anions, e.g. atropine *sulfate*, ephedrine *HCl*, chloroquine *phosphate*, etc. conversely ionize more at acidic pH. Ions being lipid insoluble, do not diffuse and a pH difference across a membrane can cause differential distribution of weakly acidic and weakly basic drugs on the two sides (Fig. 2.3).

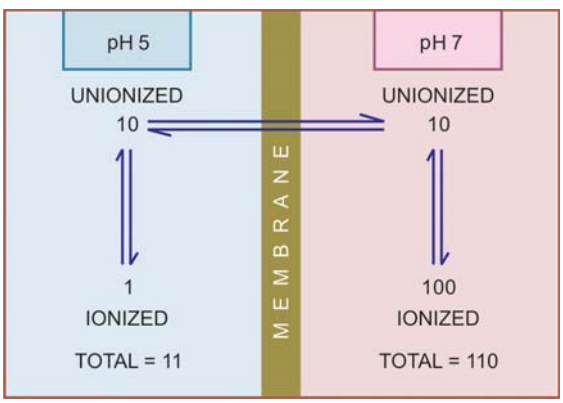


Fig. 2.3: Influence of pH difference on two sides of a biological membrane on the distribution of a weakly acidic drug with *pKa* = 6

Implications of this consideration are:
(a) Acidic drugs, e.g. aspirin (*pKa* 3.5) are largely unionized at acid gastric pH and are absorbed from stomach, while bases, e.g. atropine (*pKa* 10) are largely ionized and are absorbed only when they reach the intestines.
(b) The unionized form of acidic drugs which crosses the surface membrane of gastric mucosal cell, reverts to the ionized form within the cell (pH 7.0) and then only slowly passes to the extracellular fluid. This is called *ion trapping*, i.e. a weak electrolyte crossing a membrane to encounter a pH from which it is not able to escape easily. This may contribute to gastric mucosal cell damage caused by aspirin.
(c) Basic drugs attain higher concentration intracellularly (pH 7.0 *vs* 7.4 of plasma).
(d) Acidic drugs are ionized more in alkaline urine—do not back diffuse in the kidney tubules and are excreted faster. Accordingly, basic drugs are excreted faster if urine is acidified.

Lipid-soluble nonelectrolytes (e.g. ethanol, diethyl-ether) readily cross biological membranes and their transport is pH independent.

Filtration

Filtration is passage of drugs through aqueous pores in the membrane or through paracellular spaces. This can be accelerated if hydrodynamic flow of the solvent is occurring under hydrostatic or osmotic pressure gradient, e.g. across most capillaries including glomeruli. Lipid-insoluble drugs cross biological membranes by filtration if their molecular size is smaller than the diameter of the pores. Majority of cells (intestinal mucosa, RBC, etc.) have very small pores (4 Å) and drugs with MW > 100 or 200 are not able to penetrate. However, capillaries (except those in brain) have large pores (40 Å) and most drugs (even albumin) can filter through these (*see* Fig. 2.6A). As such, diffusion of drugs across capillaries is dependent on rate of blood flow through them rather than on lipid-solubility of the drug or pH of the medium.

Specialized transport

This can be carrier mediated or by pinocytosis.

Carrier transport The drug combines with a carrier present in the membrane and the complex then translocates from one face of the membrane to the other. Substances permitting transit of ions across membranes are called *ionophores*. Carrier transport is specific, saturable and competitively inhibited by analogues which utilize the same carrier. This is of two types:

(a) *Active transport* Movement occurs against the concentration gradient, needs energy and is inhibited by metabolic poisons. It results in selective accumulation of the substance on one side of the membrane. Drugs related to normal metabolites, e.g. levodopa and methyldopa are actively absorbed from the gut by aromatic amino acid transport process.

(b) *Facilitated diffusion* This proceeds more rapidly than simple diffusion and translocates even nondiffusible substrates, but along their concentration gradient, therefore, does not need energy.

Nonspecific active transport of drugs, their metabolites and some endogenous products occurs in renal tubules and hepatic sinusoids which have separate mechanisms for organic acids and organic bases. Certain drugs have been found to be actively transported in the brain and choroid plexus also.

Pinocytosis It is the process of transport across the cell in particulate form by formation of vesicles. This is applicable to proteins and other big molecules, and contributes little to transport of most drugs.

ABSORPTION

Absorption is the movement of drug from its site of administration into the circulation. Not only the fraction of the administered dose that gets absorbed, but also the rate of absorption is important. Except when given i.v., the drug has to cross biological membranes; absorption is governed by the above described principles. Other factors affecting absorption are:

Aqueous solubility Drugs given in solid form must dissolve in the aqueous biophase before they

are absorbed. For poorly water-soluble drugs (aspirin, griseofulvin) rate of dissolution governs rate of absorption. Obviously, a drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.

Concentration Passive transport depends on concentration gradient; drug given as concentrated solution is absorbed faster than from dilute solution.

Area of absorbing surface Larger it is, faster is the absorption.

Vascularity of the absorbing surface Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface. Increased blood flow hastens drug absorption just as wind hastens drying of clothes.

Route of administration This affects drug absorption, because each route has its own peculiarities.

Oral

The effective barrier to orally administered drugs is the epithelial lining of the gastrointestinal tract, which is lipoidal. Nonionized lipid-soluble drugs, e.g. ethanol are readily absorbed from stomach as well as intestine at rates proportional to their lipid : water partition coefficient. Acidic drugs, e.g. salicylates, barbiturates, etc. are predominantly unionized in the acid gastric juice and are absorbed from stomach, while basic drugs, e.g. morphine, quinine, etc. are largely ionized and are absorbed only on reaching the duodenum. However, even for acidic drugs absorption from stomach is slower, because the mucosa is thick, covered with mucus and the surface area is small. Thus, faster gastric emptying accelerates drug absorption in general. Dissolution is a surface phenomenon, therefore, *particle size* of the drug in solid dosage form governs rate of dissolution and in turn rate of absorption.

Presence of food dilutes the drug and retards absorption. Further, certain drugs form poorly absorbed complexes with food constituents, e.g. tetracyclines with calcium present in milk; also, food delays gastric emptying. Thus, most drugs are absorbed better if taken in empty stomach. Highly ionized drugs, e.g. gentamicin, neostigmine, are poorly absorbed when given orally.

Certain drugs are degraded in the gastrointestinal tract, e.g. penicillin G by acid, insulin by peptidases, and are ineffective orally. Enteric coated tablets (having acid resistant coating) and sustained release preparations (drug particles coated with slowly dissolving material) can be used to overcome acid lability, gastric irritancy and brief duration of action.

Absorption of a drug can be affected by other concurrently ingested drugs. This may be a *luminal effect*: formation of insoluble complexes, e.g. tetracyclines with iron preparations and antacids, ciprofloxacin with sucralfate. This can be minimized by administering the two drugs at 2–3 hour intervals. Alteration of gut flora by antibiotics may disrupt the enterohepatic cycling of oral contraceptives and digoxin. Drugs can also alter absorption by *gut wall effects*: altering motility (anticholinergics, tricyclic antidepressants, opioids, metoclopramide) or causing mucosal damage (neomycin, methotrexate, vinblastine).

Subcutaneous and intramuscular

By these routes the drug is deposited directly in the vicinity of the capillaries. Lipid-soluble drugs pass readily across the whole surface of the capillary endothelium. Capillaries being highly porous do not obstruct absorption of even large lipid-insoluble molecules or ions (*see* Fig. 2.6A). Very large molecules are absorbed through lymphatics. Thus, many drugs not absorbed orally are absorbed parenterally. Absorption from s.c. site is slower than that from i.m. site, but both are generally faster and more consistent/predictable than oral absorption. Application of heat and muscular exercise accelerate drug absorption by increasing blood flow, while vasoconstrictors, e.g. adrenaline injected with the drug (local anaesthetic) retard absorption. Many depot preparations, e.g. benzathine penicillin, protamine zinc insulin, depot progestins, etc. can be given by these routes.

Topical sites (skin, cornea, mucous membranes) Systemic absorption after topical application depends primarily on lipid solubility of drugs. However, only few drugs significantly penetrate intact skin. Glyceryl trinitrate, fentanyl and estradiol (*see* p. 8) have been used in this manner. Corticosteroids applied over extensive areas can produce systemic effects and pituitary-adrenal suppression. Absorption can be promoted by rubbing the drug incorporated in an olegenous base or by use of occlusive dressing which increases hydration of the skin. Organophosphate insecticides coming in contact with skin can produce systemic toxicity. Abraded surfaces readily absorb drugs, e.g. tannic acid applied over burnt skin has produced hepatic necrosis.

Cornea is permeable to lipid soluble, unionized physostigmine but not to highly ionized neostigmine. Similarly, mucous membranes of mouth, rectum, vagina absorb lipophilic drugs.

BIOAVAILABILITY

Bioavailability refers to the rate and extent of absorption of a drug from a dosage form as determined by its concentration-time curve in blood or by its excretion in urine (Fig. 2.4). It is a measure of the fraction (*F*) of administered dose of a drug that reaches the systemic circulation in the unchanged form. Bioavailability of drug injected i.v. is 100%, but is frequently lower after oral ingestion because—

(a) the drug may be incompletely absorbed.

(b) the absorbed drug may undergo first pass metabolism in intestinal wall/liver or be excreted in bile.

Incomplete bioavailability after s.c. or i.m. injection is less common, but may occur due to local binding of the drug.

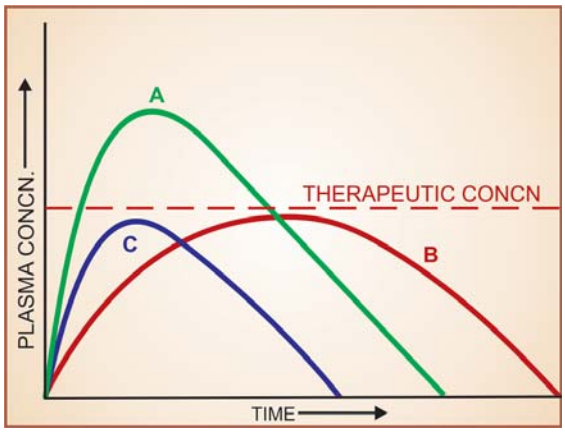


Fig. 2.4: Plasma concentration-time curves depicting bioavailability differences between three preparations of a drug containing the same amount
Note that formulation *B* is more slowly absorbed than *A*, and though ultimately both are absorbed to the same extent (area under the curve same), *B* may not produce therapeutic effect; *C* is absorbed to a lesser extent—lower bioavailability

Oral formulation of a drug from different manufacturers or different batches from the same manufacturer may have the same amount of the drug (chemically equivalent) but may not yield same blood levels—*biologically inequivalent*. Two preparations of a drug are considered *bioequivalent* when the rate and extent of bioavailability of the drug from them is not significantly different under suitable test conditions.

Before a drug administered orally in solid dosage form can be absorbed, it must break into individual particles of the active drug (disintegration). Tablets and capsules contain a number of other materials—diluents, stabilizing agents, binders, lubricants, etc. The nature of these as well as details of the manufacture process, e.g. force used in compressing the tablet, may affect *disintegration*. The released drug must then *dissolve* in the aqueous gastrointestinal contents. The rate of dissolution is governed by the inherent solubility, particle size, crystal form and other physical properties of the drug. Differences in bioavailability may arise due to variations in disintegration and dissolution rates.

Differences in bioavailability are seen mostly with poorly soluble and slowly absorbed drugs. Reduction in particle size increases the rate of absorption of aspirin (microfine tablets). The amount of griseofulvin and spironolactone in the tablet can be reduced to half if the drug particle is microfined. There is no need to reduce the particle size of freely water-soluble drugs, e.g. paracetamol.

Bioavailability variation assumes practical significance for drugs with low safety margin (digoxin) or where dosage needs precise control (oral hypoglycaemics, oral anticoagulants). It may also be responsible for success or failure of an antimicrobial regimen.

However, for a large number of drugs bioavailability differences are negligible and the risks of changing formulation have often been exaggerated.

DISTRIBUTION

Once a drug has gained access to the bloodstream, it gets distributed to other tissues that initially had no drug, concentration gradient being in the direction of plasma to tissues. The extent of distribution of a drug depends on its lipid solubility, ionization at physiological pH (dependent on pKa), extent of binding to plasma and tissue proteins and differences in regional blood flow. Movement of drug proceeds until an equilibrium is established between unbound drug in plasma and tissue fluids. Subsequently, there is a parallel decline in both due to elimination.

Apparent volume of distribution (V) Presuming that the body behaves as a single homogeneous compartment with volume *V* into which drug gets immediately and uniformly distributed

$$V = \frac{\text{dose administered i.v.}}{\text{plasma concentration}} \quad ...(3)$$

Since in the example shown in Fig. 2.5 the drug does not actually distribute into 20 L of body water, with the exclusion of the rest of it, this is only an apparent volume of distribution which can be defined as "the volume that would accommodate all the drug in the body, if the concentration throughout was the same as in plasma." Thus, it describes the amount of drug present in the body as a multiple of that contained in a unit volume of plasma. Considered together with drug clearance, this is a very useful pharmacokinetic concept.

Lipid-insoluble drugs do not enter cells—*V* approximates extracellular fluid volume, e.g. streptomycin, gentamicin 0.25 L/kg.

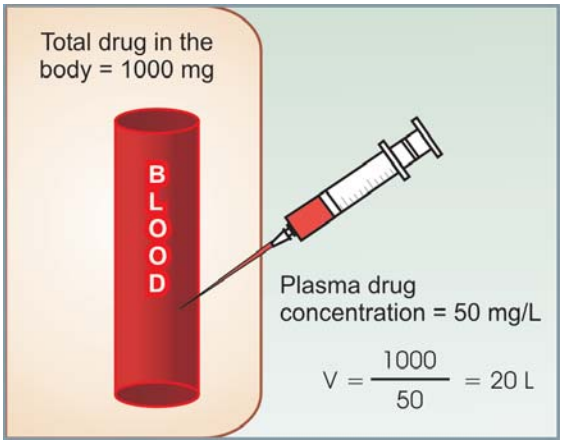


Fig. 2.5: Illustration of the concept of apparent volume of distribution (V).

In this example, 1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L, apparent volume of distribution is 20 L

Distribution is not only a matter of dilution but also binding and sequestration. Drugs extensively bound to plasma proteins are largely restricted to the vascular compartment and have low values, e.g. diclofenac and warfarin (99% bound) *V* = 0.15 L/kg.

Drugs sequestrated in other tissues may have *V* much more than total body water or even body mass, e.g. digoxin 6 L/kg, chlorpromazine 25 L/kg, morphine 3.5 L/kg because most of the drug is present in other tissues, and plasma concentration is low.

Pathological states, e.g. congestive heart failure, uraemia, cirrhosis of liver, etc. can alter the *V* of many drugs by altering distribution of body water, permeability of membranes, binding proteins or by accumulation of metabolites that displace the drug from binding sites.

Factors governing volume of drug distribution

- Lipid : water partition coefficient of the drug
- *pKa* value of the drug
- Degree of plasma protein binding
- Affinity for different tissues
- Fat : lean body mass ratio
- Diseases like CHF, uraemia, cirrhosis

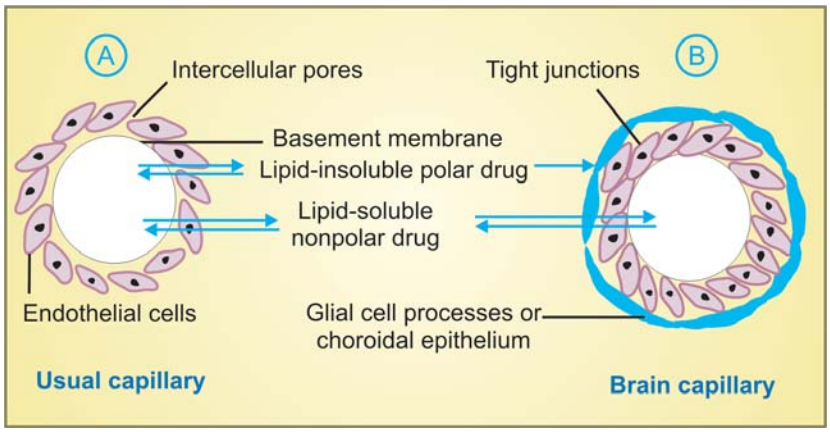


Fig. 2.6: Passage of drugs across capillaries
A. Usual capillary with large intercellular pores through which even large lipid-insoluble molecules diffuse
B. Capillary constituting blood-brain or blood-CSF barrier. Tight junctions between capillary endothelial cells and investment of glial processes or choroidal epithelium do not allow passage of nonlipid-soluble molecules/ions

Redistribution Highly lipid-soluble drugs get initially distributed to organs with high blood flow, i.e. brain, heart, kidney, etc. Later, less vascular but more bulky tissues (muscle, fat) take up the drug—plasma concentration falls and the drug is withdrawn from these sites. If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of drug action. Greater the lipid solubility of the drug, faster is its redistribution. Anaesthetic action of thiopentone injected i.v. is terminated in a few minutes due to redistribution. A relatively short (6-8 hr) hypnotic action due to redistribution is exerted by oral diazepam or nitrazepam despite their elimination half-life of > 30 hr. However, when the same drug is given repeatedly or by continuous i.v. infusion over long periods, the low perfusion high capacity sites get progressively filled up and the drug becomes longer acting.

Penetration into brain and CSF The capillary endothelial cells in brain have tight junctions and lack large intercellular pores. Further, an investment of neural tissue (Fig. 2.6B) covers the capillaries. Together they constitute the so-called *blood-brain barrier.* A similar *blood-CSF barrier* is located in the choroid plexus, capillaries are lined by choroidal epithelium having tight junctions. Both these barriers are lipoidal and limit the entry of nonlipid-soluble drugs, e.g. gentamicin, neostigmine, etc. Only lipid-soluble drugs, therefore, are able to penetrate and have action on the central nervous system. Efflux carriers like P-glycoprotein present in brain capillary endothelial cells extrude many drugs that enter brain by other processes. Dopamine does not enter brain, but its precursor levodopa does; as such, the latter is used in parkinsonism. Inflammation of meninges or brain increases permeability of these barriers.

There is also an enzymatic blood-brain barrier; monoamine oxidase (MAO), cholinesterase and some other enzymes are present in the capillary walls or in the cells lining them. They do not allow catecholamines, 5-HT, acetylcholine, etc. to enter brain in the active form.

The blood-brain barrier is deficient at the CTZ in the medulla oblongata (even lipid-insoluble drugs are emetic) and at certain periventricular sites—(anterior hypothalamus). Exit of drugs from the CSF and brain, however, is not dependent on

lipid solubility and is rather unrestricted. Bulk flow of CSF (along with drug dissolved in it) occurs through the arachnoid villi, and non-specific organic ion transport processes (similar to those in renal tubule) operate at the choroid plexus.

Passage across placenta Placental membranes are lipoidal and allow free passage of lipophilic drugs while restricting hydrophilic drugs. The placental efflux P-glycoprotein also serves to limit foetal exposure to maternally administered drugs. However, restricted amounts of nonlipid-soluble drugs, when present in high concentration or for long periods in maternal circulation, gain access to the foetus. Thus, it is an incomplete barrier and almost any drug taken by the mother can affect the foetus or the newborn (drug taken just before delivery, e.g. morphine).

Plasma protein binding

Most drugs possess physicochemical affinity for plasma proteins. Acidic drugs generally bind to plasma albumin and basic drugs to α_1 acid glycoprotein. Binding to albumin is quantitatively more important. Extent of binding depends on the individual compound; no generalization for a pharmacological or chemical class can be made (even small chemical change can markedly alter protein binding), for example:

Flurazepam	10%	Alprazolam	70%
Lorazepam	90%	Diazepam	99%

Increasing concentrations of the drug can progressively saturate the binding sites; fractional binding may be lower when large amounts of the drug are given. The generally expressed percentage binding refers to the usual therapeutic plasma concentrations of a drug. The clinically significant implications of plasma protein binding are:

(i) Highly plasma protein bound drugs are largely restricted to the vascular compartment and tend to have lower volumes of distribution.

(ii) The bound fraction is not available for action. However, it is in equilibrium with the free drug in plasma and dissociates when the concentration of the latter is reduced due to elimination. Plasma protein binding thus tantamounts to temporary storage of the drug.

Drugs highly bound to plasma protein

To Albumin	*To α_1-acid glycoprotein*
Barbiturates	β-blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lignocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Warfarin	Verapamil

(iii) High degree of protein binding generally makes the drug long acting, because bound fraction is not available for metabolism or excretion, unless it is actively extracted by liver or kidney tubules. Glomerular filtration does not reduce the concentration of the free form in the efferent vessels because water is also filtered. Active tubular secretion, however, removes the drug without the attendant solvent → concentration of free drug falls → bound drug dissociates and is eliminated resulting in a higher renal clearance value of the drug than the total renal blood flow (*See* Fig. 2.8). Same is true of active transport of highly extracted drugs in liver. Plasma protein binding in this situation acts as a carrier mechanism and hastens drug elimination, e.g. excretion of penicillin; metabolism of lignocaine. Highly protein bound drugs are not removed by haemodialysis and need special techniques for treatment of poisoning.

(iv) Generally expressed plasma concentrations of the drug refer to bound as well as free drug. Degree of protein binding should be taken into account while relating these to concentrations of the drug that are active *in vitro*, e.g. MIC of an antimicorbial.

(v) One drug can bind to many sites on the albumin molecule. Conversely, more than one drug can bind to the same site. This can give rise to displacement interactions among drugs bound to the same site(s); drug bound with higher affinity will displace that bound with lower affinity. If just 1% of a drug that is 99% bound is displaced, the concentration of free form will be doubled. This, however, is often transient because the displaced drug will diffuse into the tissues as well as get metabolized or excreted; the new steady-state free drug concentration is only marginally higher unless the displacement extends to tissue binding or there is concurrent inhibition of metabolism and/or excretion. The overall impact of many displacement interactions is minimal; clinical significance being attained only in case of highly bound drugs with limited volume of distribution (many acidic drugs bound to albumin) and where interaction is more complex. Moreover, two highly bound drugs do not necessarily displace each other—their binding sites may not overlap, e.g. probenecid and indomethacin are highly bound to albumin but do not displace each other. Similarly, acidic drugs do not generally displace basic drugs and *vice versa*. Some clinically important displacement interactions are:

- Salicylates displace sulfonylureas.
- Indomethacin, phenytoin displace warfarin.
- Sulfonamides and vit K displace bilirubin (kernicterus in neonates).
- Salicylates displace methotrexate.

(vi) In hypoalbuminaemia, binding may be reduced and high concentrations of free drug may be attained, e.g. phenytoin and furosemide. Other diseases may also alter drug binding, e.g. digitoxin, phenytoin and pethidine binding is reduced in uraemia; propranolol binding is increased in pregnant women and in patients with inflammatory disease (acute phase reactant α_1 acid-glycoprotein increases).

Tissue storage Drugs may also accumulate in specific organs or get bound to specific tissue constituents, e.g.—

Drugs concentrated in tissues

Skeletal muscle, heart	—	digoxin, emetine (to muscle proteins).
Liver	—	chloroquine, tetracyclines, emetine, digoxin.
Kidney	—	digoxin , chloroquine, emetine.
Thyroid	—	iodine.
Brain	—	chlorpromazine, acetazolamide, isoniazid.
Retina	—	chloroquine (to nucleoproteins).
Iris	—	ephedrine, atropine (to melanin).
Bone and teeth	—	tetracyclines, heavy metals (to mucopolysaccharides of connective tissue).
Adipose tissue	—	thiopentone, ether, minocycline, DDT dissolve in neutral fat due to high lipid solubility; remain stored due to poor blood supply of fat.

Drugs sequestrated in various tissues are differentially distributed, tend to have large volume of distribution and long duration of action. Some may exert local toxicity due to high concentration, e.g. tetracyclines on bone and teeth, chloroquine on retina, emetine on heart and skeletal muscle. Drugs may also selectively bind to specific intracellular organelle, e.g. tetracycline to mitochondria, chloroquine to nuclei.

BIOTRANSFORMATION (Metabolism)

Biotransformation means chemical alteration of the drug in the body. It is needed to render nonpolar (lipid soluble) compounds polar (lipid insoluble) so that they are not reabsorbed in the renal tubules and are excreted. Most hydrophilic drugs, e.g. gentamicin, neostigmine, decamethonium, etc. are not biotransformed and are excreted unchanged.

The primary site for drug metabolism is liver; others are—kidney, intestine, lungs and plasma. Biotransformation of drugs may lead to the following.

(i) *Inactivation* Most drugs and their active metabolites are rendered inactive or less active, e.g. lignocaine, ibuprofen, paracetamol, chloramphenicol, propranolol and its active metabolite 4-hydroxypropranolol.

(ii) *Active metabolite from an active drug* Many drugs have been found to be partially converted to one or more active metabolite (*see* box); the effects observed are the sum total of that due to the parent drug and its active metabolite(s).

(iii) *Activation of inactive drug* Few drugs are inactive as such and need conversion in the body to one or more active metabolite(s). Such a drug is called a *prodrug*. The prodrug may offer advantages over the active form in being more stable, having better bioavailability or other desirable pharmacokinetic properties or less side effects and toxicity. Some prodrugs are activated selectively at the site of action.

Active drug		Active metabolite
Allopurinol	—	Alloxanthine
Procainamide	—	N-acetyl-procainamide
Primidone	—	Phenobarbitone, phenylethylmalonamide
Cefotaxime	—	Deacetyl cefotaxime
Diazepam	—	Desmethyl-diazepam, oxazepam
Digitoxin	—	Digoxin
Imipramine	—	Desipramine
Amitriptyline	—	Nortriptyline
Codeine	—	Morphine
Morphine	—	Morphine-6-glucuronide
Spironolactone	—	Canrenone
Losartan	—	E 3174

Biotransformation reactions can be classified into:

(a) Nonsynthetic/Phase I reactions—metabolite may be active or inactive.

Prodrug		Active form
Levodopa	—	Dopamine
Enalapril	—	Enalaprilat
α-Methyldopa	—	α-Methylnorepinephrine
Dipivefrine	—	Epinephrine
Sulindac	—	Sulfide metabolite
Proguanil	—	Cycloguanil
Prednisone	—	Prednisolone
Bacampicillin	—	Ampicillin
Sulfasalazine	—	5-Aminosalicylic acid
Acyclovir	—	Acyclovir triphosphate
Cyclophosphamide	—	Aldophosphamide, phosphoramide mustard, acrolein
Fluorouracil	—	Fluorouridine monophosphate
Mercaptopurine	—	Methylmercaptopurine ribonucleotide

(b) Synthetic/Conjugation/ Phase II reactions—metabolite is mostly inactive.

Nonsynthetic reactions

(i) Oxidation This reaction involves addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical. Oxidations are the most important drug metabolizing reactions. Various oxidation reactions are:

hydroxylation; oxygenation at C, N or S atoms; N or O-dealkylation, oxidative deamination, etc.

In many cases, the initial insertion of oxygen atom into the drug molecule produces short lived highly reactive quinone/epoxide/superoxide intermediates which then convert to more stable compounds.

Oxidative reactions are mostly carried out by a group of monooxygenases in the liver, which in the final step involve a cytochrome P-450 haemoprotein, NADPH, cytochrome P-450 reductase and molecular O_2. More than 100 cytochrome P-450 isoenzymes differing in their affinity for various substrates (drugs), have been identified.

Depending upon the extent of amino acid sequence homology, the cytochrome P-450 (CYP) isoenzymes are grouped into families designated by numerals (1, 2, 3,...), each having several subfamilies designated by capital letters (A, B, C,...), while individual isoenzymes are again alloted numerals (1, 2, 3,...). In human beings, only a few members of *three* isoenzyme families (CYP 1, 2 and 3) carry out metabolism of most of the drugs, and many drugs such as tolbutamide, barbiturates, nifedipine are substrates for more than one isoform. The CYP isoenzymes important in man are:

CYP3A4/5 Carry out biotransformation of largest number (nearly 50%) of drugs. In addition to liver, these isoforms are expressed in intestine (responsible for first pass metabolism at this site) and kidney as well. Inhibition of this isoenzyme by erythromycin, clarithromycin, ketoconazole, itraconazole is responsible for the important drug interaction with terfenadine, astemizole and cisapride (*see* p. 102) which are its substrates. Verapamil, diltiazem, ritonavir and a constituent of grape fruit juice are other important inhibitors, while rifampicin, barbiturates and other anticonvulsants are the important inducers.

CYP2D6 This is the next most important CYP isoform which metabolizes nearly 20% drugs including tricyclic antidepressants, selective serotonin reuptake inhibitors, many neuroleptics, antiarrhythmics, β-blockers and opiates.

CYP2C8/9 Important in the biotransformation of >15 commonly used drugs including phenytoin and warfarin which are narrow safety margin drugs.

CYP2C19 Metabolizes > 12 frequently used drugs including omeprazole, lansoprazole.

Rifampicin and carbamazepine are potent inducers of the CYP2C subfamily.

CYP1A1/2 Though this subfamily participates in the metabolism of only few drugs, it is more important for activation of procarcinogens. Apart from rifampicin and carbamazepine, polycyclic hydrocarbons, cigarette smoke and charbroiled meat are its potent inducers.

CYP2E1 It catalyzes formation of minor metabolites of few drugs, notably the hepatotoxic N-acetyl benzoquinoneimine from paracetamol; chronic alcoholism induces this isoenzyme.

The relative amount of different cytochrome P-450s differs among species and among individuals of the same species. These differences largely account for the marked interspecies and interindividual differences in rate of metabolism of drugs.

Barbiturates, phenothiazines, paracetamol, steroids, phenytoin, benzodiazepines, theophylline and many other drugs are oxidized in this way. Some other drugs, e.g. adrenaline, alcohol, mercaptopurine are oxidized by mitochondrial or cytoplasmic enzymes.

(ii) Reduction This reaction is the converse of oxidation and involves cytochrome P-450 enzymes working in the opposite direction. Drugs primarily reduced are chloramphenicol, halothane and warfarin.

(iii) Hydrolysis This is cleavage of drug molecule by taking up a molecule of water.

$$\text{Ester} + H_2O \xrightarrow{\textit{esterase}} \text{Acid} + \text{Alcohol}$$

Similarly, amides and polypeptides are hydrolyzed by amidases and peptidases. Hydrolysis occurs in liver, intestines, plasma and other tissues. Examples are choline esters, procaine, lignocaine, procainamide, pethidine, oxytocin.

Synthetic reactions

These involve conjugation of the drug or its phase I metabolite with an endogenous substrate, generally derived from carbohydrate or amino acid, to form a polar highly ionized organic acid, which is easily excreted in urine or bile.

(i) Glucuronide conjugation This is the most important synthetic reaction. Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose. Examples are chloramphenicol, aspirin, morphine, metronidazole. Not only drugs but endogenous substrates like bilirubin, steroidal hormones and thyroxine utilize this pathway. Drug glucuronides excreted in bile can be hydrolyzed by bacteria in the gut—the liberated drug is reabsorbed and undergoes the same fate. This enterohepatic cycling of the drug prolongs its action, e.g. phenolphthalein, oral contraceptives.

(ii) Acetylation Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A, e.g. sulfonamides, isoniazid, PAS, hydralazine. Multiple genes control the acetyl transferases and rate of acetylation shows genetic polymorphism (slow and fast acetylators).

(iii) Methylation The amines and phenols can be methylated; methionine and cysteine acting as methyl donors, e.g. adrenaline, histamine, nicotinic acid.

(iv) Sulfate conjugation The phenolic compounds and steroids are sulfated by sulfokinases, e.g. chloramphenicol, adrenal and sex steroids.

(v) Glycine conjugation Salicylates and other drugs having carboxylic acid group are conjugated with glycine, but this is not a major pathway of metabolism.

(vi) Glutathione conjugation Forming a mercapturate is normally a minor pathway. However, it serves to inactivate highly reactive quinone or epoxide intermediates formed during metabolism of certain drugs, e.g. paracetamol. When a large amount of such intermediates are formed (in poisoning or after enzyme induction), glutathione supply falls short—toxic adducts are formed with tissue constituents → tissue damage.

(vii) Ribonucleoside/nucleotide synthesis It is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy.

Most drugs are metabolized by many pathways, simultaneously or sequentially as illustrated in Fig. 2.7. As such, a variety of metabolities of a drug may be produced.

Only few drugs are metabolized by enzymes of intermediary metabolism, e.g. alcohol by dehydrogenase, allopurinol by xanthine oxidase, succinylcholine and procaine by plasma cholinesterase, adrenaline by monoamine oxidase. Majority of drugs are acted on by relatively nonspecific enzymes which are directed to types of molecules rather than to specific drugs. The same enzyme can metabolize many drugs. The drug metabolizing enzymes are divided into two types:

Microsomal These are located on smooth endoplasmic reticulum (a system of microtubules inside the cell), primarily in liver, also in kidney, intestinal mucosa and lungs. The monooxygenases, cytochrome P 450, glucuronyl transferase, etc. are microsomal enzymes.

They catalyze most of the oxidations, reductions, hydrolysis and glucuronide conjugation. Microsomal enzymes are inducible by drugs, diet and other agencies.

Nonmicrosomal These are present in the cytoplasm and mitochondria of hepatic cells as well as in other tissues including plasma. The flavoprotein oxidases, esterases, amidases and conjugases are nonmicrosomal. Reactions catalyzed are:

Some oxidations and reductions, many hydrolytic reactions and all conjugations except glucuronidation.

The nonmicrosomal enzymes are not inducible but many show genetic polymorphism (acetyl transferase, pseudocholinesterase).

Both microsomal and nonmicrosomal enzymes are deficient in the newborn, especially premature, making them more susceptible to many drugs, e.g. chloramphenicol, opioids. This deficit is made up in first few months, more quickly in case of oxidation and other phase I reactions than in case of glucuronide and other conjugations taking 3 or more months.

Amount and kind of drug metabolizing enzymes is controlled genetically and is also altered by environmental factors. Thus, marked interspecies and interindividual differences are seen, e.g. cats are deficient in glucuronyl transferase

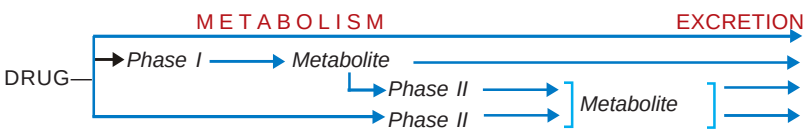


Fig. 2.7: Simultaneous and/or sequential metabolism of a drug by phase I and phase II reactions

while dogs are deficient in acetyl transferase. Up to 6-fold difference in the rate of metabolism of a drug among normal human adults may be observed. This is one of the major causes of individual variation in drug response.

Hofmann elimination This refers to inactivation of the drug in the body fluids by spontaneous molecular rearrangement without the agency of any enzyme, e.g. atracurium.

INHIBITION OF DRUG METABOLISM

One drug can competitively inhibit the metabolism of another if it utilizes the same enzyme or cofactors. However, such interactions are not as common as one would expect, because often different drugs are substrates for different cytochrome P-450 isoenzymes. Moreover, a drug may inhibit one isoenzyme while being itself a substrate of another isoenzyme, e.g. quinidine is metabolized by CYP3A4 but inhibits CYP2D6. Also most drugs, at therapeutic concentrations are metabolized by non-saturation kinetics, i.e. the enzyme is present in excess. Clinically significant inhibition of drug metabolism occurs in case of drugs having affinity for the same isoenzyme, especially if they are metabolized by saturation kinetics or if kinetics changes from first order to zero order over the therapeutic range (capacity limited metabolism). Obviously, inhibition of drug metabolism occurs in a dose-related manner and can precipitate toxicity of the object drug (whose metabolism has been inhibited).

Drugs that inhibit drug metabolizing enzymes

Allopurinol	Diltiazem
Omeprazole	Amiodarone
Erythromycin	Propoxyphene
Clarithromycin	Isoniazid
Chloramphenicol	Cimetidine
Ketoconazole	Quinidine
Itraconazole	Metronidazole
Ciprofloxacin	Disulfiram
Sulfonamides	Verapamil

Because enzyme inhibition occurs by direct effect on the enzyme, it has a fast time course (within hours) compared to enzyme induction (*see* below).

Metabolism of drugs with high hepatic extraction is dependent on liver blood flow (blood flow limited metabolism). Propranolol reduces rate of lignocaine metabolism by decreasing hepatic blood flow.

MICROSOMAL ENZYME INDUCTION

Many drugs, insecticides and carcinogens interact with DNA and increase the synthesis of microsomal enzyme protein, especially cytochrome P-450 and glucuronyl transferase. As a result, rate of metabolism of inducing drug itself and/or other drugs is increased.

Different inducers are relatively selective for certain cytochrome P-450 enzyme families, e.g.:

- Anticonvulsants including phenobarbitone, rifampin, glucocorticoids induce CYP3A isoenzymes.
- Phenobarbitone also induces CYP2B1 and rifampin also induces CYP2D6.
- Isoniazid and chronic alcohol consumption induce CYP2E1.
- Polycyclic hydrocarbons like 3-methylcholanthrene and benzopyrene found in cigarette smoke, charcoalbroiled meat and industrial pollutants induce CYP1A isoenzymes.
- Other important enzyme inducers are: chloral hydrate, griseofulvin, DDT.

Since different CYP isoenzymes are involved in the metabolism of different drugs, every inducer increases biotransformation of certain drugs but not that of others. However, phenobarbitone like inducers of CYP3A and CYP2D6 affect the metabolism of a large number of drugs, because these isoenzymes act on many drugs. On the other hand, induction by polycyclic hydrocarbons is limited to a few drugs (like theophylline, phenacetin) because CYP1A isoenzyme metabolizes only few drugs.

Induction involves microsomal enzymes in liver as well as other organs and increases the rate of metabolism by 2–4-fold. Induction takes 4–14 days to reach its peak and is maintained till the inducing agent is being given. Thereafter, the enzymes return to their original value over 1 to 3 weeks.

Consequences of microsomal enzyme induction

1. Decreased intensity and/or duration of action of drugs that are inactivated by metabolism, e.g. failure of contraception with oral contraceptives.
2. Increased intensity of action of drugs that are activated by metabolism. Acute paracetamol toxicity is due to one of its metabolites—toxicity occurs at lower doses in patients receiving enzyme inducers.
3. Tolerance—if the drug induces its own metabolism (autoinduction), e.g. carbamazepine, rifampin.
4. Some endogenous substrates (steroids, bilirubin) are also metabolized faster.
5. Precipitation of acute intermittent porphyria: enzyme induction increases porphyrin synthesis by derepressing δ-aminolevulenic acid synthetase.
6. Intermittent use of an inducer may interfere with adjustment of dose of another drug prescribed on regular basis, e.g. oral anticoagulants, oral hypoglycaemics, antiepileptics, antihypertensives.

Drugs whose metabolism is significantly affected by enzyme induction are—phenytoin, warfarin, tolbutamide, imipramine, oral contraceptives, chloramphenicol, doxycycline, theophylline, griseofulvin.

Possible uses of enzyme induction

1. Congenital nonhaemolytic jaundice: phenobarbitone causes rapid clearance of jaundice.
2. Cushing's syndrome: phenytoin may reduce the manifestations.
3. Chronic poisonings.
4. Liver disease.

FIRST PASS (PRESYSTEMIC) METABOLISM

This refers to metabolism of a drug during its passage from the site of absorption into the systemic circulation. All orally administered drugs are exposed to drug metabolizing enzymes in the intestinal wall and liver (where they first reach through the portal vein). Presystemic metabolism, of limited magnitude, can also occur in the skin (transdermally administered drug) and in lungs (for drug reaching venous blood through any route). The extent of first pass metabolism differs for different drugs (Table 2.1) and is an important determinant of oral bioavailability.

Attributes of drugs with high first pass metabolism

(a) Oral dose is considerably higher than sublingual or parenteral dose.
(b) There is marked individual variation in the oral dose due to differences in the extent of first pass metabolism.
(c) Oral bioavailability is apparently increased in patients with severe liver disease.

Table 2.1: Extent of first pass metabolism of some important drugs

Low	*Intermediate*	*High*	
		not given orally	*high oral dose*
Phenobarbitone	Aspirin	Isoprenaline	Propranolol
Tolbutamide	Quinidine	Lignocaine	Alprenolol
Theophylline	Desipramine	Hydrocortisone	Verapamil
Pindolol	Nortriptyline	Testosterone	Salbutamol
Isosorbide mononitrate	Chlorpromazine		Glyceryl trinitrate
	Pentazocine		Morphine
	Metoprolol		Pethidine

(d) Oral bioavailability of a drug is increased if another drug competing with it in first pass metabolism is given concurrently, e.g. chlorpromazine and propranolol.

EXCRETION

Excretion is the passage out of systemically absorbed drug. Drugs and their metabolites are excreted in:

1. Urine Through the kidney. It is the most important channel of excretion for majority of drugs (*see* below).

2. Faeces Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Liver actively transports into bile organic acids (especially drug glucuronides), organic bases and steroids by separate nonspecific active transport mechanisms. Relatively larger molecules (MW > 300) are preferentially eliminated in the bile. Most of the drug, including that released by deconjugation of glucuronides by bacteria in intestines is reabsorbed (enterohepatic cycling) and ultimate excretion occurs in urine. Drugs that attain high concentrations in bile are erythromycin, ampicillin, rifampin, tetracycline, oral contraceptives, phenolphthalein.

Certain drugs are excreted directly in colon, e.g. anthracene purgatives, heavy metals.

3. Exhaled air Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility. Alveolar transfer of the gas/vapour depends on its partial pressure in the blood. Lungs also serve to trap and extrude any particulate matter injected i.v.

4. Saliva and sweat These are of minor importance for drug excretion. Lithium, pot. iodide, rifampin and heavy metals are present in these secretions. Most of the saliva along with the drug in it, is swallowed and meets the same fate as orally taken drug.

5. Milk The excretion of drug in milk is not important for the mother, but the suckling infant inadvertently receives the drug. Most drugs enter breast milk by passive diffusion. As such, more lipid soluble and less protein bound drugs cross better. Milk has a lower pH (7.0) than plasma, basic drugs are somewhat more concentrated in it. However, the total amount of drug reaching the infant through breastfeeding is generally small and majority of drugs can be given to lactating mothers without ill effects on the infant. Nevertheless, it is advisable to administer any drug to a lactating women only when essential.

RENAL EXCRETION

The kidney is responsible for excreting all water-soluble substances. The amount of drug or its metabolites ultimately present in urine is the sum total of glomerular filtration, tubular reabsorption and tubular secretion (Fig. 2.8).

$$\text{Net renal excretion} = (\text{glomerular filtration} + \text{tubular secretion}) - \text{tubular reabsorption}$$

Glomerular filtration Glomerular capillaries have pores larger than usual; all nonprotein bound drug (whether-lipid soluble or insoluble) presented to the glomerulus is filtered. Thus, glomerular filtration of a drug depends on its plasma protein binding and renal blood flow. Glomerular filtration rate (g.f.r.), normally ~ 120 mL/min, declines progressively after the age of 50 and is low in renal failure.

Tubular reabsorption This depends on lipid solubility and ionization of the drug at the existing urinary pH. Lipid-soluble drugs filtered at the glomerulus back diffuse passively in the tubules because 99% of glomerular filtrate is reabsorbed, but nonlipid-soluble and highly ionized drugs are unable to do so. Thus, rate of excretion of such drugs, e.g. aminoglycoside antibiotics, quaternary ammonium compounds parallels g.f.r. (or creatinine clearance). Changes in urinary pH

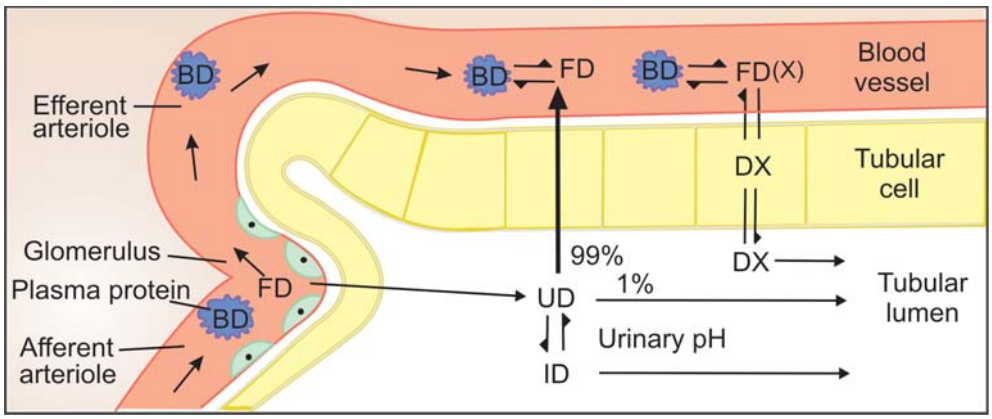


Fig. 2.8: Schematic depiction of glomerular filtration, tubular reabsorption and tubular secretion of drugs
FD—free drug; BD—bound drug; UD—unionized drug; ID—ionized drug, Dx—highly secreted organic acid (or base) drug

affect tubular reabsorption of drugs that are partially ionized—

- Weak bases ionize more and are less reabsorbed in acidic urine.
- Weak acids ionize more and are less reabsorbed in alkaline urine.

This principle is utilized for facilitating elimination of drug in poisoning, i.e. urine is alkalinized in barbiturate and salicylate poisoning, while it is acidified in morphine and amphetamine poisoning.

Tubular secretion This is the active transfer of organic acids and bases by two separate nonspecific mechanisms which operate in the proximal tubules. Efflux transporters P-glycoprotein and MRP2 are located in luminal membrane of proximal tubular cells. If renal clearance of a drug is greater than 120 mL/min (g.f.r.), additional tubular secretion can be assumed to be occurring.

Active transport of the drug across tubules reduces concentration of its free form in the tubular vessels and promotes dissociation of protein bound drug, which again is secreted. Thus, protein binding, which is a hinderance for glomerular filtration of the drug, is not so (may even be facilitatory) to excretion by tubular secretion.

(a) *Organic acid transport* for penicillin, probenecid, uric acid, salicylates, sulfinpyrazone, nitrofurantoin, methotrexate, drug glucuronides, etc.

(b) *Organic base transport* for thiazides, quinine, procainamide, choline, cimetidine, amiloride, etc.

Inherently both transport processes are bidirectional, i.e. they can transport their substrates from blood to tubular fluid and *vice versa*. However, for drugs and their metabolites (exogenous substances) secretion into the tubular lumen predominates, whereas an endogenous substrate like uric acid is predominantly reabsorbed.

Drugs utilizing the same active transport compete with each other. Probenecid is an organic acid which has high affinity for the tubular organic anion carrier. It blocks the active transport of both penicillin and uric acid, but whereas the net excretion of the former is decreased, that of the latter is increased. This is because penicillin is primarily secreted while uric acid is primarily reabsorbed. Many drug interactions occur due to competition for tubular secretion, e.g.

(i) Salicylates block uricosuric action of probenecid and sulfinpyrazone and decrease tubular secretion of methotrexate.

(ii) Probenecid decreases the concentration of nitrofurantoin in urine, increases the duration of

action of penicillin/ampicillin and impairs secretion of methotrexate.

(iii) Quinidine decreases renal and biliary clearance of digoxin by inhibiting efflux carrier P-glycoprotein.

Tubular transport mechanisms are not well developed at birth. As a result, duration of action of many drugs, e.g. penicillin, cephalosporins, aspirin is longer in neonates. These systems mature during infancy.

KINETICS OF ELIMINATION

The knowledge of kinetics of elimination of a drug provides the basis for, as well as serves to devise rational dosage regimens and to modify them according to individual needs. There are three fundamental pharmacokinetic parameters, viz. bioavailability (*F*), volume of distribution (*V*) and clearance (*CL*) which must be understood. The first two have already been considered.

Drug elimination is the sum total of metabolic inactivation and excretion. As depicted in Fig. 2.1, drug is eliminated only from the central compartment (blood) which is in equilibrium with peripheral compartments including the site of action. Depending upon the ability of the body to eliminate a drug, a certain fraction of the central compartment may be considered to be totally 'cleared' of that drug in a given period of time to account for elimination over that period.

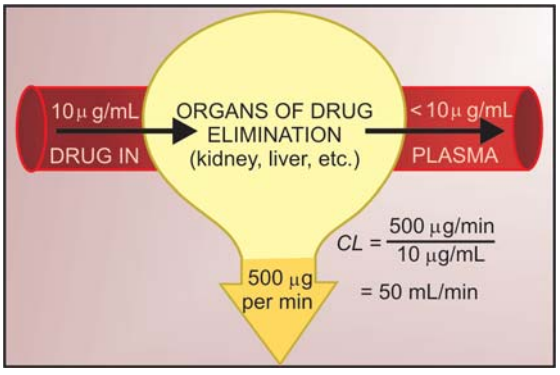


Fig. 2.9: Illustration of concept of drug clearance. A fraction of the drug molecules present in plasma are removed on each passage through the organs of elimination. In the case shown, it requires 50 mL of plasma to account for the amount of drug being eliminated every minute: clearance is 50 mL/min

Clearance (CL) The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time (analogy creatinine clearance). It can be calculated as

$$CL = \text{Rate of elimination}/C \quad ...(4)$$

where *C* is the plasma concentration.

For majority of drugs the processes involved in elimination are not saturated over the clinically obtained concentrations, they follow:

First order (exponential) kinetics The rate of elimination is directly proportional to drug concentration, *CL* remains constant; or a constant *fraction* of the drug present in the body is eliminated in unit time.

Few drugs, however, saturate eliminating mechanisms and are handled by—

Zero order (linear) kinetics The rate of elimination remains constant irrespective of drug concentration, *CL* decreases with increase in concentration; or a constant *amount* of the drug is eliminated in unit time, e.g. ethyl alcohol.

The elimination of some drugs approaches saturation over the therapeutic range, kinetics changes from first order to zero order at higher doses. As a result, plasma concentration increases disproportionately with increase in dose, e.g. phenytoin, tolbutamide, theophylline, warfarin.

Plasma half-life The plasma half-life (t½) of a drug is the time taken for its plasma concentration to be reduced to half of its original value.

Taking the simplest case of a drug which has rapid one compartment distribution and first order elimination, and is given i.v., a semilog plasma concentration-time plot as shown in Fig. 2.10 is obtained. The plot has two slopes:

(i) initial rapidly declining (α) phase—due to distribution.

(ii) later less declined (β) phase—due to elimination.

At least two half-lives (distribution t½ and elimination t½) can be calculated from the two

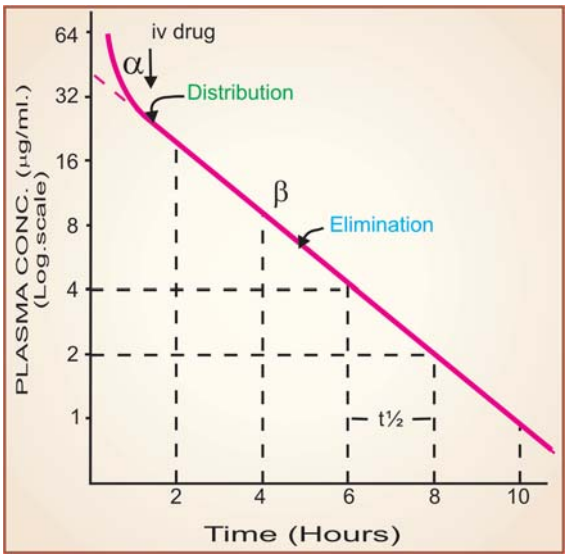


Fig. 2.10: Semilog plasma concentration-time plot of a drug eliminated by first order kinetics after intravenous injection

slopes. The elimination half-life derived from the β slope is simply called the 'half-life' of the drug. Mathematically, elimination t½ is

$$t½ = \frac{\ln 2}{k} \quad ...(5)$$

Where ln2 is the natural logarithm of 2 (or 0.693) and *k* is the *elimination rate constant* of the drug, i.e. the fraction of the total amount of drug in the body which is removed per unit time. For example, if 2 g of the drug is present in the body and 0.1 g is eliminated every hour, then $k = 0.1/2 = 0.05$. It is calculated as:

$$k = \frac{CL}{V} \quad ...(6)$$

therefore,
$$t½ = 0.693 \times \frac{V}{CL} \quad ...(7)$$

As such, half-life is a derived parameter from two variables *V* and *CL* both of which may change independently. It, therefore, is not an exact index of drug elimination. Nevertheless, it is a simple and useful guide to the sojourn of the drug in the body, i.e. after

1 t½ – 50% drug is eliminated.
2 t½ – 75% (50 + 25) drug is eliminated.
3 t½ – 87.5% (50 + 25 + 12.5) drug is eliminated.
4 t½ – 93.75% (50 + 25 + 12.5 + 6.25) drug is eliminated.

Thus, nearly complete drug elimination occurs in 4–5 half-lives.

For drugs eliminated by—

First order kinetics—t½ remains constant because *V* and *CL* do not change with dose.

Zero order kinetics—t½ increases with dose because *CL* progressively decreases as dose is increased.

Half-life of some representative drugs

Aspirin	4 hr	Digoxin	40 hr
Penicillin-G	30 min	Digitoxin	7 days
Doxycycline	20 hr	Phenobarbitone	90 hr

Repeated drug administration

When a drug is repeated at relatively short intervals, it accumulates in the body until elimination balances input and a *steady-state* plasma concentration (*Cpss*) is attained—

$$Cpss = \frac{\text{dose rate}}{CL} \quad ...(8)$$

From this equation it is implied that doubling the dose rate would double the average *Cpss* and so on. Further, if the therapeutic plasma concentration of the drug has been worked out and its *CL* is known, the dose rate needed to achieve the target *Cpss* can be determined—

$$\text{dose rate} = \text{target } Cpss \times CL \quad ...(9)$$

After oral administration, often only a fraction (*F*) of the dose reaches systemic circulation in the active form. In such a case—

$$\text{dose rate} = \frac{\text{target } Cpss \times CL}{F} \quad ...(10)$$

The dose rate-*Cpss* relationship is linear only in case of drugs eliminated by first order kinetics. For drugs (e.g. phenytoin) which follow Michaelis Menten kinetics, elimination changes from first order to zero order kinetics over the therapeutic

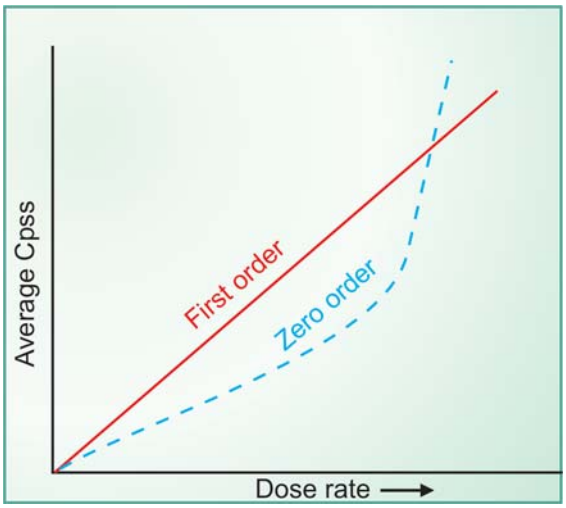


Fig. 2.11: Relationship between dose rate and average steady-state plasma concentration of drugs eliminated by first order and Michaelis Menten (zero order) kinetics

range. Increase in their dose beyond saturation levels causes an increase in *Cpss* which is out of proportion to the change in dose rate (Fig. 2.11). In their case:

$$\text{Rate of drug elimination} = \frac{(V_{max})\,(C)}{K_m + C} \quad \ldots(11)$$

where C is the plasma concentration of the drug, V_{max} is the maximum rate of drug elimination, and K_m is the plasma concentration at which elimination rate is half maximal.

Plateau principle

When constant dose of a drug is repeated before the expiry of 4 t½, it would achieve higher peak concentration, because some remnant of the previous dose will be present in the body. This continues with every dose until progressively increasing rate of elimination (which increases with increase in concentration) balances the amount administered over the dose interval. Subsequently, plasma concentration plateaus and fluctuates about an average steady-state level. This is known as the plateau principle of drug accumulation. Steady state is reached in 4–5 half-

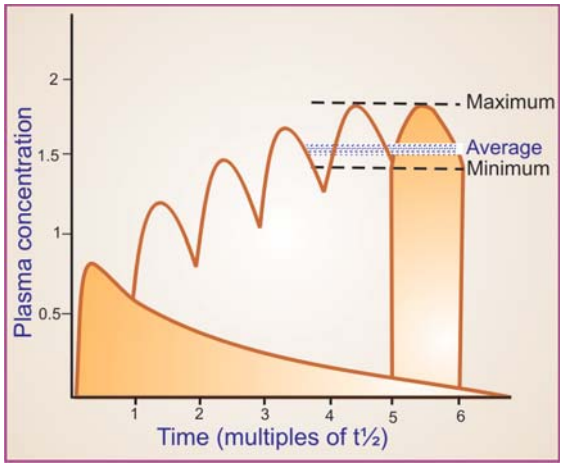


Fig. 2.12: Plateau principle of drug accumulation on repeated oral dosing.
Note. The area of the two shaded portions is equal

lives unless dose interval is very much longer than t½ (Fig. 2.12).

The amplitude of fluctuations in plasma concentration at steady state depends on the dose interval relative to t½, i.e. the difference between the maximum and minimum levels is less if smaller doses are repeated more frequently (dose rate remaining constant). However, if the dose rate is changed, a new average *Cpss* is attained over the next 4–5 half-lives. When the drug is administered orally (absorption takes some time), average *Cpss* is approximately 1/3rd of the way between the minimal and maximal levels in a dose interval.

Target level strategy For drugs whose effects are not easily quantifiable and safety margin is not big, e.g. anticonvulsants, antidepressants, lithium, some antimicrobials, etc. or those given to prevent an event, it is best to aim at achieving a certain plasma concentration which has been defined to be in the therapeutic range; such data are now available for most drugs of this type.

Drugs with short t½ (up to 2–3 hr) administered at conventional intervals (6–12 hr) achieve the target levels only intermittently and fluctuations in plasma concentration are marked. In case of many drugs (penicillin, ampicillin, chloramp-

henicol, erythromycin, propranolol) this, however, is therapeutically acceptable.

For drugs with longer t½ a dose that is sufficient to attain the target concentration after single administration, if repeated will accumulate according to plateau principle and produce toxicity later on. On the other hand, if the dosing is such as to attain target level at steady state, the therapeutic effect will be delayed by about 4 half-lives (this may be clinically unacceptable). Such drugs are often administered by initial loading and subsequent maintenance doses.

Loading dose This is a single or few quickly repeated doses given in the beginning to attain target concentration rapidly. It may be calculated as—

$$\text{Loading dose} = \frac{\text{target } Cp \times V}{F} \quad ...(12)$$

Thus, loading dose is governed only by V and not by CL or t½.

Maintenance dose This dose is one that is to be repeated at specified intervals after the attainment of target $Cpss$ so as to maintain the same by balancing elimination. The maintenance dose rate is computed by equation (10) and is governed by CL (or t½) of the drug. If facilities for measurement of drug concentration are available, attainment of target level in a patient can be verified subsequently and dose rate adjusted if required.

Such two phase dosing provides rapid therapeutic effect with long-term safety; frequently applied to digoxin, chloroquine, doxycycline, etc. The concept of loading and maintenance dose is valid also for short t½ drugs and i.v. administration in critically ill patients, e.g. lignocaine (t½ 1.5 hr) used for cardiac arrhythmias is given as an i.v. bolus dose followed by slow i.v. infusion or intermittent fractional dosing.

PROLONGATION OF DRUG ACTION

It is sometimes advantageous to modify a drug in such a way that it acts for a longer period. By doing so:

(i) Frequency of administration is reduced—more convenient.

(ii) Improved patient compliance—a single morning dose is less likely to be forgotten/omitted than a 6 or 8 hourly regimen.

(iii) Large fluctuations in plasma concentration are avoided—side effects related to high peak plasma level just after a dose would be minimized (e.g. nifedipine); better round-the-clock control of blood sugar, etc.

(iv) Drug effect could be maintained overnight without disturbing sleep, e.g. antiasthmatics, anticonvulsants, etc.

However, all drugs do not need to be made long acting, e.g. those used for brief therapeutic effect (sleep inducing hypnotic, headache remedy) or those with inherently long duration of action (digoxin, amlodipine, doxycycline, omeprazole). Drugs with t½ < 4 hr are suitable for controlled release formulations, while there is no need of such formulations for drugs with t½ >12 hr. Methods utilized for prolonging drug action are summarized below. Some of these have already been described.

1. By prolonging absorption from site of administration

(a) *Oral* Sustained release tablets, spansule capsules, etc.; drug particles are coated with resins, plastic materials or other substances which temporally disperse release of the active ingredient in the g.i.t. The controlled release tablet/capsule preparation utilizes a semipermeable membrane to control the release of drug from the dosage form. Such preparations prolong the action by 4 to 6 hours and no more because in that time drug particles reach the colon.

(b) *Parenteral* The s.c. and i.m. injection of drug in insoluble form (benzathine penicillin, lente insulin) or as oily solution (depot progestins); pellet implantation, sialistic and biodegradable implants can provide for its absorption over a couple of days to several months or even years. Inclusion of a vasoconstrictor with the drug also delays absorption (adrenaline with local anaesthetics).

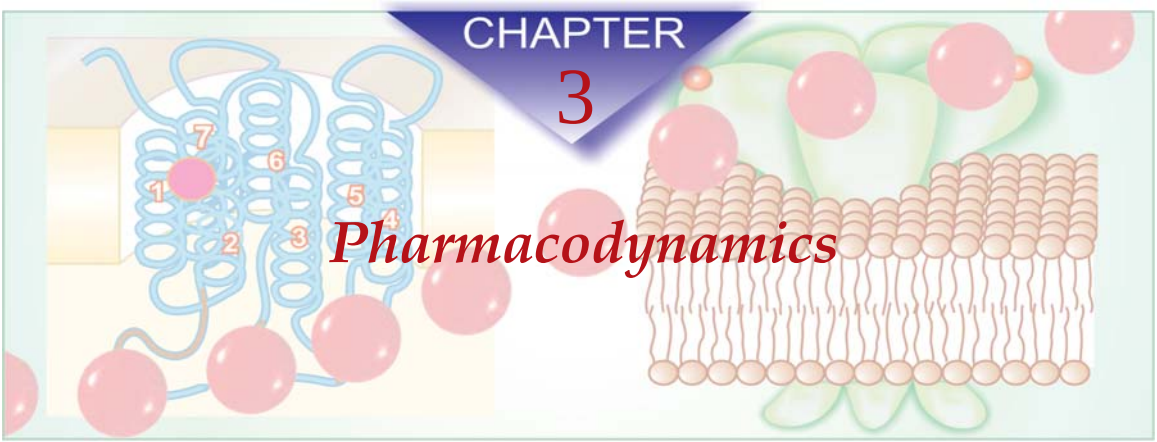
(c) *Transdermal drug delivery systems* The drug impregnated in adhesive patches, strips or as

ointment applied on skin is becoming popular, e.g. glyceryl trinitrate.

2. By increasing plasma protein binding
Drug congeners have been prepared which are highly bound to plasma protein and are slowly released in the free active form, e.g. sulfadoxine.

3. By retarding rate of metabolism Small chemical modification can markedly affect the rate of metabolism without affecting the biological action, e.g. addition of ethinyl group to estradiol makes it longer acting and suitable for use as oral contraceptive. Inhibition of specific enzyme by one drug can prolong the action of another drug, e.g. allopurinol inhibits degradation of 6-mercaptopurine; ritonavir boosts the action of indinavir, cilastatin protects imipenem from degradation in kidney.

4. By retarding renal excretion The tubular secretion of drug being an active process, can be suppressed by a competing substance, e.g. probenecid prolongs duration of action of penicillin and ampicillin.



CHAPTER 3

Pharmacodynamics

Pharmacodynamics is the study of drug effects. It attempts to elucidate the complete action-effect sequence and the dose-effect relationship. Modification of the effects of one drug by another drug and by other factors is also a part of pharmacodynamics.

PRINCIPLES OF DRUG ACTION

Drugs (except those gene based) do not impart new functions to any system, organ or cell; they only alter the pace of ongoing activity. The basic types of drug action can be broadly classed as:

1. Stimulation It refers to selective enhancement of the level of activity of specialized cells, e.g. adrenaline stimulates heart, pilocarpine stimulates salivary glands. However, excessive stimulation is often followed by depression of that function, e.g. high dose of picrotoxin, a central nervous system (CNS) stimulant, produces convulsions followed by coma and respiratory depression.

2. Depression It means selective diminution of activity of specialized cells, e.g. barbiturates depress CNS, quinidine depresses heart, local anaesthetics depress nerve conduction.

Certain drugs stimulate one type of cells but depress the other, e.g. acetylcholine stimulates intestinal smooth muscle but depresses SA node in heart. Thus, most drugs cannot be just classed as stimulants or depressants.

3. Irritation This connotes a nonselective, often noxious effect and is particularly applied to less specialized cells (epithelium, connective tissue). Mild irritation may stimulate associated function, but strong irritation results in inflammation, corrosion, necrosis and morphological damage. This may result in diminution or loss of function.

4. Replacement This refers to the use of natural metabolites, hormones or their congeners in deficiency states, e.g. levodopa in parkinsonism, insulin in diabetes mellitus, iron in anaemia.

5. Cytotoxic action Selective cytotoxic action for invading parasites or cancer cells, attenuating them without significantly affecting the host cells is utilized for cure/palliation of infections and neoplasms, e.g. penicillin, chloroquine, zidovudine, cyclophosphamide, etc.

MECHANISM OF DRUG ACTION

Only a handful of drugs act by virtue of their simple physical or chemical property; examples are:

- Bulk laxatives—physical mass
- Charcoal—adsorptive property
- Mannitol—osmotic activity
- ^{131}I and other radioisotopes—radioactivity
- Antacids—neutralization of gastric HCl
- Pot. permanganate—oxidizing property
- Dimercaprol—chelation of heavy metals.

Majority of drugs produce their effects by interacting with a discrete target biomolecule, which usually is a protein. This also confers selectivity of action to the drug. Functional proteins that are targets of drug action can be grouped into *four* basic categories, viz. enzymes, ion channels, carriers and receptors. However, a few drugs do act on other proteins (e.g. colchicine, vinca alkaloids, taxanes bind to the structural protein tubulin) or on nucleic acids (alkylating agents).

I. ENZYMES

Almost all biological reactions are carried out under catalytic influence of enzymes; hence, enzymes are a very important target of drug action. Drugs can either increase or decrease the rate of enzymatically mediated reactions. However, in physiological systems enzyme activities are often optimally set. Thus, stimulation of enzymes by drugs, that are truly foreign substances, is unusual. Enzyme stimulation is relevant to some natural metabolites only, e.g. pyridoxine acts as a cofactor and increases decarboxylase activity. Stimulation of an enzyme increases its affinity for the substrate so that rate constant (*kM*) of the reaction is lowered (Fig. 3.1).

Apparent increase in enzyme activity can also occur by *enzyme induction*, i.e. synthesis of more enzyme protein. This cannot be called stimulation because the *kM* does not change. Many drugs induce microsomal enzymes (*see* p. 22).

Inhibition of enzymes is a common mode of drug action.

A. Nonspecific inhibition Many chemicals and drugs are capable of denaturing proteins. They would alter the tertiary structure of any enzyme with which they come in contact and thus inhibit it. Heavy metal salts, strong acids and alkalies, alcohol, formaldehyde, phenol inhibit enzymes nonspecifically.

B. Specific inhibition Many drugs inhibit a particular enzyme without affecting others. Such inhibition is either competitive or noncompetitive.

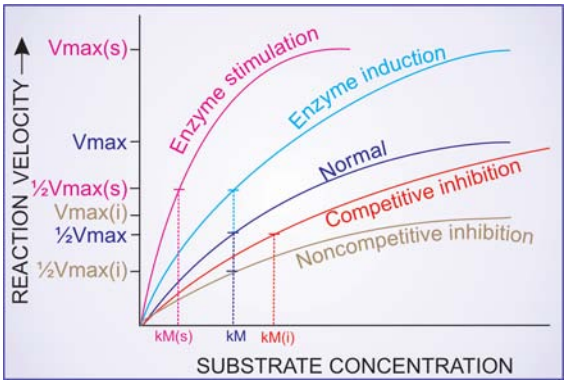


Fig. 3.1: Effect of enzyme induction, stimulation and inhibition on kinetics of the reaction
Vmax—Maximum velocity of reaction; *Vmax (s)* of stimulated enzyme; *Vmax (i)*—in presence of noncompetitive inhibitor; *kM*—rate constant of the reaction; *kM (s)*—of stimulated enzyme; *kM (i)*—in presence of competitive inhibitor
Note: Enzyme induction and noncompetitive inhibition do not change the affinity of the enzyme (*kM* is unaltered), whereas enzyme stimulation and competitive inhibition respectively decrease and increase the *kM*.

(i) Competitive *(equilibrium type)* The drug being structurally similar competes with the normal substrate for the catalytic binding site of the enzyme so that a new equilibrium is achieved in the presence of the drug. Such inhibitors increase the *kM* but the *Vmax* remains unchanged, i.e. higher concentration of the substrate is required to achieve ½ maximal reaction velocity, but if substrate concentration is sufficiently increased, it can displace the drug and the same maximal reaction velocity can be attained.

- Physostigmine and neostigmine compete with acetylcholine for cholinesterase.
- Sulfonamides compete with PABA for bacterial folate synthetase.
- Allopurinol competes with hypoxanthine for xanthine oxidase.
- Carbidopa and methyldopa compete with levodopa for dopa decarboxylase.

A *nonequilibrium type* of enzyme inhibition can also occur with drugs which react with the same catalytic site of the enzyme but either form strong covalent bonds or have such high affinity for the

enzyme that the normal substrate is not able to displace the inhibitor, e.g.

- Organophosphates react covalently with the esteretic site of the enzyme cholinesterase.
- Methotrexate has 50,000 times higher affinity for dihydrofolate reductase than the normal substrate DHFA.

In these situations, *kM* is increased and *Vmax* is reduced.

(ii) Noncompetitive The inhibitor reacts with an adjacent site and not with the catalytic site, but alters the enzyme in such a way that it loses its catalytic property. Thus, *kM* is unchanged but *Vmax* is reduced. Examples are:

Acetazolamide	—	Carbonic anhydrase
Aspirin, indomethacin	—	Cyclooxygenase
Disulfiram	—	Aldehyde dehydrogenase
Omeprazole	—	H^+ K^+ ATPase
Digoxin	—	Na^+ K^+ ATPase
Theophylline	—	Phosphodiesterase
Propylthiouracil	—	Peroxidase in thyroid
Lovastatin	—	HMG-CoA reductase

II. ION CHANNELS

Proteins which act as ion selective channels participate in transmembrane signaling and regulate intracellular ionic composition. This makes them a common target of drug action. Drugs can affect ion channels either through specific receptors (ligand gated ion channels, G-protein operated ion channels, *see* p. 37, 39 and 40), or by directly binding to the channel and affecting ion movement through it, e.g. local anaesthetics which physically obstruct voltage sensitive Na^+ channels (*See* Ch 25). In addition, certain drugs modulate opening and closing of the channel, e.g.:

- Nifedipine blocks L-type of voltage sensitive Ca^{2+} channel.
- Nicorandil opens ATP-sensitive K^+ channels.
- Sulfonylurea hypoglycaemics inhibit pancreatic ATP- sensitive K^+ channels.
- Amiloride inhibits renal epithelial Na^+ channels.

III. CARRIERS

Several substrates are translocated across membranes by binding to specific carriers which either facilitate diffusion in the direction of the concentration gradient or pump the metabolite/ion against the concentration gradient using metabolic energy. Many drugs produce their action by directly interacting with the carrier protein to inhibit the ongoing physiological transport of the metabolite/ion. Examples are:

- Imipramine blocks neuronal reuptake of noradrenaline and 5-HT.
- Reserpine blocks the granular reuptake of noradrenaline and 5-HT.
- Furosemide inhibits the Na^+-K^+-$2Cl^-$ cotransporter in the ascending limb of loop of Henle.
- Hydrochlorothiazide inhibits the Na^+-Cl^- symporter in the early distal tubule.
- Probenecid inhibits active transport of organic acids (uric acid, penicillin) in renal tubules.

IV. RECEPTORS

A large number of drugs act through specific macromolecular components of the cell which regulate critical functions like enzyme activity, permeability/transport processes, structural features, template function, etc.). These macromolecules or the sites on them which bind and interact with the drug are called 'receptors'.

Receptor It is defined as a macromolecule or binding site that serves to recognize and initiate the response to a signal molecule or drug, but itself has no other function. In this sense, effectors (enzymes, channels, carriers, etc.) which bind and interact directly with a drug are not referred to as receptors; e.g. xanthine oxidase is not called the receptor for allopurinol. Receptors are situated on the surface or inside the effector cell, and specific signal molecules combine with them to initiate the characteristic response.

Agonist It activates a receptor to produce an effect similar to that of the physiological signal molecule.

Inverse agonist It activates a receptor to produce an effect in the opposite direction to that of the well-recognized agonist.

Antagonist It prevents the action of an agonist on a receptor or the subsequent response but does not have any effect of its own.

Partial agonist It activates a receptor to produce submaximal effect but antagonizes the action of a full agonist.

Ligand (Latin: *ligare*—to bind) It is a molecule which attaches selectively to particular receptors or sites. The term only indicates affinity without regard to functional change: agonists and competitive antagonists are both ligands of the same receptor.

Basic evidences for drug action through receptors

(i) Many drugs exhibit structural specificity of action, i.e. specific chemical configuration is associated with a particular action, e.g. isopropyl substitution on the ethylamine side chain of sympathetic drugs produces compounds with marked cardiac and bronchial activity—most β adrenergic agonists and antagonists have this substitution.

Further, many drugs have shown stereospecificity in action, e.g. *levo* noradrenaline is 10 times more potent than *dextro* noradrenaline; *d*-propranolol is about 100 times less potent in blocking β receptors than the *l*-isomer, but both are equipotent local anaesthetics.

Thus, the cell must have some mechanism to recognize a particular chemical configuration and three-dimensional structure.

(ii) Competitive antagonism is seen between specific agonists and antagonists. Langley in 1878 was so impressed by the mutual antagonism among two alkaloids pilocarpine and atropine that he proposed that both reacted with the same 'receptive substance' on the cell.

(iii) It was calculated by Clark that adrenaline and acetylcholine produce their maximal effect on frog's heart by occupying only 1/6,000th of the cardiac cell surface—thus, special regions of reactivity to such drugs must be present on the cell.

Receptor occupation theory

After studying quantitative aspects of drug action, Clark (1937) propounded a theory of drug action based on occupation of receptors by specific drugs and that the pace of a cellular function can be altered by interaction of these receptors with drugs (small molecular ligands). He perceived the interaction between the two molecular species, *viz.* drug (*D*) and receptor (*R*) to be governed by the law of mass action, and the effect (*E*) to be a direct function of the drug-receptor complex (*DR*) formed:

$$D + R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} DR \longrightarrow E \qquad ...(1)$$

Accordingly, the cardinal postulates of this theory were:

1. The intensity of response is proportional to the fraction of receptors occupied by a drug, and maximal response occurs when all receptors are occupied.
2. Drugs exert an 'all or none' action on each receptor, i.e. either a receptor is fully activated or not at all, there is no partial activation.
3. A drug and its receptor have complementary structural features and stand in rigid 'lock and key' relationship.

This theory gave a fundamental concept, but the postulates were later found to be only partially correct and needed to be modified. Ariens and Stephenson in 1950s found that:

Agonists like adrenaline and histamine could still produce the maximal response when >99% receptors were occluded by a noncompetitive antagonist. Thus, all receptors need not be occupied for a maximal response; for full agonists there often was a large receptor reserve. In other words, a number of *spare receptors* are present.

In relation to action through receptors, they introduced the concept of:

Affinity: It is the ability of the drug to combine with the receptor.

Intrinsic activity (efficacy): It is the ability of the drug to activate (induce a conformational change in) the receptor consequent to receptor occupation.

Different drugs had different capacities to induce a response; consequently, they must occupy different fractions of the available receptors while inducing equal response. Accordingly, it should be possible to submaximally activate a receptor and 'all or none' action is not necessary.

They interposed a theoretical quantity (*S*) denoting strength of stimulus imparted to the cell by activation of the receptor:

$$D + R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} DR \rightsquigarrow S \longrightarrow E \qquad ...(2)$$

Depending on the agonist, DR could generate a stronger or weaker S, probably as a function of the conformational change brought about by the agonist in the receptor.

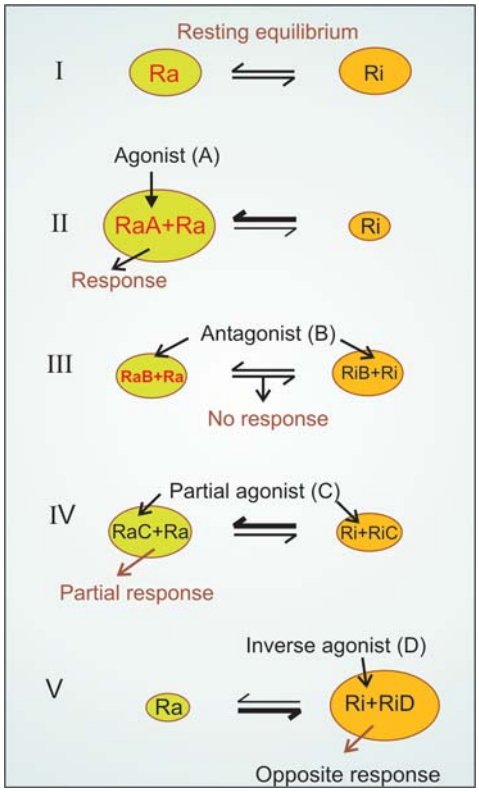
Partial agonists, because they submaximally stimulate a receptor, should be capable of bringing about intermediate degrees of conformational change in the receptor. Further, a drug could induce changes in the receptor which may make it either more or less favourably aligned to combine with the drug. Thus, a receptor cannot be considered to have rigid conformation.

The two properties of affinity and intrinsic activity (IA) are independently variable, i.e. drugs with the same affinity can possess different degrees of intrinsic activity and *vice versa*. Accordingly:

Agonists have both affinity and maximal intrinsic activity (IA = 1), e.g. adrenaline, histamine, morphine.

Competitive antagonists have affinity but no intrinsic activity (IA = 0), e.g. propranolol, atropine, chlorpheniramine, naloxone.

Partial agonists have affinity and submaximal intrinsic activity (IA between 0 and 1), e.g. dichloroisoproterenol, nalorphine.



Inverse agonists have affinity but intrinsic activity with a minus sign (IA between 0 and –1), e.g. DMCM.

The two-state receptor model

A very attractive alternative model for explaining the action of agonists, antagonists, partial agonists and inverse agonists has been proposed.

The receptor is believed to exist in two interchangeable states:

Ra (active) and *Ri* (inactive) which are in equilibrium such that no/low intensity signal is generated in the resting state (I). The agonist (A) binds preferentially to the *Ra* conformation and shifts the equilibrium → *Ra* predominates and a response is generated (II) depending on the concentration of A. The competitive antagonist (B) binds to *Ra* and *Ri* with equal affinity → the equilibrium is not altered → no response is

generated (III) but fewer *Ra* are available to bind the agonist. If an agonist has only slightly greater affinity for *Ra* than for *Ri*, the equilibrium is only modestly shifted towards *Ra* (IV) even at saturating concentrations → a submaximal response is produced and the drug is called a partial agonist. The inverse agonist (D) has high affinity for the *Ri* state (V), therefore, it can produce an opposite response, provided the resting equilibrium was in favour of the *Ra* state and the receptor was constitutively active, i.e. a certain level of activation existed even when no ligand was bound. Because only few receptors (benzodiazepine receptor, cannabinoid receptor and some others) are constitutively active, only a limited number of inverse agonists are known.

This model provides an explanation for the phenomenon of positive cooperativity often seen with neurotransmitters, and is supported by studies of conformational mutants of the receptor with altered equilibrium and constitutive activation.

Nature of receptors

Receptors are regulatory macromolecules, mostly proteins, though nucleic acids may also serve as receptors. They are no longer hypothetical. Hundreds of receptor proteins have been isolated, purified, cloned and their primary amino acid (AA) sequence has been worked out. Molecular cloning has also helped in obtaining the receptor protein in larger quantity to study its structure and properties, and in subclassifying receptors. The surface receptors with their coupling and effector proteins are considered to be floating in a sea of membrane lipids; the folding, orientation and topography of the system being determined by interactions between the lipophilic and hydrophilic domains of the peptide chains with solvent molecules (water on one side and lipids on the other). Nonpolar portions of the AA chain tend to bury within the membrane, while polar groups tend to come out in the aqueous medium. In such a delicately balanced system, it is not difficult to visualize that a small molecular ligand binding to one site in the receptor molecule could be capable of tripping the balance (by altering distribution of charges, etc.) and bringing about conformational changes at distant sites. Majority of receptor molecules are made up of several non-identical subunits (heteropolymeric), and agonist binding has been shown to bring about changes in their quaternary structure or relative alignment of the subunits, e.g. on activation the subunits of nicotinic receptor move apart opening a centrally located cation channel.

Radioligand binding studies have helped in characterizing and classifying receptors even when they have been dissociated from the effector system.

Many drugs act upon *physiological receptors* which mediate responses to transmitters, hormones, autacoids and other endogenous signal molecules; examples are cholinergic, adrenergic, histaminergic, steroid, leukotriene and other receptors. In addition, now some truly *drug receptors* have been described for which there are no known physiological ligands, e.g. benzodiazepine receptor, sulfonylurea receptor.

ACTION-EFFECT SEQUENCE

'Drug action' and 'drug effect' are often loosely used interchangeably, but are not synonymous.

Drug action It is the initial combination of the drug with its receptor resulting in a conformational change in the latter (in case of agonists), or prevention of conformational change through exclusion of the agonist (in case of antagonists).

Drug effect It is the ultimate change in biological function brought about as a consequence of drug action, through a series of intermediate steps (transducer).

Receptors subserve two essential functions, *viz*, *recognition* of the specific ligand molecule and *transduction* of the signal into a response. Accordingly, the receptor molecule has a *ligand binding domain* (spatially and energetically suitable for binding the specific ligand) and an *effector domain* (Fig. 3.2.) which undergoes a functional conformational change. These domains have now actually been identified in some receptors.

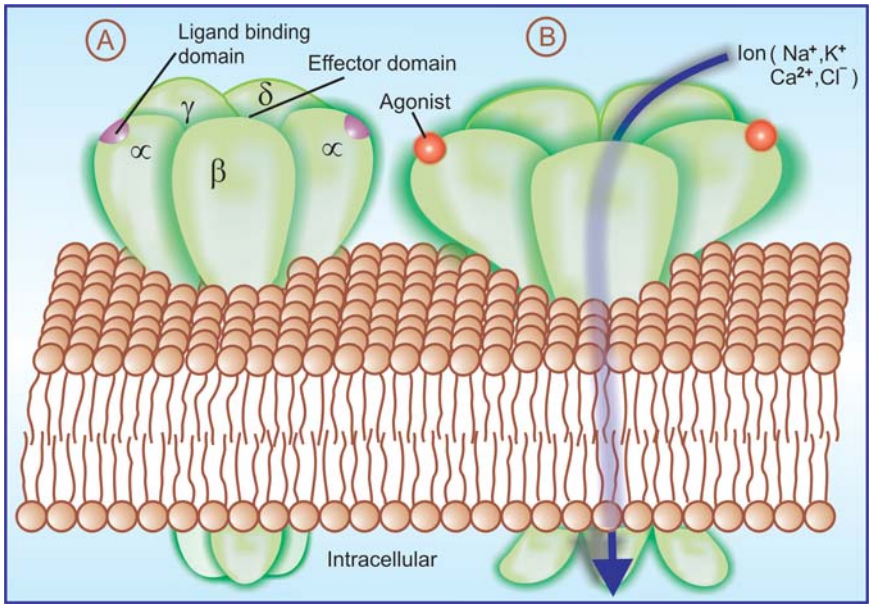


Fig. 3.2: Diagrammatic representation of direct receptor mediated operation of membrane ion channel.
In case of nicotinic cholinergic receptor, the molecule (8 nm in diameter) is composed of 5 subunits ($2\alpha + \beta + \gamma + \delta$) enclosing a cylindrical ion channel. Normally the channel is closed (A). When two molecules of acetylcholine bind to the two α subunits (B), all subunits move apart opening the central pore to 0.7 nm, enough to allow passage of partially hydrated Na^+ ions. Anions are blocked from passage through the channel by positive charges lining it.
In other cases, K^+, Ca^{2+} or Cl^- ions move through the channel depending on its ion selectivity.

The perturbation in the receptor molecule is variously translated into the response. The sequential relationship between drug action, transducer and drug effect can be seen in Fig. 3.4.

Transducer mechanisms

Considerable progress has been made in the understanding of transducer mechanisms which in most instances have been found to be highly complex multistep processes that provide for amplification and integration of concurrently received extra- and intracellular signals at each step. These mechanisms of translation of receptor activation into functional response can be grouped into *four* major categories. Receptors falling in one category have also been found to possess considerable structural homology, and may be considered to belong to one family of receptors.

1. G-protein coupled receptors These are a large family of cell membrane receptors which

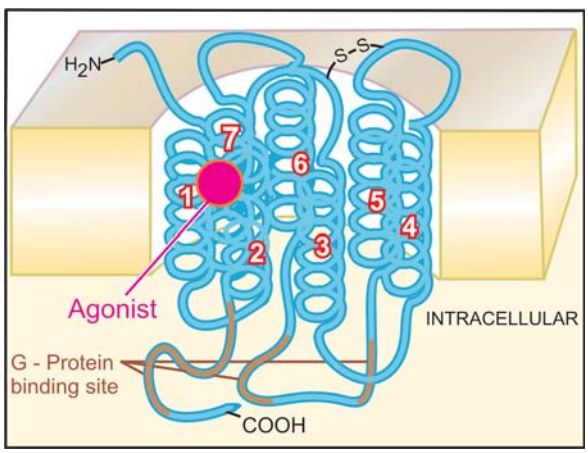


Fig. 3.3: Diagrammatic representation of G-protein coupled receptor molecule.
The receptor consists of 7 membrane spanning helical segments of hydrophobic amino acids. The intervening segments connecting the helices form 3 loops on either side of the membrane. The amino terminus of the chain lies on the extracellular face, while the carboxy terminus is on the cytosolic side. The approximate location of the agonist and G-protein-binding sites is indicated

are linked to the effector (enzyme/channel/carrier protein) through one or more GTP-activated proteins (G-proteins) for response effectuation. All such receptors have a common pattern of structural organization (Fig. 3.3). The molecule has 7 α-helical membrane spanning hydrophobic amino acid (AA) segments which run into 3 extracellular and 3 intracellular loops. The agonist-binding site is located somewhere between the helices on the extracellular face, while another recognition site formed by cytosolic segments binds the coupling G-protein. The G-proteins float in the membrane with their exposed domain lying in the cytosol, and are heterotrimeric in composition (α, β and γ subunits). In the inactive state GDP is bound to their exposed domain; activation through the receptor leads to displacement of GDP by GTP. The active α-subunit carrying GTP dissociates from the other two subunits and either activates or inhibits the effector. The βγ subunits have also been shown to modulate certain effectors like receptor operated K^+ channels, adenylyl cyclase and phospholipase C.

A number of G-proteins distinguished by their α subunits have been described. The important ones with their action on the effector are:

Gs : Adenylylcyclase ↑, Ca^{2+} channel ↑
Gi : Adenylylcyclase ↓, K^+ channel ↑
G_0 : Ca^{2+} channel ↓
Gq : Phospholipase C ↑
G_{13} : Na^+/H^+ exchange ↑

The α-subunit has GTPase activity: the bound GTP is slowly hydrolyzed to GDP: the α-subunit then dissociates from the effector to rejoin its other subunits, but not before the effector has been activated/inhibited for a few seconds and the signal has been amplified.

There are three major effector pathways (Table 3.1) through which G-protein coupled receptors function:

(a) *Adenylyl cyclase: cAMP pathway* Activation of AC results in intracellular accumulation of second messenger cAMP which functions almost exclusively through cAMP-dependent protein kinase (PK_A). The PK_A phosphorylates and alters the function of many enzymes, ion channels, carriers and structural proteins to manifest as increased contractility/impulse generation (heart, Fig. 3.4), relaxation (smooth muscle), glycogenolysis, lipolysis, inhibition of secretion/mediator release, modulation of junctional transmission, hormone synthesis, etc. The reverse occurs when AC is inhibited through inhibitory Gi-protein.

(b) *Phospholipase C: IP_3-DAG pathway* Activation of phospholipase C (PLc) hydrolyzes the membrane phospholipid phosphatidyl inositol 4, 5-bisphosphate (PIP_2) to generate the second messengers inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG), IP_3 mobilizes Ca^{2+} from intracellular organellar depots and DAG enhances protein kinase C (PKc) activation by Ca^{2+} (Fig. 3.5).

Table 3.1: Major functional pathways of G-protein coupled receptor transduction

Adenylylcyclase: cAMP		*Phospholipase IP_3-DAG*	*Channel regulation*		
↑	↓		Ca^{2+}↑	Ca^{2+}↓	K^+↑
Adrenergic-β	Adrenergic-α_2	Adrenergic-α_1	Adrenergic-β_1	Dopamine-D2	Adrenergic-α_2
Histamine-H_2	Muscarinic-M_2	Histamine-H_1	(Heart,	GABA-$_B$	Muscarinic-M_2
Dopamine-D1	Dopamine-D2	Muscarinic-M_1, M_3	Sk. muscle)	Opioid-κ	Dopamine-D2
Glucagon	5-HT_1	5-HT_2		Adenosine-A_1	5-HT_{1A}
FSH & LH	GABA-$_B$	Vasopressin-Oxytocin		Somatostatin	GABA-$_B$
ACTH	Opioid-μ, δ	Bradykinin-B_2			Opioid-μ, δ
TSH	Angiotensin	Angiotensin			Adenosine-A_1
Prostaglandin-EP_2	Prostaglandin-EP_3	Prostaglandin-FP, EP_1, EP_3			
Prostacyclin-IP	Somatostatin	Thromboxane-TP			
Adenosine-A_2	Adenosine-A_1	Leukotriene			
		Cholecystokinin-Gastrin			
		PAF			

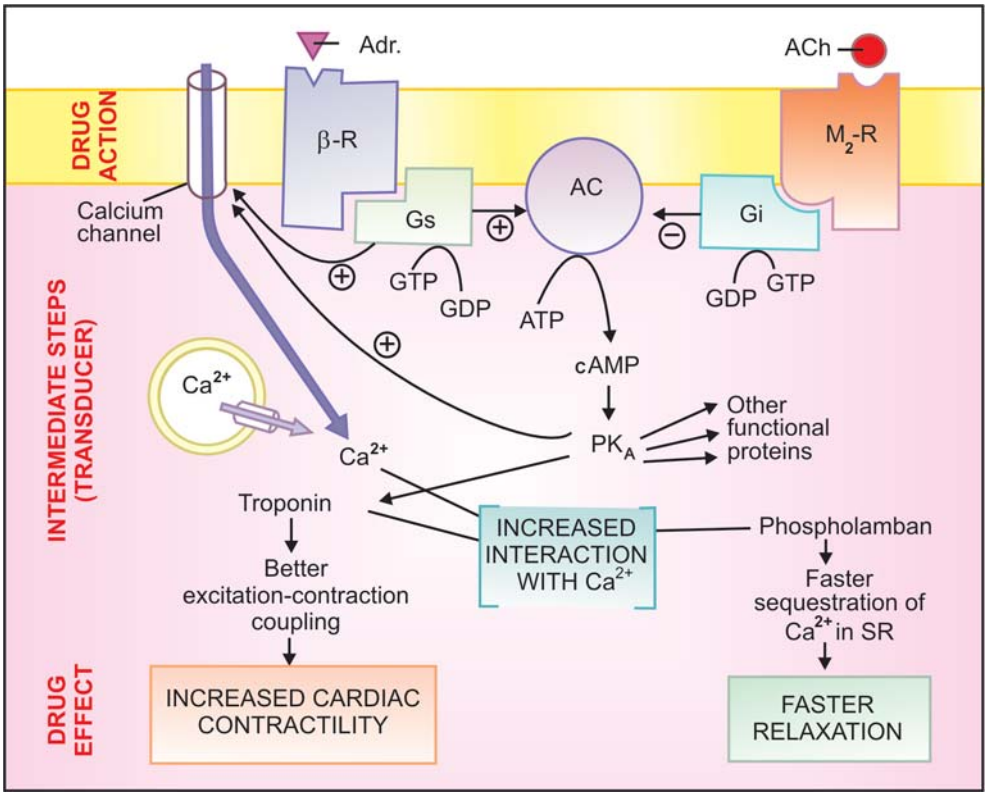


Fig. 3.4: The action-effect sequence of β adrenergic receptor activation in myocardial cell

Adrenaline (Adr) binds to β-adrenergic receptor (β-R) on the cell surface inducing a conformational change which permits interaction of the G-protein binding site with the stimulatory G-protein (Gs). The activated Gs now binds GTP (in place of GDP), causing its active subunit to dissociate and inturn activate the enzyme adenylyl cyclase (AC) located on the cytosolic side of the membrane: ATP is hydrolyzed to cAMP which phosphorylates and thus activates cAMP-dependent protein kinase (PK_A). The PK_A phosphorylates many functional proteins including troponin and phospholamban, so that they interact with Ca^{2+}, respectively resulting in increased force of contraction and faster relaxation. Calcium is made available by entry from outside (direct activation of myocardial membrane Ca^{2+} channels by Gs and through their phosphorylation by PK_A) as well as from intracellular stores.

One of the other proteins phosphorylated by cAMP is phosphorylase kinase which then activates the enzyme phosphorylase resulting in breakdown of glycogen to be utilized as energy source for increased contractility.

Action of acetylcholine (ACh) on muscarinic M_2 receptor (M_2–R), also located in the myocardial membrane, can similarly activate an inhibitory G-protein (Gi) which can oppose the activation of AC by Gs.

Cytosolic Ca^{2+} (third messenger in this setting) is a highly versatile regulator acting through calmodulin (CAM), PKc and other effectors—mediates/modulates contraction, secretion/transmitter release, neuronal excitability, intracellular movements, membrane function, metabolism, cell proliferation, etc. Like AC, the PLc can also be inhibited through inhibitory G-protein when directionally opposite responses would be expected.

(c) *Channel regulation* The activated G-proteins can also open or close ionic channels specific for Ca^{2+}, K^+ or Na^+ without the intervention of second messengers like cAMP or IP_3, and bring about hyperpolarization/depolarization/changes in

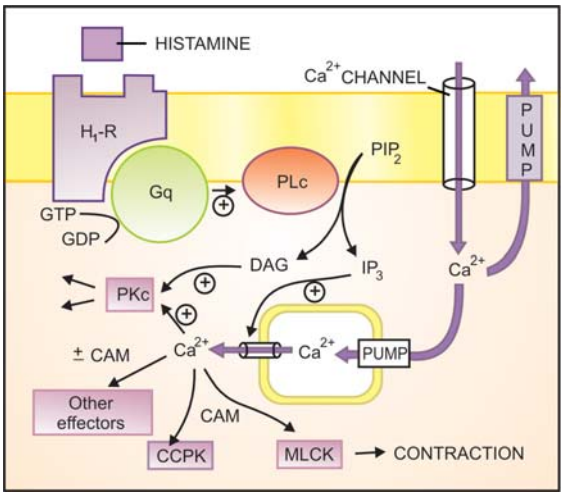


Fig. 3.5: The important steps of phospholipase C(PLc) pathway of response effectuation (in smooth muscle)

The agonist, e.g. histamine binds to its H_1 receptor (H_1 R) and activates the G-protein G_q, which in turn activates membrane bound phospholipase C (PLc) that hydrolyzes phosphatidyl inositol 4, 5-bisphosphate (PIP_2), a membrane bound phospholipid. The products inositol 1, 4, 5-trisphosphate (IP_3) and diacylglycerol (DAG) act as second messengers. The primary action of IP_3 is facilitation of Ca^{2+} mobilization from intracellular organellar pools, while DAG in conjunction with Ca^{2+} activates protein kinase C (PKc) which phosphorylates and alters the activity of a number of functional and structural proteins. Cytosolic Ca^{2+} is a veritable messenger: combines with calmodulin (CAM) to activate myosin light chain kinase (MLCK) inducing contraction, and another important regulator calcium-calmodulin protein kinase (CCPK). Several other effectors are regulated by Ca^{2+} in a CAM dependent or independent manner.

intracellular Ca^{2+}; e.g. Gs opens Ca^{2+} channels in myocardium and skeletal muscles, while Gi and G_o open K^+ channels in heart and smooth muscle as well as close neuronal Ca^{2+} channels. Physiological responses like changes in inotropy, chronotropy, transmitter release, neuronal activity and smooth muscle relaxation follow. Receptors found to regulate ionic channels through G-proteins are listed in Table 3.1.

2. Receptors with intrinsic ion channel These cell surface receptors enclose ion selective channels (for Na^+, K^+, Ca^{2+} or Cl^-) within their molecules. Agonist binding opens the channel (Fig. 3.2) and causes depolarization/hyperpolarization/changes in cytosolic ionic composition, depending on the ion that flows through. The nicotinic cholinergic, GABA-$_A$, glycine (inhibitory), excitatory AA (kainate, NMDA or N-methyl-D-aspartate, quisqualate) and 5-HT_3 receptors fall in this category.

The receptor is usually a pentameric protein; all subunits, in addition to large intra- and extracellular segments, generally have four membrane spanning domains in each of which the AA chain traverses the width of the membrane six times. The subunits are thought to be arranged round the channel like a rosette and the α subunits usually bear the agonist-binding sites.

Certain receptor operated ion channels also have secondary ligands which bind to an allosteric site and modulate the gating of the channel by the primary ligand, e.g. the benzodiazepine receptor modulates $GABA_A$ gated Cl^- channel.

Thus, in these receptors, agonists directly operate ion channels, without the intervention of any coupling protein or second messenger. The onset and offset of responses through this class of receptors is the fastest.

3. Enzyme-linked receptors This class of receptors are directly linked to or have a subunit with enzymatic property. The agonist-binding site and the catalytic site lie respectively on the outer and inner face of the plasma membrane (Fig. 3.6). These two domains are interconnected through a single transmembrane stretch of peptide chain,

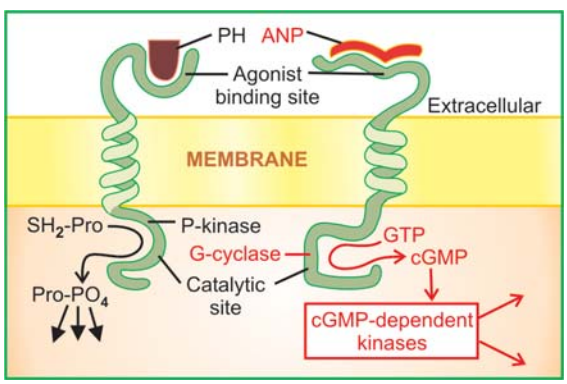


Fig. 3.6: Models of enzyme-linked receptors
PH—peptide hormone; P-kinase—protein kinase; SH_2-Pro—SH_2-domain protein; ANP—atrial natriuretic peptide; G-cyclase—guanylylcyclase; Pro-PO_4—phosphorylated protein

and this class of receptors can generate a response within minutes. Some peptide hormones and some cytokines utilize this class of receptors. The enzyme in most cases is a tyrosine protein kinase (in case of insulin, EGP or epidermal growth factor, certain interleukins) and the intracellular events are triggered by phosphorylation of relevant proteins which carry the -SH_2 domain. In addition, the receptor itself gets autophosphorylated on tyrosine residues which promotes association of several receptor molecules → organizing the complex signalling mechanisms. A common feature of this class of receptors is that their activation and association also promotes receptor internalization and downregulation. In some cases the enzyme is serine or threonine protein kinase.

The enzyme can also be guanylyl cyclase (GC), as in the case of atrial natriuretic peptide (ANP): agonist activation of the receptor generates cGMP as the second messenger in the cytosol which in turn activates cGMP-dependent protein kinase and modulates cellular activity.

4. Receptors regulating gene expression (Transcription factors) In contrast to the above 3 classes of receptors, these are intracellular (cytoplasmic or nuclear) soluble proteins which respond to lipid-soluble chemical messengers that penetrate the cell (Fig. 3.7). The receptor protein (specific for each hormone/regulator) is inherently capable of binding to specific genes, but is kept inhibited till the hormone binds near its carboxy terminus and exposes the DNA binding regulatory segment located in the middle of the molecule. Attachment of the receptor protein to the genes facilitates their expression so that specific mRNA is synthesized on the template of the gene. This mRNA moves to the ribosomes and directs synthesis of specific proteins which regulate the activity of target cells. All steroidal hormones (glucocorticoids, mineralocorticoids, androgens, estrogens, progesterone), thyroxine, vit D and vit A function in this manner. This transduction mechanism is the slowest in its time course of action.

Receptor regulation

Receptors exist in a dynamic state; their density and efficacy is subject to regulation by the level of ongoing activity and other physiopathological influences. In tonically active systems, prolonged deprivation of the agonist (by denervation or continued use of an antagonist or a drug which reduces input) results in supersensitivity of the receptor as well as the effector system to the agonist. This has clinical relevance in clonidine and CNS depressant/opioid withdrawal syndromes, sudden discontinuation of propranolol in angina pectoris, etc. The mechanisms involved may be unmasking of receptors or their proliferation (*upregulation*) or accentuation of signal amplification by the transducer.

Conversely, continued intense receptor stimulation causes desensitization or refractoriness: the receptor becomes less sensitive to the agonist. This can be easily demonstrated experimentally (Fig. 3.8); clinical examples are bronchial asthma patients treated continuously with β-adrenergic agonists and parkinsonian patients treated with high doses of levodopa. The changes may be brought about by:

(i) Masking or internalization of the receptor (it becomes inaccessible to the agonist). In this case refractoriness develops as well as fades quickly.

(ii) Decreased synthesis/increased destruction of the receptor (*downregulation*): refractoriness develops over weeks or months and recedes slowly. Receptor downregulation is particularly exhibited by the tyrosine protein kinase receptors.

Sometimes response to all agonists which act through different receptors but produce the same overt effect (e.g. histamine and acetylcholine both contract intestinal smooth muscle) is decreased by exposure to any one of these agonists (heterologous desensitization), showing that mechanisms of response effectuation have become less efficient. However, often desensitization is limited to agonists of the receptor being repeatedly activated (homologous desensitization).

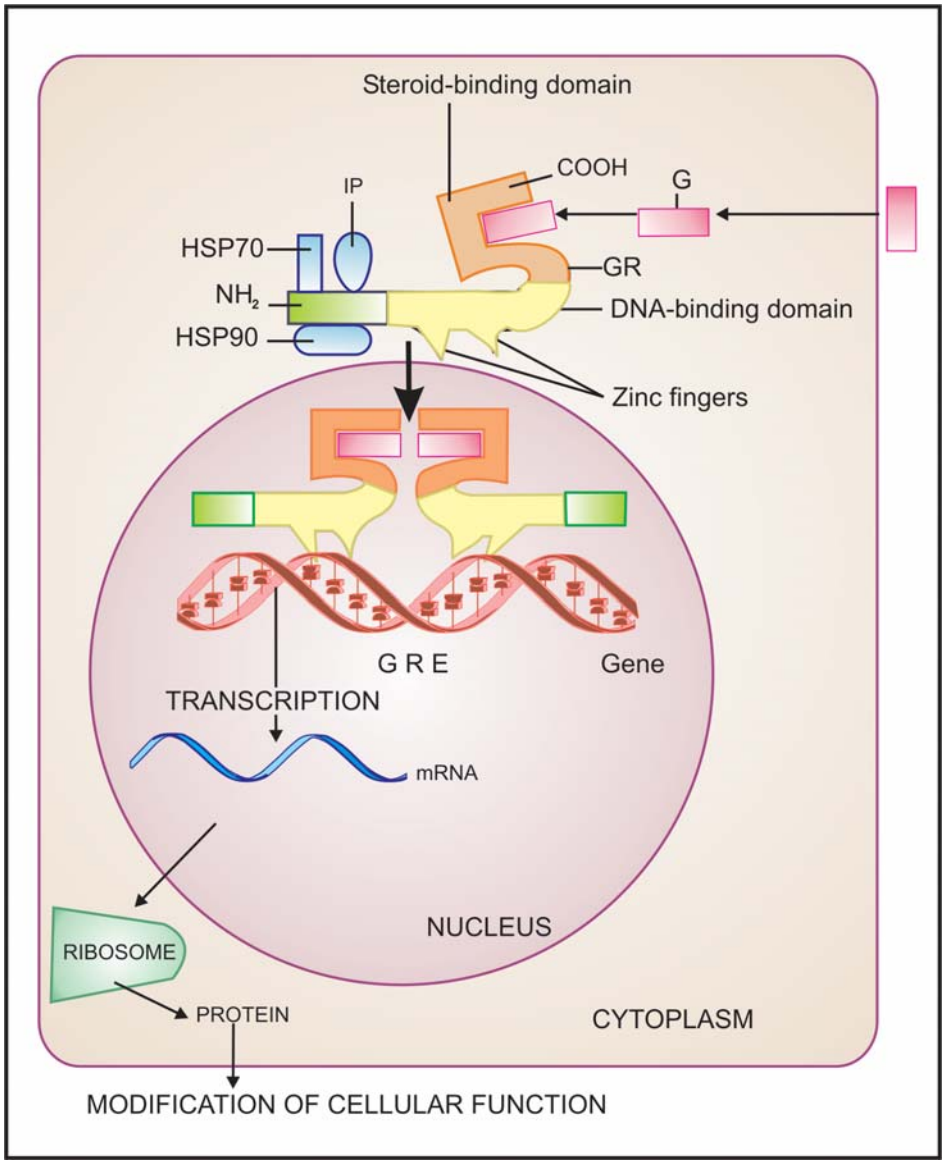


Fig. 3.7: Operational scheme of intracellular (glucocorticoid) receptor

The glucocorticoid (G) penetrates the cell membrane and binds to the glucocorticoid receptor (GR) protein that normally resides in the cytoplasm in association with 3 other proteins, *viz.* heat shock protein 90 (HSP90), HSP70 and immunophilin (IP). The GR has a steroid-binding domain near the carboxy terminus and a mid-region DNA-binding domain having two 'zinc fingers', each made up of a loop of amino acids with chelated zinc ion. Binding of the steroid to GR dissociates the complexed proteins (HSP90, etc.) removing their inhibitory influence on it. A dimerization region that overlaps the steroid-binding domain is exposed, promoting dimerization of the occupied receptor. The steroid bound receptor diamer translocates to the nucleus and interacts with specific DNA sequences called 'glucocorticoid responsive elements' (GREs) within the regulatory region of appropriate genes. The expression of these genes is consequently altered resulting in promotion (or suppression) of their transcription. The specific mRNA thus produced is directed to the ribosome where the message is translated into a specific pattern of protein synthesis, which in turn modifies cell function.

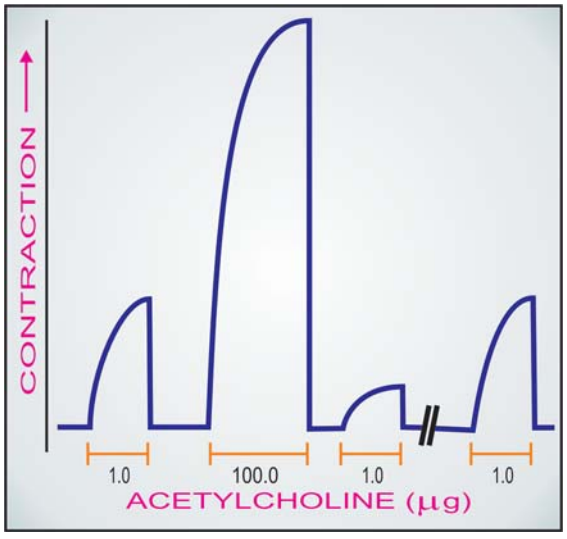


Fig. 3.8: Illustration of the phenomenon of desensitization

Contractile responses of frog's rectus abdominis muscle to acetylcholine. Note that shortly after exposure to a high (100-fold) dose of the agonist, the response is markedly attenuated, but is regained if sufficient time is allowed to elapse.

Functions of receptors These can be summarized as:

(a) To propagate regulatory signals from outside to within the effector cell when the molecular species carrying the signal cannot itself penetrate the cell membrane.

(b) To amplify the signal.

(c) To integrate various extracellular and intracellular regulatory signals.

(d) To adapt to short-term and long-term changes in the regulatory melieu and maintain homeostasis.

DOSE-RESPONSE RELATIONSHIP

When a drug is administered systemically, the dose-response relationship has two components: *dose-plasma concentration* relationship and *plasma concentration-response* relationship. The former is determined by pharmacokinetic considerations and ordinarily, descriptions of dose-response relationship refer to the latter, which can be more easily studied *in vitro*.

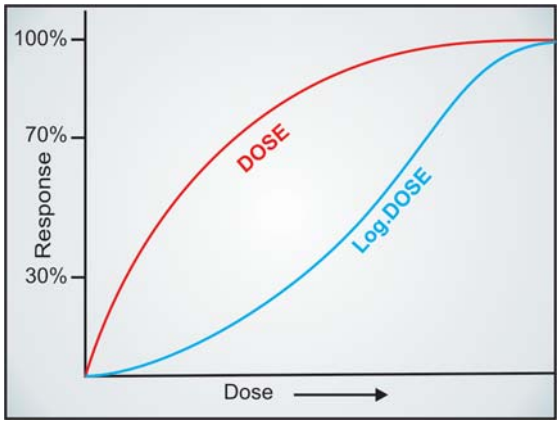


Fig. 3.9: Dose-response and log dose-response curves

Generally, the intensity of response increases with increase in dose (or more precisely concentration at the receptor) and the dose-response curve is a rectangular hyperbola (Fig. 3.9). This is because drug-receptor interaction obeys law of mass action, accordingly—

$$E = \frac{Emax \times [D]}{K_D + [D]} \quad ...(3)$$

where E is the observed effect at a dose [D] of the drug, E*max* is the maximal response, K_D is the dissociation constant of the drug-receptor complex, which is equal to the dose of drug at which half maximal response is produced. If the dose is plotted on a logarithmic scale, the curve becomes sigmoid and a linear relationship between log of dose and the response is seen in the intermediate (30-70% response) zone, as can be predicted from equation (3). This is not peculiar to drugs. In fact, all stimuli are graded biologically by the fractional change in stimulus intensity, e.g. 1 kg and 2 kg weights held in two hands can be easily differentiated, but not 10 kg and 11 kg weights; though the absolute difference remains 1 kg, there is a 100% fractional change in the former case but only 10% change in the latter case. In other words, response is proportional to an exponential function (log) of the dose.

The log dose-response curve (DRC) can be characterized by its shape (slope) and position.

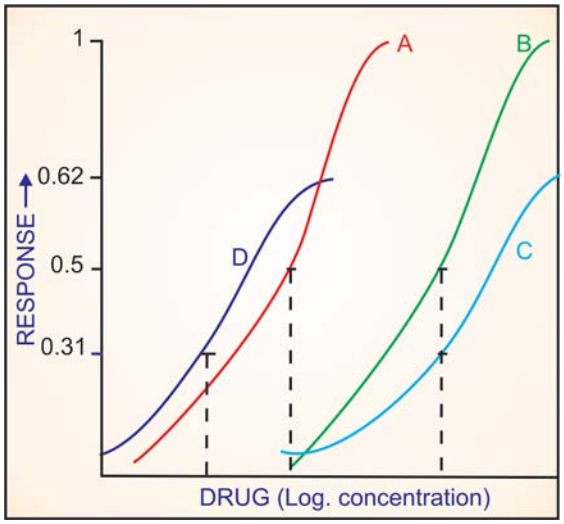


Fig. 3.10: Illustration of drug potency and drug efficacy. Dose-response curve of four drugs producing the same qualitative effect
Note:
Drug B is less potent but equally efficacious as drug A.
Drug C is less potent and less efficacious than drug A, but equally potent and less efficacious than drug B.
Drug D is more potent than drugs A, B, & C, but less efficacious than drugs A & B, and equally efficacious as drug C

Drug potency and efficacy

The position of DRC on the dose axis is the index of *drug potency* which refers to the amount of drug needed to produce a certain response. A DRC positioned rightward indicates lower potency (Fig. 3.10). Relative potency is often more meaningful than absolute potency, e.g. if 10 mg of morphine = 100 mg of pethidine, morphine is 10 times more potent than pethidine. However, a higher potency, in itself, does not confer clinical superiority unless the potency for therapeutic effect is selectively increased over potency for adverse effect.

The upper limit of DRC is the index of *drug efficacy* and refers to the maximal response that can be elicited by the drug, e.g. morphine produces a degree of analgesia not obtainable with any dose of aspirin—morphine is more efficacious than aspirin. Efficacy is a more decisive factor in the choice of a drug.

Often, the terms 'drug potency' and 'drug efficacy' are used interchangeably, but these are not synonymous and refer to different characteristics of the drug. The two can vary independently:

(a) Aspirin is less potent as well as less efficacious analgesic than morphine.
(b) Pethidine is less potent but equally efficacious analgesic as morphine.
(c) Furosemide is less potent but more efficacious diuretic than metolazone.
(d) Diazepam is more potent but less efficacious CNS depressant than pentobarbitone.

Depending on the type of drug, both higher efficacy (as in the case of furosemide) or lower efficacy (as in the case of diazepam) could be clinically advantageous.

The slope of the DRC is also important. A steep slope indicates that a moderate increase in dose will markedly increase the response (dose needs individualization), while a flat one implies that little increase in response will occur over a wide dose range (standard doses can be given to most patients). Hydralazine has a steep, while hydrochlorothiazide has a flat DRC of antihypertensive effect (Fig. 3.11).

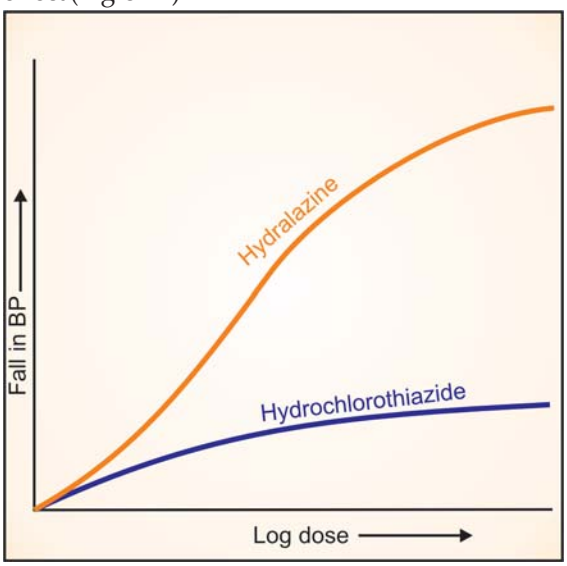


Fig. 3.11: Steep and flat dose-response curves, illustrated by antihypertensive effect of hydralazine and hydrochlorothiazide

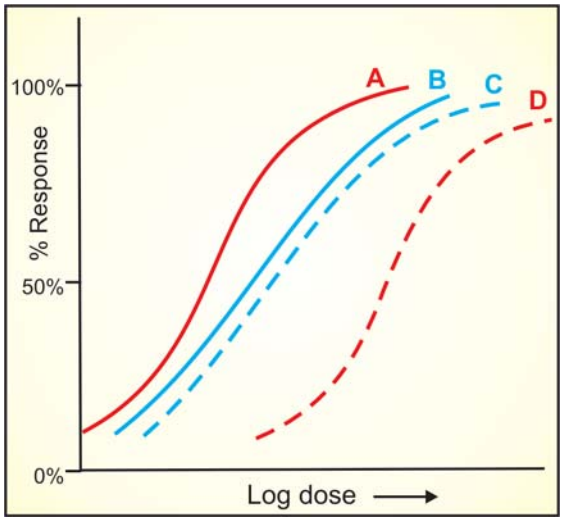


Fig. 3.12: Illustration of drug selectivity.
Log dose-response curves of salbutamol for bronchodilatation (A) and cardiac stimulation (D)
Log dose-response curves of isoprenaline for bronchodilatation (B) and cardiac stimulation (C)

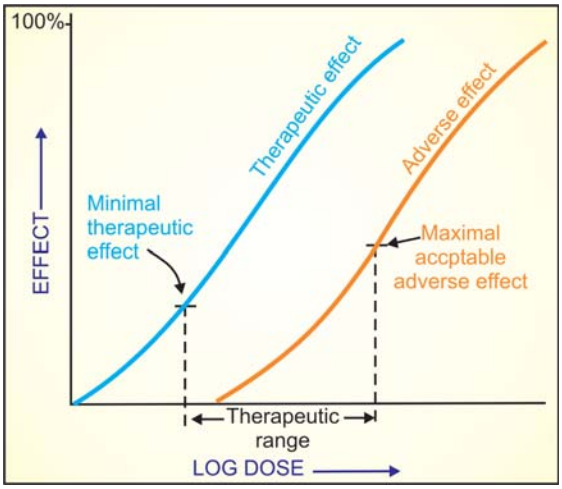


Fig. 3.13: Illustrative dose-response curves for therapeutic effect and adverse effect of the same drug

Selectivity Drugs seldom produce just one action: the DRCs for different effects of a drug may be different. The extent of separation of DRCs of a drug for different effects is a measure of its selectivity, e.g. the DRCs for bronchodilatation and cardiac stimulation (Fig. 3.12) are quite similar in case of isoprenaline but far apart in case of salbutamol—the latter is a more selective drug.

The gap between the therapeutic effect DRC and the adverse effect DRC defines the *safety margin* or the *therapeutic index* of a drug. In experimental animals, therapeutic index is often calculated as:

$$\text{Therapeutic index} = \frac{\text{median lethal dose}}{\text{median effective dose}}$$

$$\text{or} \quad \frac{LD_{50}}{ED_{50}}$$

But this is irrelevant in the clinical set up where the *therapeutic range* is bounded by the dose which produces minimal therapeutic effect and the dose which produces maximal acceptable adverse effect (Fig. 3.13). A drug may be capable of inducing a higher therapeutic response (have higher efficacy), but development of intolerable adverse effects may preclude use of higher doses, e.g. prednisolone in bronchial asthma.

Risk-benefit ratio This term is very frequently used, and conveys a judgement on the estimated harm (adverse effects, inconvenience) *vs* expected advantages (relief of symptoms, cure, reduction of complications/mortality, improvement in quality of life). A drug should be prescribed only when the benefits outweigh the risks. However, risk-benefit ratio can hardly ever be accurately measured for each instance of drug use. The physician has to rely on data from use of drugs in large populations (pharmacoepidemiology) and his own experience of the drug and the patient.

COMBINED EFFECT OF DRUGS

When two or more drugs are given simultaneously or in quick succession, they may be either indifferent to each other or exhibit *synergism* or *antagonism*. The interaction may take place at pharmacokinetic level (*see* Ch. 2) or at pharmacodynamic level.

SYNERGISM

(Greek: *Syn*—together; *ergon*—work)

When the action of one drug is facilitated or increased by the other, they are said to be synergistic. In a synergistic pair both the drugs can have action in the same direction or given alone one may be inactive but still enhance the action of the other when given together. Synergism can be:

(a) Additive The effect of the two drugs are in the same direction and simply add up:

effect of drugs A + B = effect of drug A + effect of drug B

Examples are—

Aspirin + paracetamol	:	as analgesic/ antipyretic
Nitrous oxide + ether	:	as general anaesthetic
Amlodipine + atenolol	:	as antihypertensive
Glibenclamide + metformin	:	as hypoglycaemic

Side effects of components of an additive pair may be different—do not add up—the combination is better tolerated than higher dose of one component.

(b) Supra-additive (potentiation) The effect of combination is greater than the individual effects of the components:

effect of drug A + B > effect of drug A + effect of drug B

This is always the case when one component is inactive as such. Examples are:

Acetylcholine + physostigmine	(inhibition of breakdown)
Levodopa + carbidopa/ benserazide	(inhibition of peripheral metabolism)
Adrenaline + cocaine/ desipramine	(inhibition of neuronal uptake)
Sulfamethoxazole + trimethoprim	(sequential blockade)
Enalapril + hydrochlorothiazide	(tackling two contributory factors)
Tyramine + MAO inhibitors	(increasing releasable CA store)

ANTAGONISM

When one drug decreases or abolishes the action of another, they are said to be antagonistic:

effect of drugs A + B < effect of drug A + effect of drug B.

Usually, in an antagonistic pair one drug is inactive as such but decreases the effect of the other. Depending on the mechanism involved, antagonism may be:

(a) Physical Based on the physical property of the drugs, e.g. charcoal adsorbs alkaloids and can prevent their absorption—used in alkaloidal poisonings.

(b) Chemical The two drugs react chemically and form an inactive product, e.g.

- $KMnO_4$ oxidizes alkaloids—used for gastric lavage in poisoning.
- Tannins + alkaloids—insoluble alkaloidal tannate is formed.
- Chelating agents (BAL, Cal. disod. edetate) complex metals (As, Pb).
- Nitrites form methaemoglobin which reacts with cyanide radical.

Drugs may react when mixed in the same syringe or infusion bottle:

- Thiopentone sod. + succinylcholine chloride
- Penicillin-G sod. + succinylcholine chloride
- Heparin + penicillin/tetracyclines/streptomycin/hydrocortisone

(c) Physiological / functional The two drugs act on different receptors or by different mechanisms, but have opposite overt effects on the same physiological function, i.e. have pharmacological effects in opposite direction, e.g.

Histamine and adrenaline on bronchial muscles and BP.

Hydrochlorothiazide and triamterene on urinary K^+ excretion.

Glucagon and insulin on blood sugar level.

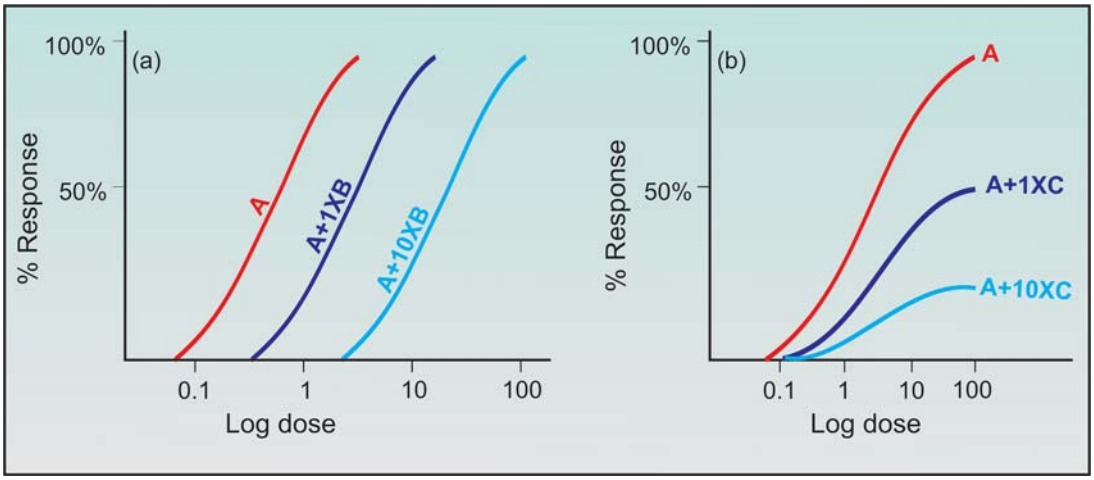


Fig. 3.14: Dose-response curves showing competitive (a) and noncompetitive (b) antagonism
A—agonist, B—competitive antagonist, C—noncompetitive antagonist

	Competitive (equilibrium type)	*Noncompetitive*
1.	Antagonist binds with the same receptor as the agonist.	Binds to another site of receptor
2.	Antagonist resembles chemically with the agonist	Does not resemble
3.	Parallel rightward shift of agonist DRC	Flattening of agonist DRC
4.	The same maximal response can be attained by increasing dose of agonist (surmountable antagonism)	Maximal response is suppressed (unsurmountable antagonism)
5.	The antagonist apparently reduces affinity (potency) of the agonist or appears to have inactivated a certain number of agonist molecules	The antagonist apparently reduces intrinsic activity (efficacy) of the agonist or appears to have inactivated a certain number of receptors
6.	Intensity of response depends on concentration of both agonist and antagonist	Response depends only on the concentration of antagonist
7.	Examples: ACh—Atropine Morphine—Naloxone	Diazepam—Bicuculline

(d) Receptor The antagonist interferes with binding of the agonist with its receptor or inhibits the generation of response consequent to such binding. Receptor antagonism is specific, e.g. an anticholinergic will decrease the spasm of intestine induced by cholinergic agonists but not by histamine or 5-HT which act through different set of receptors. Such antagonism may be competitive (equilibrium and nonequilibrium types) or noncompetitive (Fig. 3.14). Features of competitive and noncompetitive antagonism are compared above.

Nonequilibrium antagonism If the antagonist binds to the receptor with strong (covalent) bonds, it would irreversibly block the receptor. The law

of mass action cannot apply in this situation and the antagonist will shift the DRC to the right as well as suppress the maxima if spare receptors are few. Thus, though the antagonist combines with the same site as the agonist, antagonism has some characteristics of the noncompetitive type as well, e.g. adrenaline and phenoxybenzamine.

DRUG DOSAGE

'Dose' is the appropriate amount of a drug needed to produce a certain degree of response in a patient. Accordingly, dose of a drug has to be qualified in terms of the chosen response, e.g. the analgesic dose of aspirin for headache is 0.3–0.6 g, its antiplatelet dose is 75–150 mg/day, while its anti-inflammatory dose for rheumatoid arthritis is 3–5 g per day. Similarly, there could be *prophylactic dose*, a *therapeutic dose* or a *toxic dose* of the same drug.

The dose of a drug is governed by its inherent potency, i.e. the concentration at which it should be present at the target site, and its pharmacokinetic characteristics. In addition, it is modified by a number of factors (*see* below). However, different strategies are adopted for individualizing drug dosage.

1. Standard dose The same dose is appropriate for most patients—individual variations are minor or the drug has a wide safety margin so that enough can be given to cover them, e.g. oral contraceptives, penicillin, chloroquine, mebendazole, amantadine.

2. Regulated dose The drug modifies a finely regulated body function which can be easily measured. The dosage is accurately adjusted by repeated measurement of the affected physiological parameter, e.g. antihypertensives, hypoglycaemics, anticoagulants, diuretics, general anaesthetics.

3. Target level dose (*see* p. 28) The response is not easily measurable but has been demonstrated to be obtained at a certain range of drug concentration in plasma. An empirical dose aimed at attaining the target level is given in the beginning and adjustments are made later by actual monitoring of plasma concentrations. When facilities for drug level monitoring are not available, crude adjustments are made by observing the patient at relatively long intervals, e.g. antidepressants, antiepileptics, digoxin, lithium, theophylline.

4. Titrated dose The dose needed to produce maximal therapeutic effect cannot be given because of intolerable adverse effects. Optimal dose is arrived at by titrating it with an acceptable level of adverse effect. Low initial dose and upward titration (in most non-critical situations) or high initial dose and downward titration (in critical situations) can be practised. Often, a compromise between submaximal therapeutic effect but tolerable side effects can be struck, e.g. anticancer drugs, corticosteroids, levodopa.

Fixed dose ratio combination preparations

A large number of pharmaceutical preparations contain two or more drugs in a fixed dose ratio. *Advantages* offered by these are:

1. Convenience and better patient compliance—when all the components present in a formulation are actually needed by the patient.
2. Certain drug combinations are synergistic, e.g. sulfamethoxazole + trimethoprim; levodopa + carbidopa/benserazide; combination oral contraceptives.
3. The therapeutic effect of two components being same may add up while the side effects being different may not.
4. The side effect of one component may be counteracted by the other, e.g. a thiazide + a potassium sparing diuretic.

Before prescribing a combination, the physician must consider whether any of the ingredients is unnecessary; if it is, the combination should not be prescribed. It can never be justified that a drug is given to a patient who does not need it in order to provide him another one that he needs.

There are many inbuilt *disadvantages* of fixed dose ratio combinations:

1. The patient may not actually need all the drugs present in a combination: he is subjected to additional side effects and expense (often due to ignorance of the physician about the exact composition of the combined formulations).
2. The dose of most drugs needs to be adjusted and individualized. When a combined formulation is used, this cannot be done without altering the dose of the other component(s).
3. The time course of action of the components may be different.
4. Altered renal or hepatic function of the patient may differently affect the pharmacokinetics of the components.
5. Adverse effect, when it occurs, cannot be easily ascribed to the particular drug causing it.
6. Contraindication to one component (allergy, other conditions) contraindicates the whole preparation.
7. Confusion of therapeutic aims and false sense of superiority of two drugs over one is fostered, especially in case of antimicrobials whose combinations should be avoided. Corticosteroids should never be combined with any other drug meant for internal use.

Thus, only a handful of fixed dose ratio combinations are rational and justified, while far too many are available and vigorously promoted.

FACTORS MODIFYING DRUG ACTION

Variation in response to the same dose of a drug between different patients and even in the same patient on different occasions is a rule rather than exception. One or more of the following categories of differences among individuals are responsible for the variations in drug response:

(1) Individuals differ in pharmacokinetic handling of drugs: attain varying plasma/target site concentration of the drug. This is more marked for drugs disposed by metabolism (e.g. propranolol) than for drugs excreted unchanged (e.g. atenolol).

(2) Variations in number or state of receptors, coupling proteins or other components of response effectuation.

(3) Variations in neurogenic/hormonal tone or concentrations of specific constituents, e.g. atropine tachycardia depends on vagal tone, propranolol bradycardia depends on sympathetic tone, captopril hypotension depends on body Na^+ status.

A multitude of host and environmental factors influence drug response. Though individual variation cannot be totally accounted for by these factors, their understanding can guide choice of appropriate drug and dose for an individual patient. However, final adjustments have to be made by observing the response in a given patient on a given occasion.

These factors modify drug action either:

(a) *Quantitatively* The plasma concentration and/or the action of the drug is increased or decreased. Most of the factors introduce this type of change and can be dealt with by adjustment of drug dosage.

(b) *Qualitatively* The type of response is altered, e.g. drug allergy or idiosyncrasy. This is less common but often precludes further use of that drug in the affected patient.

The various factors are discussed below—

1. Body size It influences the concentration of the drug attained at the site of action. The average adult dose refers to individuals of medium built. For exceptionally obese or lean individuals and for children dose may be calculated on body weight (BW) basis:

$$\text{Individual dose} = \frac{\text{BW (kg)}}{70} \times \text{average adult dose}$$

In the case of few drugs, doses are calculated more precisely on the basis of body surface area (BSA).

2. Age The dose of a drug for children is often calculated from the adult dose

$$\text{Child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose} \quad \text{... (Young's formula)}$$

Age	Ideal BW (kg)	% of Adult dose
6 months	7.5	22
1 year	10	25
3 years	14	33
5 years	18	40
7 years	23	50
12 years	37	75

$$\text{Child dose} = \frac{\text{Age}}{20} \times \text{adult dose}$$ ...(Dilling's formula)

It can also be calculated (more accurately) on BW basis, and for many drugs, manufacturers give dosage recommendations on mg/kg basis. Average figures for children are given in the box.

However, *infants and children* are not small adults. They have important physiological differences from adults.

Children are growing and are susceptible to special adverse effects of drugs, e.g. suppression of growth can occur with corticosteroids; tetracyclines get deposited in growing teeth and discolour/deform them. Dystonic reactions to phenothiazines are more common in children.

Elderly In the elderly, renal function progressively declines (intact nephron loss) and drug doses have to be reduced, e.g. daily dose of streptomycin is 0.75 g after 50 years and 0.5 g after 70 years of age compared to 1 g for young adults. There is also a reduction in the hepatic microsomal drug metabolizing activity and liver blood flow: oral bioavailability of drugs with high hepatic extraction is generally increased, but the overall effects on drug metabolism are not uniform. Other affected aspects of drug handling are slower absorption due to reduced motility of and blood flow to intestines, lesser plasma protein binding due to lower plasma albumin, increased or decreased volume of distribution of lipophilic and hydrophilic drugs respectively. The responsiveness of β adrenergic receptors to both agonists and antagonists is reduced in the elderly and sensitivity to other drugs also may be altered. Due to prostatism in elderly males, even mild anticholinergic activity of the drug can accentuate bladder voiding difficulty. Elderly are also likely to be on multiple drug therapy for hypertension, ischaemic heart disease, diabetes, arthritis, etc. which increases many fold the chances of drug interactions. They are more prone to develop postural instability (e.g. on standing from dental chair), giddiness and mental confusion. In general, the incidence of adverse drug reactions is much higher in the elderly.

3. Sex Females have smaller body size and require doses that are on the lower side of the range. Subjective effects of drugs may differ in females because of their mental makeup. A number of antihypertensives (clonidine, methyldopa, β-blockers, diuretics) interfere with sexual function in males but not in females. Gynaecomastia is a side effect (of ketoconazole, metoclopramide, chlorpromazine, digitalis) that can occur only in men. Ketoconazole causes loss of libido in men but not in women. Obviously, androgens are unacceptable to women and estrogens to men. In women consideration must also be given to menstruation, pregnancy and lactation.

Drugs given during *pregnancy* can affect the foetus (*see* Ch. 4). There are marked physiological changes during pregnancy, especially in the third trimester, which can alter drug disposition.

(i) Gastrointestinal motility is reduced → delayed absorption of orally administered drug.
(ii) Plasma and extracellular fluid volume expands—volume of drug distribution may increase.
(iii) While plasma albumin level falls, that of α_1 acid glycoprotein increases—the unbound fraction of acidic drugs increases but that of basic drugs decreases.
(iv) Renal blood flow increases markedly—polar drugs are eliminated faster.
(v) Hepatic microsomal enzymes undergo induction—many drugs are metabolized faster.

Thus, the overall effect on drug disposition is complex and often difficult to predict.

4. Species and race There are many examples of differences in responsiveness to drugs among different species.

Among human beings some racial differences have been observed, e.g. blacks require higher and mongols require lower concentrations of atropine and ephedrine to dilate their pupil. β-blockers are less effective as antihypertensive in blacks. Indians tolerate thiacetazone better than whites. Considering the widespread use of chloramphenicol in India and Hong Kong, relatively few cases of aplastic anaemia have been reported compared to its incidence in the west. Similarly, quiniodochlor related cases of subacute myelooptic neuropathy (SMON) occurred in epidemic proportion in Japan, but there is no confirmed report of its occurrence in India despite extensive use.

5. Genetics The dose of a drug to produce the same effect may vary by 4 to 6-fold among different individuals. This is mainly because of differing rates of drug metabolism, because the amount and isoform pattern of drug metabolizing enzymes is genetically controlled. There are also differences in target organ sensitivity. A continuous variation with Gaussian frequency distribution is seen in the case of most drugs. However, there are some specific genetic defects which lead to discontinuous variation in drug responses, e.g.

(i) Atypical pseudocholinesterase—prolonged succinylcholine apnoea.
(ii) G-6-PD deficiency—haemolysis with primaquine and other oxidizing drugs like sulfonamides, dapsone, quinine, nalidixic acid, nitrofurantoin and menadione, etc.
(iii) Acetylator polymorphism—isoniazid neuropathy, procainamide and hydralazine induced lupus in slow acetylators.
(iv) CYP2D6 abnormality causes poor metoprolol/debrisoquin metabolizer status.
(v) Precipitation of an attack of angle closure glaucoma by mydriatics in individuals with narrow iridocorneal angle.

6. Route of administration Route of administration governs the speed and intensity of drug response (*see* Ch. 1). Parenteral administration is often resorted to for more rapid, more pronounced and more predictable drug action.

7. Environmental factors and time of administration Several environmental factors affect drug responses. Exposure to insecticides, carcinogens, tobacco smoke and consumption of charcoal broiled meat are well known to induce drug metabolism. Type of diet and temporal relation between drug ingestion and meals can alter drug absorption. Subjective effect of a drug may be markedly affected by the setup in which it is taken. Hypnotics taken at night and in quiet, familiar surroundings may work more easily. It has been shown that corticosteroids taken as a single morning dose cause less pituitary-adrenal suppression. Local anaesthetics have been found to produce more prolonged dental anaesthesia when injected in the afternoon than in the morning.

8. Psychological factor Efficacy of a drug can be affected by patient's beliefs, attitudes and expectations. This is particularly applicable to centrally acting drugs, e.g. a nervous and anxious patient requires more general anaesthetic; alcohol generally impairs performance but if punishment (which induces anxiety) is introduced, it may actually improve performance.

Placebo This is an inert substance which is given in the garb of a medicine. It works by psychological rather than pharmacological means and often produces responses equivalent to the active drug. Some individuals are more suggestible and easily respond to a placebo—'placebo reactors'. Placebos are used in two situations:

1. As a control device in clinical trial of drugs (dummy medication).
2. To treat a patient who, in the opinion of the physician, does not require an active drug.

Placebo is a Latin word meaning 'I shall please'. A patient responds to the whole therapeutic setting; placebo-effect largely depends on the physician-patient relationship.

Placebos do induce physiological responses, e.g. they can release endorphins in brain—causing analgesia. Naloxone, an opioid antagonist, blocks placebo analgesia. Placebo effects can thus supplement pharmacological effects. However, placebo effects are highly variable even in the same individual, e.g. a placebo may induce sleep on the first night but not subsequently. Thus, it has a very limited role in practical therapeutics. Substances commonly used as placebo are lactose tablets/capsules and distilled water injection.

9. Pathological states Not only drugs modify disease processes, several diseases can influence drug disposition and drug action:

Gastrointestinal diseases These can alter absorption of orally administered drugs. The changes are complex and drug absorption may increase or decrease, e.g. in coeliac disease absorption of amoxicillin is decreased but that of cephalexin and cotrimoxazole is increased. Thus, malabsorption syndrome does not necessarily reduce absorption of all drugs. Achlorhydria decreases aspirin absorption by favouring its ionization. Nonsteroidal antiinflammatory drugs can aggravate peptic ulcer disease.

Liver disease Liver disease (especially cirrhosis) can influence drug disposition in several ways:

(i) Bioavailability of drugs having high first pass metabolism (*see* Ch. 2) is increased due to loss of hepatocellular function and portocaval shunting.

(ii) Serum albumin is reduced—protein binding of acidic drugs (diclofenac, warfarin , etc.) is reduced and more drug is present in the free form.

(iii) Metabolism and elimination of some drugs (morphine, lignocaine, propranolol) is decreased: their dose should be reduced. Alternative drugs that do not depend on hepatic metabolism for elimination and/or have shorter t½ should be preferred, e.g. oxazepam or lorazepam in place of diazepam; atenolol as β-blocker.

(iv) Prodrugs needing hepatic metabolism for activation, e.g. prednisone, bacampicillin, are less effective and should be avoided.

The changes are complex and there is no simple test (like creatinine clearance for renal disease) to guide the extent of alteration in drug disposition; kinetics of different drugs is affected to different extents.

The action of certain drugs can also be altered in liver disease, e.g.

- The sensitivity of brain to depressant action of morphine and barbiturates is markedly increased in cirrhotics—normal doses can produce coma.
- Brisk diuresis can precipitate mental changes in patients with impending hepatic encephalopathy because diuretics cause hypokalemic alkalosis which favours conversion of NH_4^+ to $NH_3 \rightarrow$ enters brain more easily.
- Oral anticoagulants can markedly increase prothrombin time because clotting factors are already low.
- Lactic acidosis due to metformin is accentuated.

Hepatotoxic drugs should be avoided in liver disease.

Kidney disease It markedly affects pharmacokinetics of many drugs as well as alters the effects of some drugs.

Clearance of drugs that are primarily excreted unchanged (aminoglycosides, digoxin, phenobarbitone) is reduced parallel to decrease in creatinine clearance (CL_{cr}). Loading dose of such a drug is not altered (unless edema is present), but maintenance doses should be reduced or dose interval prolonged proportionately. A rough guideline is given in the box:

CL_{cr} (patient)	Dose rate to be reduced to
50–70 ml/min	70%
30–50 ml/min	50%
10–30 ml/min	30%
5–10 ml/min	20%

Dose rate of drugs only partly excreted unchanged in urine also needs reduction, but to lesser extents. If the t½ of the drug is prolonged, attainment of steady-state plasma concentration with maintenance doses is delayed proportionately.

Plasma proteins, especially albumin, are often low or altered in structure in patients with renal disease—binding of acidic drugs is reduced but that of basic drugs is not much affected.

The permeability of blood-brain barrier is increased in renal failure; opiates, barbiturates, phenothiazines, benzodiazepines, etc. produce more CNS depression. Pethidine should be avoided because its metabolite norpethidine can accumulate on repeated dosing and cause seizures. The target organ sensitivity may also be increased. Antihypertensive drugs produce more postural hypotension in patients with renal insufficiency.

Certain drugs worsen the existing clinical condition in renal failure, e.g. tetracyclines have an antianabolic effect and accentuate uraemia; nonsteroidal antiinflammatory drugs cause more fluid retention; potentially nephrotoxic drugs, e.g. cephalothin, aminoglycosides, tetracyclines (except doxycycline), sulfonamides (crystalluria), cyclosporine, vancomycin should be avoided.

Antimicrobials needing dose reduction in renal failure

Even in mild failure	*Only in severe failure*
Aminoglycosides	Cotrimoxazole
Cephalexin	Carbenicillin
Ethambutol	Cefotaxime
Vancomycin	Norfloxacin
Amphotericin B	Ciprofloxacin
Acyclovir	Metronidazole

Thiazide diuretics tend to reduce g.f.r.: are ineffective in renal failure and can worsen uraemia. Potassium-sparing diuretics are contraindicated; can cause hyperkalaemia → cardiac depression. Phenformin is more prone to induce lactic acidosis in patients with kidney disease.

Congestive heart failure It can alter drug kinetics by—

(i) Decreasing drug absorption from g.i.t. due to mucosal edema and splanchnic vasoconstriction.

(ii) Modifying volume of distribution which can increase for some drugs due to expansion of extracellular fluid volume or decrease for others as a result of decreased tissue perfusion.

(iii) Retarding drug elimination as a result of decreased perfusion and congestion of liver, reduced glomerular filtration rate and increased tubular reabsorption; dosing rate of drugs may need reduction.

(iv) The decompensated heart is more sensitive to digitalis.

Thyroid disease The hypothyroid patients are more sensitive to digoxin, morphine and other CNS depressants. Hyperthyroid patients are relatively resistant to inotropic action but more prone to arrhythmic action of digoxin. The clearance of digoxin is roughly proportional to thyroid function, but this only partially accounts for the observed changes in sensitivity.

Other examples of modification of drug response by pathological states are:

- Antipyretics lower body temperature only when it is raised (fever).
- Thiazides induce more marked diuresis in edematous patients.
- Myocardial infarction patients are more prone to adrenaline and digitalis induced cardiac arrhythmias.
- Myasthenics are very sensitive to curare.
- Schizophrenics tolerate large doses of phenothiazines.
- Head injury patients are prone to go into respiratory failure with normal doses of morphine.
- Atropine, imipramine, furosemide can cause urinary retention in individuals with prostatic hypertrophy.

- Hypnotics given to a patient in severe pain may cause mental confusion and delirium.
- Cotrimoxazole produces a much higher incidence of adverse reactions in AIDS patients.

10. Other drugs Drugs can modify the response to each other by pharmacokinetic or pharmacodynamic interaction between them. The number of reported interactions is already too large to remember. However, knowledge of drugs and patients at particular risk and the mechanism underlying the interaction can avoid most iatrogenic disasters. That two drugs interact does not necessarily mean that their concurrent use is contraindicated: many can be used together with dose adjustments or some other measures. Many drug interactions have already been considered (*see* pharmacokinetics and combined effect of drugs). Drug interactions relevant to dental practice are given in Ch. 35.

11. Cumulation Any drug will cumulate in the body if rate of administration is more than rate of elimination. However, slowly eliminated drugs are particularly liable to cause cumulative toxicity, e.g. prolonged use of chloroquine causes retinal damage.

Full loading dose of digoxin should not be given if patient has received it within the past week.

12. Tolerance It means requirement of higher dose of a drug to produce a given response. Tolerance is a widely occurring adaptive biological phenomenon. Drug tolerance may be:

Natural The species/individual is inherently less sensitive to the drug, e.g. rabbits are tolerant to atropine, black races are tolerant to mydriatics.

Acquired This occurs by repeated use of a drug in an individual who was initially responsive. Body is capable of developing tolerance to most drugs, but the phenomenon is very easily recognized in the case of CNS depressants. An uninterrupted presence of the drug in the body favours development of tolerance. However, significant tolerance does not develop to atropine, digitalis, cocaine, sodium nitroprusside, etc. Tolerance need not develop equally to all actions of a drug; consequently, therapeutic index of a drug may increase or decrease with prolonged use, e.g.:

- Tolerance develops to sedative action of chlorpromazine but not to its antipsychotic action.
- Tolerance occurs to the sedative action of phenobarbitone but not to its antiepileptic action.
- Tolerance occurs to analgesic and euphoric action of morphine but not to its constipating and miotic actions.

Cross tolerance It is the development of tolerance to pharmacologically related drugs, e.g. alcoholics are relatively tolerant to barbiturates and general anaesthetics. Closer the two drugs are, more complete is the cross tolerance between them, e.g.

There is partial cross tolerance between morphine and barbiturates but complete cross tolerance between morphine and pethidine.

Mechanisms responsible for development of tolerance are incompletely understood. However, tolerance may be:

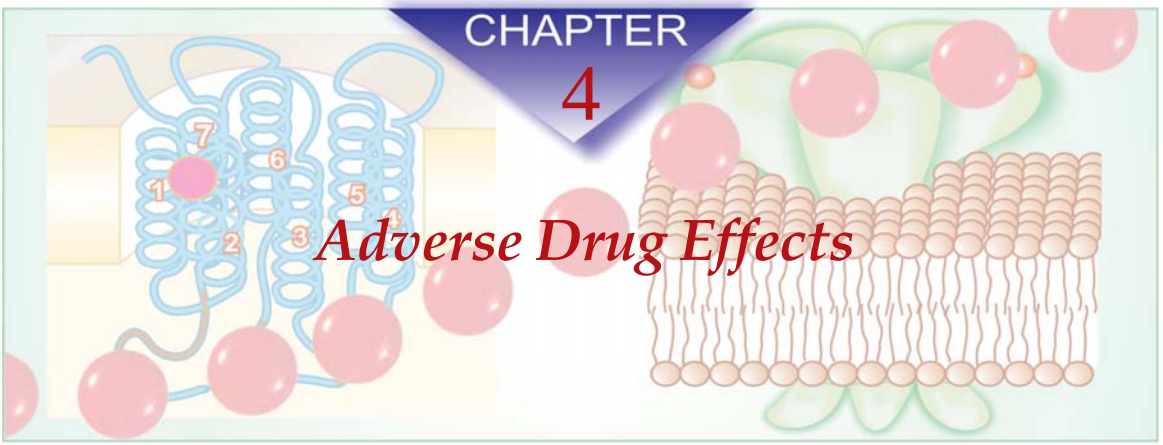
(i) Pharmacokinetic/drug disposition tolerance—the effective concentration of the drug at the site of action is decreased, mostly due to enhancement of drug elimination on chronic use, e.g. barbiturates, carbamazepine, amphetamine.

(ii) Pharmacodynamic/cellular tolerance—drug action is lessened; cells of the target organ become less responsive, e.g. morphine, barbiturates, nitrates. This may be due to downregulation of receptors (*see* p. 41), weakening of response effectuation or other compensatory homeostatic mechanisms (e.g. antihypertensives).

Tachyphylaxis (*Tachy*-fast, *phylaxis*-protection) is rapid development of tolerance—doses of a drug repeated in quick succession result in marked reduction in response. This is usually seen with

indirectly acting drugs, e.g. ephedrine, tyramine, nicotine: they act by releasing catecholamines in the body, synthesis of which is unable to match the rate of release: stores get depleted. Other mechanisms like slow dissociation of the drug from its receptor, internalization of receptor, etc. may also be involved.

Drug resistance It refers to tolerance of micro-organisms to inhibitory action of antimicrobials, e.g. *Staphylococci* to penicillin (*see* Ch. 26).



CHAPTER 4

Adverse Drug Effects

Adverse effect is 'any undesirable or unintended consequence of drug administration'. It is a broad term, includes all kinds of noxious effect—trivial, serious or even fatal.

All drugs are capable of producing adverse effects and whenever a drug is given a risk is taken. The magnitude of risk has to be considered along with the magnitude of expected therapeutic benefit in deciding whether to use or not to use a particular drug in a given patient, e.g. even risk of bone marrow depression may be justified in treating cancer while mild drowsiness caused by an antihistaminic in treating common cold may be unacceptable.

Adverse effects may develop promptly or only after prolonged medication or even after stoppage of the drug. Adverse effects are not rare; an incidence of 10–25% has been documented in different clinical settings. They are more common with multiple drug therapy and in the elderly. Adverse effects have been classified in many ways. One may divide them into:

Predictable (Type A) reactions These are based on pharmacological properties of the drug, *viz.* augmented but qualitatively normal response to the drug; include side effects, toxic effects and consequences of drug withdrawal. They are more common, dose related and mostly preventable.

Unpredictable (Type B) reactions These are based on peculiarities of the patient and not on the drug's known actions; include allergy and idiosyncrasy. They are less common, often non-dose related, generally more serious and require withdrawal of the drug. Some of these reactions can be predicted and prevented if their genetic basis is known and suitable test to characterize the individual's phenotype is performed.

Severity of adverse drug reactions has been graded as:

Minor: No therapy, antidote or prolongation of hospitalization is required.

Moderate: Requires change in drug therapy, specific treatment or prolongs hospital stay by at least one day.

Severe: Potentially life threatening, causes permanent damage or requires intensive medical treatment.

Lethal: Directly or indirectly contributes to death of the patient.

Prevention of adverse effects to drugs Adverse drug effects can be minimized but not altogether eliminated by observing the following practices:

1. Avoid all inappropriate use of drugs in the context of patient's clinical condition.
2. Use appropriate dose, route and frequency of drug administration based on patient's specific variables.
3. Elicit and take into consideration previous history of drug reactions.

4. Elicit history of allergic diseases and exercise caution (drug allergy is more common in patients with allergic diseases).
5. Rule out possibility of drug interactions when more than one drug is prescribed.
6. Adopt correct drug administration technique (e.g. NSAIDs not to be given on empty stomach).
7. Carry out appropriate laboratory monitoring (e.g. prothrombin time with warfarin, serum drug levels with lithium).

1. Side effects

These are unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses. They can be predicted from the pharmacological profile of a drug and are known to occur in a given percentage of drug recipients. Reduction in dose generally ameliorates the symptoms.

A side effect may be based on the same action as the therapeutic effect, e.g. atropine is used in preanaesthetic medication for its antisecretory action—produces dryness of mouth as a side effect; antiinflammatory as well as gastric mucosal damaging effects of NSAIDs are due to inhibition of prostaglandin synthesis.

Side effect may also be based on a different facet of action, e.g. promethazine produces sedation which is unrelated to its antiallergic action; estrogens cause nausea which is unrelated to their antiovulatory action.

An effect may be therapeutic in one context but side effect in another context, e.g. codeine used for cough produces constipation as a side effect but the latter is its therapeutic effect in traveller's diarrhoea; depression of A-V conduction is the desired effect of digoxin in atrial fibrillation, but the same may be undesirable when it is used for CHF.

2. Secondary effects

These are indirect consequences of a primary action of the drug, e.g. suppression of bacterial flora by tetracyclines paves the way for superinfections; corticosteroids weaken host defence mechanisms so that latent tuberculosis gets activated.

3. Toxic effects

These are the result of excessive pharmacological action of the drug due to overdosage or prolonged use. Overdosage may be absolute (accidental, homicidal, suicidal) or relative (i.e. usual dose of gentamicin in presence of renal failure). Toxic effects are predictable and dose related. They result from functional alteration (high dose of atropine causing delirium) or drug induced tissue damage (hepatic necrosis from paracetamol overdosage). The CNS, CVS, kidney, liver, lung, skin and blood forming organs are most commonly involved in drug toxicity.

Toxicity may result from extension of the therapeutic effect itself, e.g. hypoglycaemia due to insulin, complete A-V block by digoxin, bleeding due to heparin.

Another action may be responsible for toxicity, e.g.
Morphine (analgesic) causes respiratory failure in overdosage.
Gentamicin (antibacterial) in high dose causes vestibular damage.

Poisoning Poisoning may result from large doses of drugs because 'it is the dose which distinguishes a drug from a poison'. Poison is a 'substance which endangers life by severely affecting one or more vital functions'. Not only drugs but other household and industrial chemicals, insecticides, etc. are frequently involved in poisonings. Specific antidotes such as receptor antagonists, chelating agents or specific antibodies are available for a few poisons. General supportive and symptomatic treatment is all that can be done for others and is also important for poisons which have a selective antagonist.

(i) *Termination of exposure* by removing the patient to fresh air (for inhaled poisons), washing the skin and eyes (for poisons entering from the surface), induction of emesis with syrup ipecac or gastric lavage (for ingested poisons).

(ii) *Prevention of absorption of ingested poisons:* a suspension of 20–40 g of activated charcoal in 200 ml water may be administered.

(iii) *Maintenance of patent airway* and adequate ventilation by artificial respiration, if needed.

(iv) *Maintenance of blood pressure* and heart beat by fluid infusion, pressor agents, cardiac stimulants, etc. as the need may be.

(v) *Hastening elimination* of poison by inducing diuresis (furosemide, mannitol) altering urinary pH (alkalinization for acidic drugs, e.g. barbiturates). Haemodialysis and haemoperfusion (passage of blood through a column of charcoal or adsorbant resin) are more efficacious procedures.

4. Intolerance

It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses. It is the converse of tolerance and indicates a low threshold of the individual to the action of a drug. These are individuals who fall on the extreme left side of the Gaussian frequency distribution curve for sensitivity to the drug. Examples are:

- A single dose of triflupromazine induces muscular dystonias in some individuals, especially children.
- Only few doses of carbamazepine may cause ataxia in some people.
- One tablet of aspirin may cause gastric bleeding.

5. Idiosyncrasy

It is genetically determined abnormal reactivity to a chemical. Certain adverse effects of some drugs are largely restricted to individuals with a particular genotype (*see* p. 51). In addition, certain uncharacteristic or bizarre drug effects due to peculiarities of an individual (for which no definite genotype has been described) are included among idiosyncratic reactions, e.g.:

- Barbiturates cause excitement and mental confusion in some individuals.
- Quinine/quinidine cause cramps, diarrhoea, purpura, asthma and vascular collapse in some patients.

6. Drug allergy

It is an immunologically mediated reaction producing stereotype symptoms which are unrelated to the pharmacodynamic profile of the drug and are largely independent of dosage. This is also called drug hypersensitivity; but does not refer to increased response which is called supersensitivity.

Allergic reactions occur only in a small proportion of the population exposed to the drug and cannot be produced in other individuals at any dose. Prior sensitization is needed and a latent period of at least 1–2 weeks is required after the first exposure. The drug or its metabolite acts as antigen (AG) or more commonly *hapten* (incomplete antigen: drugs have small molecules which become antigenic only after binding with an endogenous protein) and induce production of antibody (AB)/sensitized lymphocytes. Presence of AB to a drug is not necessarily followed by allergy to it. Chemically related drugs often show cross sensitivity. One drug can produce different types of allergic reactions in different individuals, while widely different drugs can produce the same reaction. The course of drug allergy is variable; an individual previously sensitive to a drug may subsequently tolerate it without a reaction and *vice versa*.

MECHANISM AND TYPES OF ALLERGIC REACTIONS

A. Humoral

Type-I (anaphylactic) reactions Reaginic antibodies (IgE) are produced which get fixed to the mast cells. On exposure to the drug, AG: AB reaction takes place on the mast cell surface releasing mediators like histamine, 5-HT, leukotrienes, especially LT-C4 and D4, prostaglandins, PAF, etc. resulting in urticaria, itching, angioedema, asthma, rhinitis or anaphylactic shock. The mani-

festations occur quickly after challenge and are called *immediate hypersensitivity*. This is the only type of allergic drug reaction that the dentist may have to treat himself.

Type-II (cytolytic) reactions Drug + component of a specific tissue cell act as AG. The resulting antibodies (IgG, IgM) bind to the target cells; on reexposure AG: AB reaction takes place on the surface of these cells, complement is activated and cytolysis occurs, e.g. thrombocytopenia, agranulocytosis, aplastic anaemia, haemolysis, organ damage (liver, kidney, muscle), systemic lupus erythematosus.

Type-III (retarded, Arthus) reactions These are mediated by circulating antibodies (predominantly IgG, mopping AB). AG: AB complexes bind complement and precipitate on vascular endothelium giving rise to a destructive inflammatory response. Manifestations are rashes, serum sickness (fever, arthralgia, lymphadenopathy), polyarteritis nodosa, Stevens-Johnson syndrome (erythema multiforme, arthritis, nephritis, myocarditis, mental symptoms). The reaction usually subsides in 1–2 weeks.

B. Cell mediated

Type-IV (delayed hypersensitivity) reactions These are mediated through production of sensitized T-lymphocytes carrying receptors for the AG. On contact with AG, these T cells produce *lymphokines* which attract granulocytes and generate an inflammatory response, e.g. contact dermatitis, some rashes, fever, photosensitization. The reaction generally takes > 12 hours to develop. Dentists may develop contact dermatitis by repeated handling of local anaesthetics; though this is now rare due to replacement of procaine by lignocaine and use of surgical gloves.

TREATMENT OF DRUG ALLERGY

The offending drug must be immediately stopped. Most mild reactions (like skin rashes) subside by themselves and do not require specific treatment. Antihistamines (H_1) are beneficial in some type I reactions (urticaria, rhinitis, swelling of lips, etc.) and some skin rashes (*see* p. 102). In case of anaphylactic shock or angioedema of larynx, the resuscitation council of UK has recommended the following measures:

- Put the patient in reclining position, administer oxygen at high flow rate and perform cardiopulmonary resuscitation if required.
- Inject adrenaline 0.5 mg (0.5 ml of 1 in 1000 solution) i.m.; repeat every 5–10 min in case the patient does not improve or improvement is transient. This is the only life-saving measure. Adrenaline should not be injected i.v. (can itself be fatal) unless shock is immediately life threatening. If adrenaline is to be injected i.v., it should be diluted to 1:10,000 or 1:100,000 and infused slowly with constant monitoring.
- Administer a H_1 antihistaminic (chlorpheniramine 10–20 mg) i.m./slow i.v. It may have adjuvant value.
- Intravenous glucocorticoid (hydrocortisone sod. succinate 100–200 mg) should be added in severe/recurrent cases. It acts slowly, but is specially valuable for prolonged reactions and in asthmatics.

Adrenaline followed by a short course of glucocorticoids is indicated for bronchospasm attending drug hypersensitivity. Glucocorticoids are the only drugs effective in type II, type III and type IV reactions.

Drugs frequently causing allergic reactions

Penicillins	Local anaesthetics
Cephalosporins	Salicylates
Sulfonamides	Carbamazepine
Tetracyclines	Allopurinol
Quinolones	ACE inhibitors
Antitubercular drugs	Methyldopa
Phenothiazines	Hydralazine

Skin tests (intradermal, patch) or intranasal tests may forewarn in case of Type I hypersensitivity but not in case of other types. However, these tests are not entirely reliable—false positive and false negative results are not rare.

7. Photosensitivity

It is a cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. The reactions are of two types:

(a) Phototoxic Drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction followed by a photobiological reaction resulting in local tissue damage (sunburn like), i.e. erythema, edema, blistering followed by hyperpigmentation and desquamation. The shorter wavelengths (290–320 nm, UV-B) are responsible. Drugs involved in acute phototoxic reactions are tetracyclines (especially demeclocycline) and tar products. Drugs causing chronic and low-grade sensitization are nalidixic acid, fluoroquinolones, sulfones, sulfonamides, phenothiazines, thiazides, amiodarone. This type of reaction is more common than photoallergic reaction.

(b) Photoallergic Drug or its metabolite induces a cell-mediated immune response which on exposure to light of longer wavelengths (320–400 nm, UV-A) produces a papular or eczematous contact dermatitis like picture. Rarely antibodies mediate photoallergy and the reaction takes the form of immediate flare and wheal on exposure to sun. Drugs involved are sulfonamides, sulfonylureas, griseofulvin, chloroquine, chlorpromazine.

8. Drug dependence

Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, withdrawal from reality, social adjustment, etc. Drug dependence is a state in which use of drugs for personal satisfaction is accorded a higher priority than other basic needs, often in the face of known risks to health.

There is a lot of confusion in terminology and definitions; the following may serve to describe different aspects of the problem.

Psychological dependence It is said to have developed when the individual believes that optimal state of wellbeing is achieved only through the actions of the drug. It may start as liking for the drug effects and may progress to compulsive drug use in some individuals. The intensity of psychological dependence may vary from desire to craving. Obviously, certain degree of psychological dependence accompanies all patterns of self-medication.

Reinforcement is the ability of the drug to produce effects that make the user wish to take it again. Certain drugs (opioids, cocaine) are strong reinforcers, while others (benzodiazepines) are weak reinforcers. Faster the drug acts, more reinforcing it is.

Physical dependence It is an altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic *withdrawal (abstinence) syndrome*. Since the essence of the process is adaptation of the nervous system to function normally in the presence of the drug, it has been called 'neuroadaptation'.

Drugs producing physical dependence are—opioids, barbiturates and other depressants including alcohol and benzodiazepines. Stimulant drugs, e.g. amphetamines, cocaine produce little or no physical dependence.

Drug abuse Refers to use of a drug by self-medication in a manner and amount that deviates from the approved medical and social patterns in a given culture at a given time. The term conveys social disapproval of the manner and purpose of drug use. For regulatory agencies, *drug abuse* refers to any use of an ilicit drug.

Drug addiction It is a pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug. Procuring the drug and using it takes precedence over other activities. Even after withdrawal most addicts tend to relapse. Physical dependence, though a strong impetus for continued drug use, is not an essential

feature of addiction. Amphetamines, cocaine, cannabis, LSD are drugs which produce addiction but little/no physical dependence. On the other hand, drugs like nalorphine produce physical dependence without imparting addiction in the sense that there is little drug seeking behaviour.

Drug habituation It denotes less intensive involvement with the drug, so that its withdrawal produces only mild discomfort. Consumption of tea, coffee, tobacco, social drinking are regarded habituating, physical dependence is absent.

Basically, habituation and addiction imply different degrees of psychological dependence and it may be difficult to draw a clearcut line of distinction between the two. Therefore, it is better to avoid using these terms in describing drug dependence and related conditions.

9. Drug withdrawal reactions

Apart from drugs that are usually recognized as producing dependence, sudden interruption of therapy with certain other drugs also results in adverse consequences, mostly in the form of worsening of the clinical condition for which the drug was being used, e.g.:

(i) Acute adrenal insufficiency may be precipitated by abrupt cessation of corticosteroid therapy.
(ii) Severe hypertension and sympathetic overactivity may occur shortly after discontinuing clonidine.
(iii) Worsening of angina pectoris or myocardial infarction may result from stoppage of β blockers.
(iv) Frequency of seizures may increase on sudden withdrawal of an antiepileptic.

These manifestations are also due to adaptive changes and can be minimized by gradual withdrawal.

10. Teratogenicity

It refers to capacity of a drug to cause foetal abnormalities when administered to the pregnant mother. The placenta does not strictly constitute a barrier and any drug can cross it to a greater or lesser extent. The embryo is one of the most dynamic biological systems, and in contrast to adults, drug effects on embryo are often irreversible. The thalidomide disaster (1958–61) resulting in thousands of babies born with *phocomelia* (seal-like limbs) and other defects focused attention to this type of adverse effect.

Drugs can affect the foetus at three stages—

(i) *Fertilization and implantation*—conception to 17 days—failure of pregnancy which often goes unnoticed.
(ii) *Organogenesis*—18 to 55 days of gestation—most vulnerable period, deformities are produced.
(iii) *Growth and development*—56 days onwards—developmental and functional abnormalities can occur, e.g. ACE inhibitors can cause hypoplasia of organs, especially lungs and kidneys; NSAIDs may induce premature closure of ductus arteriosus.

The type of malformation depends on the drug as well as stage of exposure to the teratogen. The proven human teratogens are listed in the box.

Other drugs may be low grade teratogens and it is almost impossible to declare a drug to be absolutely safe during pregnancy. The US-FDA has graded the documentation of risk for causing birth defects into five categories (*see* box).

It is, therefore, wise to avoid all drugs during pregnancy unless compelling reasons exist for their use regardless of the assigned pregnancy category, or presumed safety. Only emergency dental treatment should be undertaken during the most vulnerable period of organogenesis.

11. Carcinogenicity and mutagenicity

It refers to capacity of a drug to cause cancer and genetic defects respectively. Usually, oxidation of the drug results in the production of reactive intermediates which affect genes and may cause structural changes in the chromosomes. Chemical carcinogenesis is a well-recognized pheno-

Human teratogenic drugs

Drug	*Abnormality*
Thalidomide	phocomelia, multiple defects
Anticancer drugs (methotrexate)	multiple defects, foetal death
Androgens	virilization; limb, esophageal, cardiac defects
Progestins	virilization of female foetus
Stilboestrol	vaginal carcinoma in teenage female offspring
Tetracyclines	discoloured and deformed teeth, retarded bone growth
Warfarin	nose, eye and hand defects, growth retardation
Phenytoin	hypoplastic phalanges, cleft lip/palate, microcephaly
Phenobarbitone	various malformations
Carbamazepine	neural tube defects, other abnormalities
Valproate sod.	spina bifida and other neural tube defects
Lithium	foetal goiter, cardiac and other abnormalities
Antithyroid drugs	foetal goiter and hypothyroidism
Indomethacin/aspirin	premature closure of ductus arteriosus
Isotretinoin	craniofacial, heart and CNS defects

Risk category of drugs during pregnancy

Category		*Examples*
A	Adequate studies in pregnant women have failed to demonstrate a risk to the foetus	Inj. Mag. sulfate, thyroxine
B	Adequate human studies are lacking, but animal studies have failed to demonstrate a risk to the foetus or Adequate studies in pregnant women have failed to demonstrate a risk to the foetus, but animal studies have shown an adverse effect on the foetus	penicillin V, amoxicillin, cefactor, erythromycin, paracetamol, naproxen, lignocaine
C	No adequate studies in pregnant women and animal studies are lacking or have shown an adverse effect on foetus, but potential benefit may warrant use of the drug in pregnant women despite potential risk	morphine, codeine, butorphanol, atropine, corticosteroids, adrenaline, thiopentone, bupivacaine
D	There is evidence of human foetal risk, but the potential benefits from use of the drug may be acceptable despite the potential risk	aspirin, phenytoin, carbamazepine, valproate, lorazepam
X	Studies in animals or humans have demonstrated foetal abnormalities, and potential risk clearly outweighs possible benefit	estrogens, isotretinoin, warfarin, ergometrine

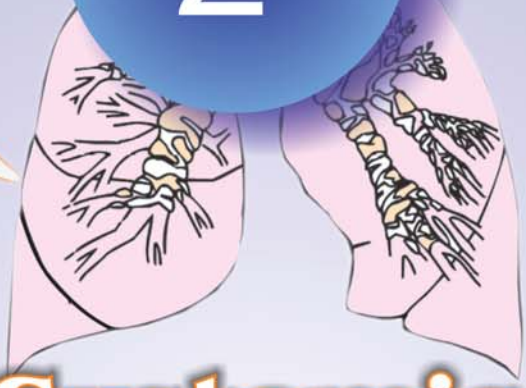
menon but generally takes several (10–40) years to develop. Drugs implicated in these adverse effects are—anticancer drugs, radioisotopes, estrogens, tobacco.

12. Drug induced diseases

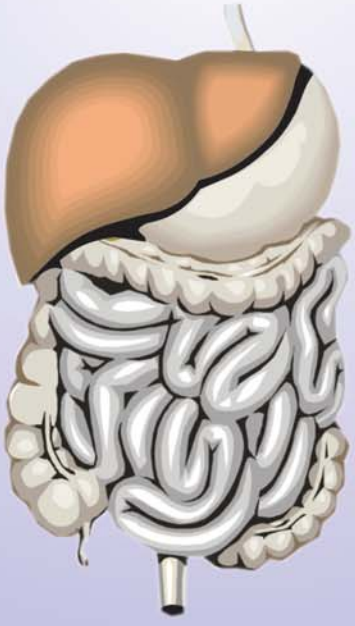
These are also called *iatrogenic* (physician induced) diseases, and are functional disturbances (disease) caused by drugs which persist even after the offending drug has been withdrawn and largely eliminated, e.g.:

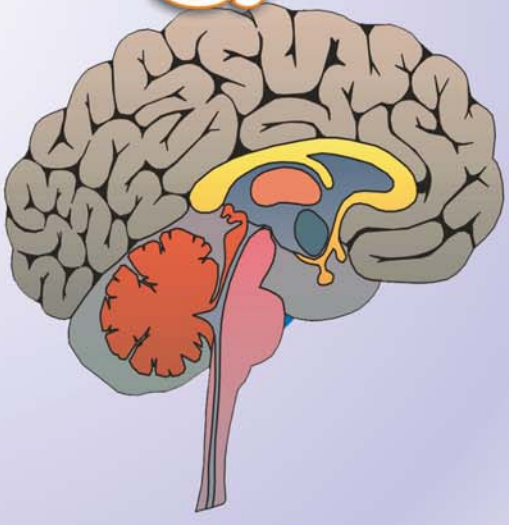
Peptic ulcer by salicylates and corticosteroids.
Parkinsonism by phenothiazines and other antipsychotics.
Hepatitis by isoniazid.
DLE by hydralazine.

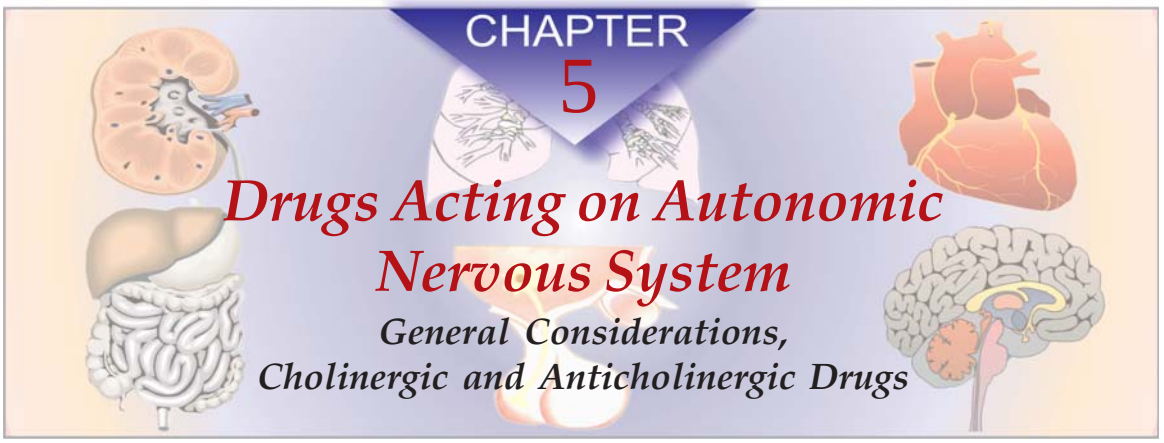
SECTION 2



Systemic Pharmacology







CHAPTER 5

Drugs Acting on Autonomic Nervous System

General Considerations, Cholinergic and Anticholinergic Drugs

ORGANIZATION OF AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system (ANS) functions largely below the level of consciousness and controls visceral functions. Like the somatic nervous system, the ANS consists of afferents, centre and efferents.

Autonomic afferents are carried in the visceral nerves, most of which are mixed nerves. They mediate visceral pain and visceral reflexes (cardiovascular, respiratory, etc.).

The highest seat regulating autonomic functions is in hypothalamus—posterior and lateral nuclei are primarily sympathetic while anterior and medial nuclei are primarily parasympathetic. Many autonomic centres (pupillary, vagal, respiratory, etc.) are located in the mid-brain and the medulla in relation to the cranial nerves. The lateral column in the thoracic spinal cord contains cells which give rise to the sympathetic outflow.

The motor limb of the ANS is anatomically divided into sympathetic and parasympathetic. In general, these subdivisions are functionally antagonistic and most organs receive both sympathetic and parasympathetic innervation. The level of activity of the innervated organ at a given moment is the algebraic sum of sympathetic and parasympathetic tone. However, most blood vessels, spleen, sweat glands and hair follicles receive only sympathetic, while ciliary muscle, gastric and pancreatic glands receive only parasympathetic innervation. The general layout of ANS is depicted in Fig. 5.1 and the important differences between its two subdivisions are given in Table 5.1.

NEUROHUMORAL TRANSMISSION

Neurohumoral transmission implies that nerves transmit their message across synapses and neuroeffector junctions by the release of humoral (chemical) messengers.

Steps in neurohumoral transmission

1. *Impulse conduction* The resting transmembrane potential (70 mV negative inside) is established by high K^+ permeability of axonal membrane and high axoplasmic concentration of this ion coupled with low Na^+ permeability and its active extrusion from the neurone. Stimulation or arrival of an electrical impulse causes a sudden increase in Na^+ conductance → depolarization and overshoot (reverse polarization: inside becoming 20 mV positive); K^+ ions then move out in the direction of their concentration gradient and repolarization occurs. Ionic distribution is normalized during the refractory period by the activation of Na^+ K^+ pump. The action potential (AP) thus generated sets up local circuit currents which activate ionic channels at the next excitable part of the membrane (next node of Ranvier in myelinated fibre) and the AP is propagated without decrement.

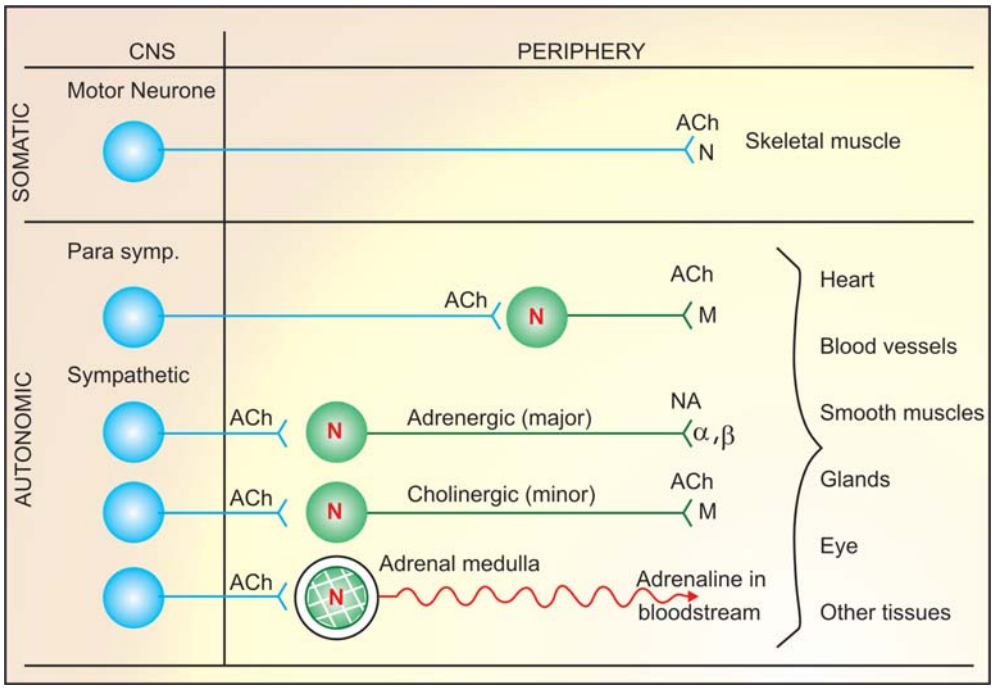


Fig. 5.1: The general outlay of autonomic nervous system. The transmitter released and the primary postjunctional receptor subtype is shown at each synapse/neuroeffector junction
N = Nicotinic, M = Muscarinic, α = α adrenergic, β = β adrenergic

II. *Transmitter release* The transmitter (excitatory or inhibitory) is stored in prejunctional nerve endings within 'synaptic vesicles' (Fig. 5.2). Nerve impulse promotes fusion of vesicular and axonal membranes, through Ca^{2+} entry which fluidizes membranes. All contents of the vesicle (transmitter, enzymes and other proteins) are extruded (exocytosis) in the junctional cleft.

The release process can be modulated by the transmitter itself and by other agents through activation of specific receptors located on the prejunctional membrane, e.g. noradrenaline (NA) release is inhibited by NA (α_2 receptors), dopamine, adenosine, prostaglandins and enkepha-

Table 5.1: Differences between sympathetic and parasympathetic divisions of the autonomic nervous system

	Sympathetic	*Parasympathetic*
1. Origin	Dorso-lumbar (T_1 to L_2 or L_3)	Cranio-sacral (III, VII, IX, X; S_2-S_4)
2. Distribution	Wide	Limited to head, neck and trunk
3. Ganglia	Away from organs	On or close to the organ
4. Postgang. fibre	Long	Short
5. Pre: post ganglionic fibre ratio	1: 20 to 1: 100	1: 1 to 1: 2 (except in enteric plexuses)
6. Transmitter (neuroeffector)	Noradrenaline (major) Acetylcholine (minor)	Acetylcholine
7. Stability of transmitter	NA stable, diffuses for wider actions	ACh—rapidly destroyed locally
8. Important function	Tackling stress and emergency	Assimilation of food, conservation of energy

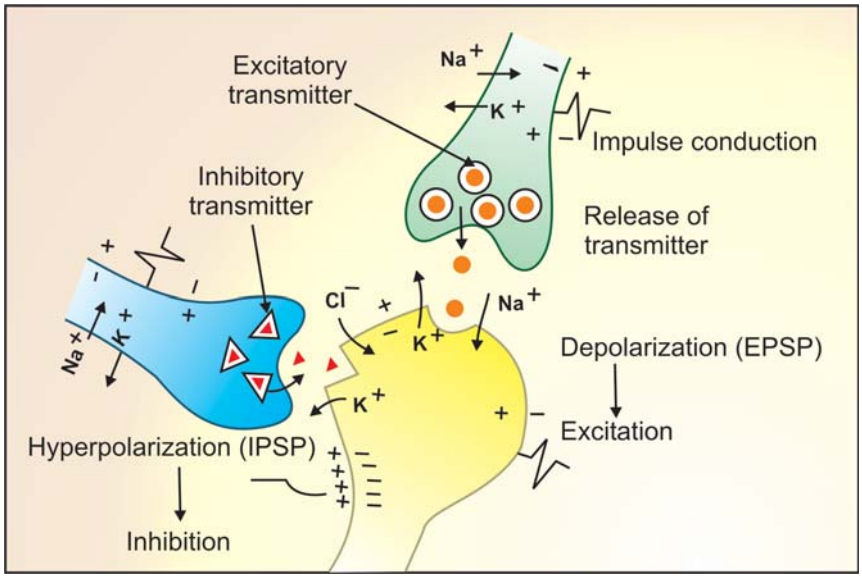


Fig. 5.2: Diagrammatic representation of steps in excitatory and inhibitory neurohumoral transmission: EPSP = Excitatory postsynaptic potential; IPSP = Inhibitory postsynaptic potential

lins while isoprenaline (β_2 receptors) increases NA release. Similarly, α_2 and muscarinic agonists inhibit acetylcholine (ACh) release at autonomic neuroeffector sites (but not in ganglia and skeletal muscles).

III. *Transmitter action on postjunctional membrane* The released transmitter combines with specific receptors on the postjunctional membrane and depending on its nature induces an excitatory postsynaptic potential (EPSP) or an inhibitory postsynaptic potential (IPSP).

EPSP Increase in permeability to all cations → Na^+ or Ca^{2+} influx (through fast or slow channels) causes *depolarization* followed by K^+ efflux. These ionic movements are passive as the flow is down the concentration gradients.

IPSP Increase in permeability to smaller ions, i.e. K^+ and Cl^- (hydrated K^+ ion is smaller than hydrated Na^+ ion) only, so that K^+ moves out and Cl^- moves in (in the direction of their concentration gradients) resulting in *hyperpolarization*.

In addition, a trophic influence on junctional morphology and functional status is exerted by the background basal release of the transmitter.

IV. *Postjunctional activity* A suprathreshold EPSP generates a propagated postjunctional AP which results in nerve impulse (in neurone), contraction (in muscle) or secretion (in gland). An IPSP stabilizes the postjunctional membrane and resists depolarizing stimuli.

V. *Termination of transmitter action* Following its combination with the receptor, the transmitter is either locally degraded (e.g. ACh) or is taken back into the prejunctional neurone by active uptake or diffuses away (e.g. NA, GABA). Rate of termination of transmitter action governs the rate at which responses can be transmitted across a junction (1 to 1000/sec).

Cotransmission

It has now become apparent that the classical 'one neurone—one transmitter' model is an over simplification. Many peripheral and central neurones have been shown to release more than one active substance when stimulated. In the ANS, besides the primary transmitters ACh and NA, neurones have been found to elaborate purines (ATP, adenosine), peptides (vasoactive intestinal

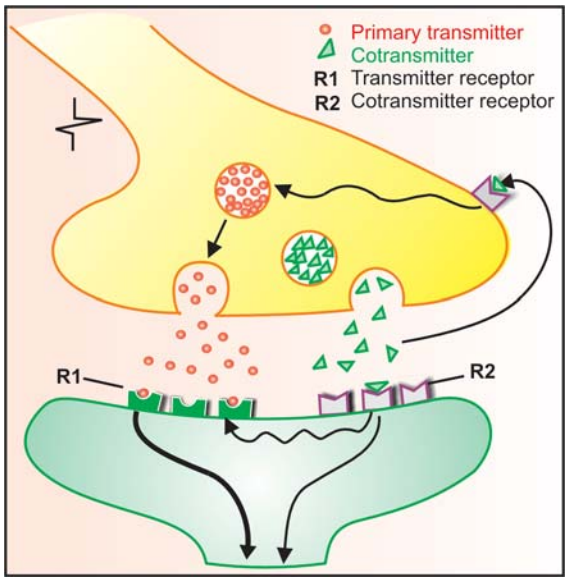


Fig. 5.3: Cotransmission
The cotransmitter is stored in the prejunctional nerve terminal along with the primary transmitter, but in separate vesicles (in some cases in the same vesicle itself). Nerve impulse releases both the transmitters concurrently. Acting on its own receptors, the cotransmitter modifies responsiveness of the effector to the primary transmitter or substitutes for it. Cotransmitter may also act on prejunctional receptors and modulate release of the transmitters

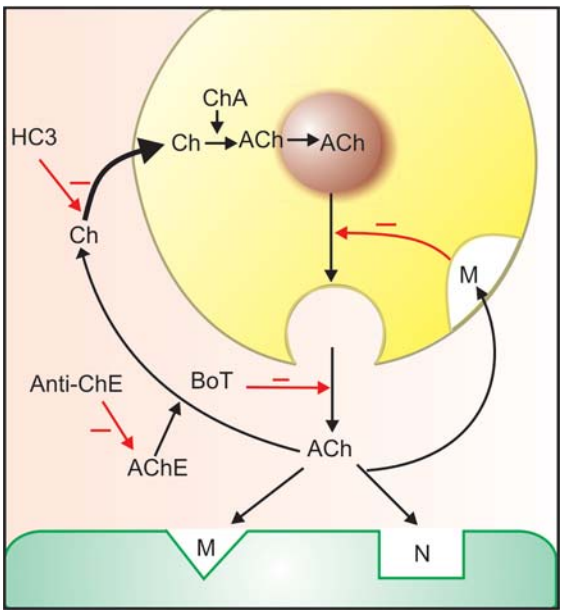


Fig. 5.4: Cholinergic neuronal mechanisms
Minus sign indicates inhibition while bold arrow indicates active transport.
Ch = Choline, ACh = Acetylcholine, ChA = Choline acetylase, AChE = Acetylcholinesterase, Anti-ChE = Anticholinesterase, M = Muscarinic receptor, N = Nicotinic receptor, HC3 = Hemicholinium, BoT = Botulinus toxin

peptide or VIP, neuropeptide-Y or NPY, substance P, enkephalins, somatostatin, etc.), nitric oxide and prostaglandins as cotransmitters. The cotransmitter is stored in the same neurone but in distinct synaptic vesicles or locations (Fig. 5.3). However, ATP is stored with NA in the same vesicle. On being released by the nerve impulse, it may serve to regulate the presynaptic release of the primary transmitter and/or postsynaptic sensitivity to it (neuromodulator role). The cotransmitter may also serve as an alternative transmitter in its own right and/or exert a trophic influence on the synaptic structures.

CHOLINERGIC TRANSMISSION

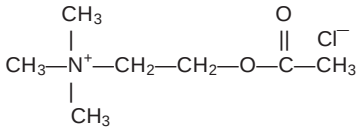
Acetylcholine (ACh) is a major neurohumoral transmitter at autonomic as well as somatic sites (Table 5.2).

Synthesis, storage and destruction of ACh

The cholinergic neuronal mechanisms are summarized in Fig. 5.4.

Acetylcholine is synthesized locally in the cholinergic nerve endings by the following pathway—

ATP + Acetate + CoEn-A
↓ Acetate activating reaction
Acetyl CoEn-A
CHOLINE → ↓ Choline acetylase
ACETYLCHOLINE + CoEn-A



Acetylcholine chloride

Table 5.2: Sites of cholinergic transmission and type of receptor involved

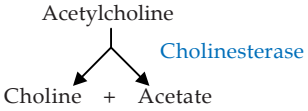
Site	Type of receptor	Selective agonist	Selective antagonist
1. *a.* All postganglionic parasymp. *b.* Few postganglionic symp (sweat glands, some blood vessels)	Muscarinic	Muscarine	Atropine
2. *a.* Ganglia (both symp. and parasymp). *b.* Adrenal medulla	Nicotinic (N_N)	DMPP*	Hexamethonium
3. Skeletal muscles	Nicotinic (N_M)	PTMA**	Curare
4. CNS (cortex, basal ganglia, spinal cord and other sites)	Muscarinic Nicotinic	Muscarine/ Oxotremorine Carbachol	Atropine Curare

* DMPP—Dimethyl phenyl piperazinium
** PTMA—Phenyl trimethyl ammonium

Choline is actively taken up by the axonal membrane and acetylated with the help of ATP and coenzyme-A by the enzyme *cholineacetylase* present in the axoplasm. Most of the ACh is stored in ionic solution within small synaptic vesicles, but some free ACh is also present in the cytoplasm of cholinergic terminals.

Release of ACh from nerve terminals occurs in small quanta—amount contained in individual vesicles is extruded by exocytosis. In response to a nerve AP synchronous release of multiple quanta triggers postjunctional events. Immediately after release, ACh is hydrolyzed by the enzyme cholinesterase and choline is recycled.

A specific (*Acetylcholinesterase*—AChE or true cholinesterase) and a nonspecific (*Butyrylcholinesterase*—BuChE or pseudocholinesterase) type of enzyme occurs in the body.



Acetylcholinesterase is strategically located at all cholinergic sites and serves to hydrolyze ACh very rapidly (in μ*S*). Pseudocholinesterase is a relatively nonspecific esterase present in plasma, liver and some other tissues; hydrolyzes ACh slowly and probably serves to metabolize ingested esters.

Cholinoceptors

Two classes of receptors for ACh are recognized—muscarinic and nicotinic; the former is a G protein coupled receptor, while the latter is a ligand gated cation channel.

Muscarinic These receptors are selectively stimulated by muscarine and blocked by atropine. They are located primarily on autonomic effector cells in heart, blood vessels, eye, smooth muscles and glands of gastrointestinal, respiratory and urinary tracts, sweat glands, etc. and in the CNS. Subsidiary muscarinic receptors are also present in autonomic ganglia where they appear to play a modulatory role by inducing a long-lasting late EPSP.

Subtypes of muscarinic receptor The muscarinic receptors have been divided into 5 subtypes M_1, M_2, M_3, M_4 and M_5. Out of these, the first 3 have been functionally characterized.

M_1: The M_1 is primarily a neuronal receptor located on ganglion cells and central neurones: especially in cortex, hippocampus and corpus striatum. It plays a major role in mediating gastric secretion and relaxation of lower esophageal sphincter (LES) on vagal stimulation.

M_2: Cardiac muscarinic receptors are predominantly M_2 and mediate vagal bradycardia. Autoreceptors on cholinergic nerve endings are also of M_2 subtype.

M_3: Visceral smooth muscle contraction and glandular secretions are elicited through M_3 receptors, which also

mediate vasodilatation through EDRF release. Together the M_2 and M_3 receptors mediate most of the well-recognized muscarinic actions including contraction of LES.

Nicotinic These receptors are selectively activated by nicotine and blocked by tubocurarine or hexamethonium. These are rosette-like pentameric structures (*see* Fig. 3.2) which enclose a ligand gated cation channel: their activation causes opening of the channel and rapid flow of cations resulting in depolarization and an action potential. On the basis of location and selective agonists and antagonists, two subtypes N_M and N_N are recognized.

N_M: These are present at skeletal muscle endplate: are selectively stimulated by phenyl trimethyl ammonium (PTMA) and blocked by tubocurarine. They mediate skeletal muscle contraction.

N_N: These are present on ganglionic cells (sympathetic as well as parasympathetic), adrenal medullary cells, in spinal cord and certain areas of brain. They are selectively stimulated by dimethyl phenyl piperazinium (DMPP), blocked by hexamethonium, and constitute the primary pathway of transmission in ganglia.

CHOLINERGIC DRUGS (Cholinomimetic, Parasympathomimetic)

These are drugs which produce actions similar to that of ACh, either by directly interacting with cholinergic receptors (cholinergic agonists) or by increasing availability of ACh at these sites (anticholinestrases).

CHOLINERGIC AGONISTS

Choline esters	*Alkaloids*
Acetylcholine	Muscarine
Methacholine	Pilocarpine
Carbachol	Arecoline
Bethanechol	

ACTIONS (of ACh as prototype)

Depending on the type of receptor through which it is mediated the peripheral actions of ACh may be classified as muscarinic or nicotinic. The central actions are not so classifiable and are described separately.

A. Muscarinic

1. *Heart* ACh hyperpolarizes the SA nodal cells and decreases the rate of diastolic depolarization. As a result, rate of impulse generation is reduced—*bradycardia* or even cardiac arrest may occur.

At the A-V node and His-Purkinje fibres refractory period (RP) is increased and *conduction is slowed*: P-R interval increases and partial to complete A-V block may be produced. The *force of atrial contraction is markedly reduced* and RP of atrial fibres is abbreviated. Due to nonuniform vagal innervation, the intensity of effect on RP and conduction of different atrial fibres varies—inducing inhomogeneity and predisposing to atrial fibrillation or flutter.

Ventricular contractility is also decreased but the effect is not marked.

2. *Blood vessels* All blood vessels are dilated, though only few (skin of face, neck) receive cholinergic innervation. Thus, fall in BP and flushing, especially in the blush area occurs. Muscarinic receptors are present on vascular endothelial cells: vasodilatation is primarily mediated through the release of an *endothelium-dependent relaxing factor* (EDRF) which is nitric oxide (NO).

3. *Smooth muscle* Smooth muscle in most organs is contracted. Tone and peristalsis in the gastrointestinal tract is increased and sphincters relax → abdominal cramps and evacuation of bowel.

Peristalsis in ureter is increased. The detrusor muscle contracts while the bladder trigone and sphincter relaxes → voiding of bladder.

Bronchial muscles constrict, asthmatics are highly sensitive → dyspnoea, precipitation of an attack of bronchial asthma.

4. *Glands* Secretion from all parasympathetically innervated glands is increased—sweating, salivation, lacrimation, tracheobronchial and gastric secretion. The effect on pancreatic and intestinal glands is not marked. Secretion of milk and bile is not affected.

5. *Eye* Contraction of circular muscle of iris → miosis.
Contraction of ciliary muscle → spasm of accommodation, increased outflow facility, reduction in intraocular tension (especially in glaucomatous patients).

B. Nicotinic

1. *Autonomic ganglia* Both sympathetic and parasympathetic ganglia are stimulated. This effect is manifested at higher doses. High dose of ACh given after atropine causes tachycardia and rise in BP.

2. *Skeletal muscles* Iontophoretic application of ACh to muscle endplate causes contraction of the fibre. Intraarterial injection of high dose can cause twitching and fasciculations, but i.v. injection is generally without any effect (due to rapid hydrolysis of ACh).

C. CNS

ACh injected i.v. does not penetrate blood-brain barrier and no central effects are seen. However, direct injection into the brain, or other cholinergic drugs which enter brain, produce a complex pattern of stimulation followed by depression.

The important features of other cholinesters are summarized in Table 5.3.

Table 5.3: Properties of choline esters

Choline ester	*Hydrolysis by*		*Actions*		*Selective action on*
	AChE	*BuChE*	*Musc.*	*Nico.*	
Acetylcholine	++	+	+	+	Nonselective
Methacholine	+	–	+	±	CVS
Carbachol	–	–	+	+	g.i.t., bladder
Bethanechol	–	–	+	–	g.i.t., bladder

Uses Choline esters are rarely if ever used clinically. ACh is not used because of evanescent and nonselective action. *Bethanechol* has been used in postoperative/postpartum nonobstructive urinary retention, neurogenic bladder, congenital megacolon and gastroesophageal reflux.

CHOLINOMIMETIC ALKALOIDS

Pilocarpine It is obtained from the leaves of *Pilocarpus microphyllus* and other species. It has prominent muscarinic actions and also stimulates ganglia—mainly through ganglionic muscarinic receptors.

Pilocarpine causes marked sweating, salivation and increases other secretions as well. The cardiovascular effects of pilocarpine are complex. Applied to the eye, it penetrates cornea and promptly causes miosis, ciliary muscle contraction and fall in intraocular tension lasting 4–8 hours. Pilocarpine is used in the eye as 0.5–4% drops primarily in open angle glaucoma. It has also been used orally for xerostomia, but is not available commercially for this purpose.

Muscarine It occurs in poisonous mushrooms *Amanita muscaria* and *Inocybe* species and has only muscarinic actions. It is not used therapeutically but is of toxicological importance in mushroom poisoning.

Arecoline It is found in betel nut *Areca catechu*. It has muscarinic as well as nicotinic actions including prominent CNS effects.

ANTICHOLINESTERASES

Anticholinesterases (anti-ChEs) are agents which inhibit ChE, protect ACh from hydrolysis—produce cholinergic effects *in vivo* and potentiate ACh both *in vivo* and *in vitro*. Some anti-ChEs have additional direct action on cholinergic receptors.

REVERSIBLE

Carbamates
Physostigmine (Eserine)
Neostigmine
Pyridostigmine
Edrophonium
Rivastigmine, Donepezil

Acridine
Tacrine

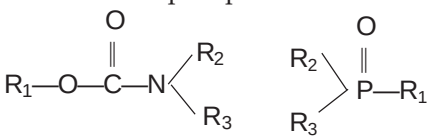
IRREVERSIBLE

Organophosphates
Dyflos (DFP)
Echothiophate
Parathion*, Malathion*
Diazinon* (TIK-20)
Tabun£, Sarin£, Soman£

Carbamates
Carbaryl* (SEVIN)
Propoxur* (BAYGON)

*Insecticides
£Nerve gases for chemical warfare

Anti-ChEs are either esters of carbamic acid or derivatives of phosphoric acid.



Carbamates Organophosphates

In carbamates R_1 may have a nonpolar tertiary amino N, e.g. in physostigmine, rendering the compound lipid soluble. In others, e.g. neostigmine, R_1 has a quaternary N^+—rendering it lipid insoluble. All organophosphates are highly lipid soluble except echothiophate which is water soluble.

The anti-ChEs react with the enzyme essentially in the same way as ACh. The carbamates and phosphates respectively carbamylate and phosphorylate the esteratic site of the enzyme. Whereas the acetylated enzyme reacts with water extremely rapidly and the esteratic site is freed in a fraction of a millisecond, the carbamylated enzyme (reversible inhibitors) reacts slowly and the phosphorylated enzyme (irreversible inhibitors) reacts extremely slowly or not at all. The half-life of reactivation of carbamylated enzyme (about 30 min) is less than that of synthesis of fresh enzyme protein, while that of phosphorylated enzyme is more than the regeneration time. Thus, apparently reversible and irreversible enzyme inhibition is obtained, though the basic pattern of inhibitor-enzyme interaction remains the same.

Pharmacological actions

The actions of anti-ChEs are qualitatively similar to that of directly acting cholinoceptor stimulants. However, relative intensities of action on muscarinic, ganglionic, skeletal muscle and CNS sites vary among the different agents.

Lipid-soluble agents (physostigmine and organophosphates) have more marked muscarinic and CNS effects; stimulate ganglia but action on skeletal muscles is less prominent.

Lipid-insoluble agents (neostigmine and other quaternary ammonium compounds) produce more marked effect on the skeletal muscles (direct action on muscle endplate cholinoceptors as well), stimulate ganglia, but muscarinic effects are less prominent. They do not penetrate CNS and have no central effects.

After treatment with anti-ChEs, the ACh released by a single nerve impulse in skeletal muscle is not immediately destroyed—rebinds to the same receptor, diffuses to act on neighbouring receptors and activates prejunctional fibres → repetitive firing → twitching and fasciculations. Force of contraction in partially curarized and myasthenic muscles is increased. Higher doses cause persistent depolarization of endplates resulting in blockade of neuromuscular transmission → weakness and paralysis.

The cardiovascular effects of anti-ChEs are complex: depend on the agent and its dose. Smooth muscles and glands of the gastrointestinal, respiratory, urinary tracts and in the eye are stimulated.

Pharmacokinetics

Physostigmine is rapidly absorbed from g.i.t. and parenteral sites. Applied to the eye, it penetrates cornea freely. It crosses blood-brain barrier and is disposed after hydrolysis by ChE.

Neostigmine and congeners are poorly absorbed orally; oral dose is 20–30 times higher than parenteral dose. They do not effectively penetrate cornea or cross blood-brain barrier.

Organophosphates are absorbed from all sites including intact skin and lungs. They are hydrolyzed as well as oxidized in the body and little is excreted unchanged.

Uses

1. *Glaucoma:* It is a progressive form of optic nerve damage associated with raised intraocular tension (i.o.t.). Miotics like pilocarpine and physostigmine lower i.o.t. by different mechanisms in the two principal types of glaucoma:

Open angle (chronic simple) glaucoma: Miotics increase the tone of ciliary muscle which pulls on and improves the outflow facility of trabecular meshwork. However, they are now 2nd or 3rd

line drugs to ocular β blockers and other agents like brimonidine (α_2 agonist clonidine congener), latanoprost ($PGF_{2\alpha}$ analogue), dorzolamide (ocular carbonic anhydrase inhibitor) and dipivefrine (prodrug of adrenaline).

Angle dosure (narrow angle, acute congestive) glaucoma: Miotics contract sphincter pupillae muscle changing the direction of forces in the iris to lessen its contact with the lens → pupillary block is removed and iridocorneal angle is freed.

2. *To reverse the effect of mydriatic* : after refraction testing.
3. *To prevent/break adhesions between iris and lens/cornea*: a miotic is alternated with a mydriatic.
4. *Myasthenia gravis*: It is an autoimmune disorder due to development of antibodies to the muscle endplate nicotinic receptors (NR) resulting in weakness and easy fatigability. Neostigmine and its congeners improve muscle contraction by preserving ACh as well as by directly depolarizing the endplate.
5. *Postoperative decurarization*: To reverse the effect of muscle relaxants.
6. *Postoperative paralytic ileus/urinary retention*
7. *Cobra bite*: To antagonize the curare-like action of cobra neurotoxin.
8. *Belladonna poisoning*: Physostigmine is the drug of choice for poisoning with atropine and other anticholinergic drugs.
9. *Alzheimer's disease*: This is a neurodegenerative disorder affecting primarily the cholinergic neurones in the brain. The relatively cerebroselective anti-ChEs tacrine, rivastigmine, donepezil and galantamine afford some symptomatic improvement.

ANTICHOLINESTERASE POISONING

Anticholinesterases are easily available and extensively used as agricultural and household insecticides; accidental as well as suicidal and homicidal poisoning is common.

Local muscarinic manifestations at the site of exposure (skin, eye, g.i.t.) occur immediately and are followed by complex systemic effects due to muscarinic, nicotinic and central actions.

Treatment

1. Termination of further exposure to the poison—fresh air, wash the skin and mucous membranes with water, gastric lavage according to need.
2. Maintain patent airway, positive pressure respiration if it is failing.
3. Supportive measures—maintain BP, hydration, control of convulsions with judicious use of diazepam.
4. Specific antidotes—

(a) *Atropine* It is highly effective in counteracting the muscarinic symptoms, but higher doses are required to antagonize the central effects. It does not reverse peripheral muscular paralysis which is a nicotinic action.

(b) *Cholinesterase reactivators* Oximes are used to restore neuromuscular transmission in case of organophosphate anti-ChE poisoning. They provide more reactive OH groups which react with phosphorylated enzyme to form oxime phosphonate and release free cholinesterase. Pralidoxime is the most commonly used oxime.

ANTICHOLINERGIC DRUGS (Muscarinic receptor antagonists, Atropinic, Parasympatholytic)

Conventionally, anticholinergic drugs are those which block actions of ACh on autonomic effectors and in the CNS exerted through muscarinic receptors. Though nicotinic antagonists also block certain actions of ACh, they are generally referred to as 'ganglion blockers' and 'neuromuscular blockers'.

Atropine, the prototype drug of this class, is highly selective for muscarinic receptors, but some of its synthetic substitutes do possess significant nicotinic blocking property in addition. All anticholinergic drugs are competitive antagonists.

CLASSIFICATION

1. *Natural alkaloids* Atropine, Hyoscine (Scopolamine).

2. *Semisynthetic derivatives* Homatropine, Atropine methonitrate, Hyoscine butyl bromide, Ipratropium bromide.
3. *Synthetic compounds*

(a) *Mydriatics:* Cyclopentolate, Tropicamide.
(b) *Antisecretory-antispasmodics*:
  (i) Quaternary compounds: Propantheline, Oxyphenonium, Clidinium, Glycopyrrolate.
  (ii) Tertiary amines: Dicyclomine, Oxybutynin, Flavoxate, Pirenzepine.
(c) *Antiparkinsonian:* Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.

In addition, many other classes of drugs, i.e. tricyclic antidepressants, phenothiazines, antihistamines, disopyramide possess significant antimuscarinic actions.

The natural alkaloids are found in plants of the solanaceae family: atropine in *Atropa belladonna* and *Datura stramonium,* hyoscine in *Hyoscyamus niger*. The levo-isomers are much more active than the dextroisomers. Atropine is racemic while scopolamine is *l*-hyoscine.

PHARMACOLOGICAL ACTIONS (Atropine as prototype)

The actions of atropine can be largely predicted from knowledge of parasympathetic responses. Prominent effects are seen in organs which normally receive strong parasympathetic tone. It blocks all subtypes of muscarinic receptors.

1. CNS Atropine has an overall CNS stimulant action. However, these effects are not appreciable at low doses which produce peripheral effects because of restricted entry into the brain.

- Atropine stimulates many medullary centres —vagal, respiratory, vasomotor.
- It depresses vestibular excitation and has antimotion sickness property.
- By blocking the relative cholinergic overactivity in basal ganglia, it suppresses tremor and rigidity of parkinsonism.
- High doses cause cortical excitation, restlessness, disorientation, hallucinations and delirium followed by respiratory depression and coma.

Hyoscine differs from atropine in producing depressant (drowsiness, amnesia, fatigue) effects at low doses.

2. CVS

Heart The most prominent effect of atropine is to cause tachycardia. It is due to blockade of M_2 receptors on SA node through which vagal tone decreases HR. Higher the existing vagal tone—more marked is the tachycardia (maximum in young adults, less in children and elderly). On i.m./s.c. injection, transient initial bradycardia often occurs. Earlier believed to be due to vagal centre stimulation, it is now thought to be caused by blockade of muscarinic autoreceptors (M_1) on vagal nerve endings augmenting ACh release. Atropine abbreviates refractory period of A-V node and facilitates A-V conduction, especially if it has been depressed by high vagal tone. P-R interval is shortened.

BP Since cholinergic impulses are not involved in maintenance of vascular tone, atropine does not have any consistent or marked effect on BP. Tachycardia and vasomotor centre stimulation tend to raise BP while histamine release and direct vasodilator action (at high doses) tend to lower BP.

Atropine blocks vasodepressor action of cholinergic agonists.

3. Eye The autonomic control of iris muscles and the action of mydriatics as well as miotics is illustrated in Fig. 5.5. Topical instillation of atropine causes mydriasis, abolition of light reflex and cycloplegia lasting 7–10 days. This results in photophobia and blurring of near vision. The ciliary muscles recover somewhat earlier than sphincter pupillae. The intraocular tension tends to rise, especially in narrow angle glaucoma; conventional systemic doses produce minor ocular effects.

4. Smooth muscles All visceral smooth muscles that receive parasympathetic motor innerva-

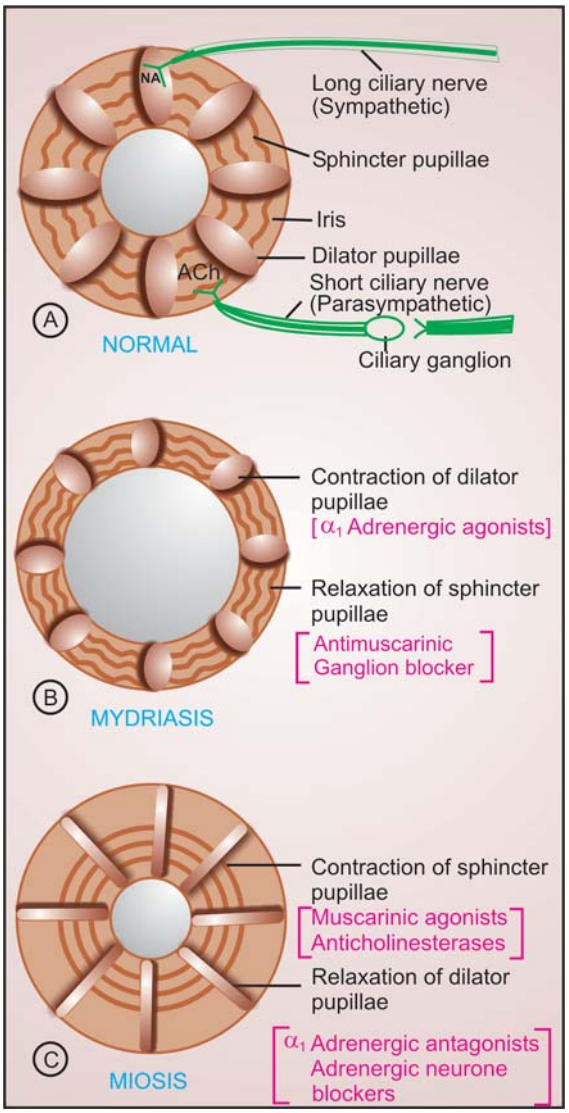


Fig. 5.5: Autonomic control of pupil (A); and site of action of mydriatics (B) and miotics (C)

tion are relaxed by atropine (M_3 blockade). Tone and amplitude of contractions of stomach and intestine are reduced; the passage of chyme is slowed—constipation may occur, spasm may be relieved. However, peristalsis is only incompletely suppressed because it is primarily regulated by local reflexes and other neurotransmitters (5-HT, enkephalin, etc.).

Atropine causes bronchodilatation and reduces airway resistance, especially in COPD and asthma patients. Inflammatory mediators like histamine, PGs and kinins increase vagal activity in addition to their direct action on bronchial muscle and glands. Atropine attenuates their action by antagonizing the reflex vagal component.

Atropine has a relaxant action on ureter and urinary bladder; urinary retention can occur in older males with prostatic hypertrophy. However, the same can be beneficial for increasing bladder capacity and controlling detrusor hyperreflexia in neurogenic bladder/enuresis. Relaxation of biliary tract is less marked and effect on uterus is minimal.

5. Glands Atropine markedly decreases sweat, salivary, tracheobronchial and lacrimal secretion (M_3 blockade). Skin and eyes become dry, talking and swallowing may be difficult.

Atropine decreases secretion of acid, pepsin and mucus in the stomach, but the primary action is on volume of secretion so that pH of gastric contents may not be elevated unless diluted by food. Relatively higher doses are needed and atropine is less efficacious than H_2 blockers in reducing acid secretion. Intestinal and pancreatic secretions are not significantly reduced. Bile production is not under cholinergic control, so not affected.

6. Body temperature Rise in body temperature occurs at higher doses. It is due to both inhibition of sweating as well as stimulation of temperature regulating centre in the hypothalamus. Children are highly susceptible to atropine fever.

The sensitivity of different organs and tissues to atropine varies and can be graded as—

Saliva, sweat, bronchial secretion > eye, bronchial muscle, heart > smooth muscle of intestine, bladder > gastric glands and smooth muscle.

PHARMACOKINETICS

Atropine and hyoscine are rapidly absorbed from g.i.t. Applied to eyes, they freely penetrate cornea.

Passage across blood-brain barrier is somewhat restricted. About 50% of atropine is metabolized in liver and rest is excreted unchanged in urine. It has a t½ of 3–4 hours. Hyoscine is more completely metabolized and has better blood-brain barrier penetration.

ATROPINE SUBSTITUTES

Many semisynthetic derivatives of belladonna alkaloids and a large number of synthetic compounds have been introduced with the aim of producing more selective action on certain functions. Most of these differ only marginally from the natural alkaloids.

Hyoscine butyl bromide and *atropine methonitrate* are quaternary derivatives which do not produce CNS effects and are used mainly for colics and functional g.i. disorders.

Ipratropium bromide is given by inhalation in bronchial asthma and chronic obstructive pulmonary disease (COPD). Unlike atropine, it does not depress mucociliary clearance by bronchial epithelium.

Propantheline, oxyphenonium, clidinium are synthetic quaternary anticholinergics mainly used as antisecretory-antispasmodic.

Glycopyrrolate acts rapidly and is almost exclusively employed before and during anaesthesia.

Dicyclomine has additional direct smooth muscle relaxant and antiemetic properties; has been used in morning sickness, motion sickness, irritable bowel and dysmenorrhoea.

Oxybutynin and *flavoxate* are relatively vasicoselective anticholinergics with direct smooth muscle relaxant property; used for detrusor instability, urinary frequency and urge incontinence.

Pirenzepine is a selective M_1 antimuscarinic which inhibits gastric secretion with few atropinic side effects.

Homatropine, cyclopentolate, tropicamide are used exclusively as mydriatic and cycloplegic. They have quicker and briefer action than atropine.

Trihexyphenidyl, procyclidine and *biperiden* have more prominent central antimuscarinic action: are used in parkinsonism.

USES (of atropine and its congeners)

1. Preanaesthetic medication: To check increased salivary and tracheobronchial secretions due to irritant general anaesthetics, prevent reflex laryngospasm and to block vagal reflexes. Atropine and glycopyrrolate are occasionally employed to prevent salivation during dental procedures and oral surgery.
2. Abdominal cramps/colics, ureteric colic, functional g.i. disorders. Use of atropinic drugs in peptic ulcer is now obsolete.
3. To relieve urinary frequency and urgency in neurogenic disorders, enuresis in children.
4. Pulmonary embolism: Atropine benefits by reducing reflex respiratory secretions.
5. Bronchial asthma and COPD: Inhaled ipratropium bromide is particularly useful in COPD and as adjuvant to inhaled β_2 agonists in severe/refractory bronchial asthma.
6. As mydriatic and cycloplegic for refraction testing and fundoscopy: tropicamide is preferred because of quickest and briefest action. The long-lasting mydriatic-cycloplegic action of atropine is very valuable for giving rest to intraocular muscles in iritis, iridocyclitis, choroiditis, keratitis and corneal ulcer.
7. To block vagal bradycardia in selected cases of myocardial infarction and digitalis toxicity.
8. Parkinsonism: Central anticholinergics reduce tremor and rigidity by counteracting unbalanced cholinergic activity in striatum.
9. Motion sickness: Hyoscine is highly effective, especially valuable for vigorous motions. Dicyclomine is used in milder cases.
10. Atropine is the specific antidote for anticholinesterase and early mushroom poisoning (due to muscarine). It is also used to block the muscarinic side effects of neostigmine.

SIDE EFFECTS AND TOXICITY

Side effects are quite common with the use of atropine and its congeners; are due to facets of its action other than for which it is being used. They cause inconvenience but are rarely serious.

Belladonna poisoning may occur due to drug overdose or consumption of seeds and berries of belladonna/datura plant. Children are highly susceptible. Manifestations are due to exaggerated pharmacological actions.

Dry mouth, difficulty in swallowing and talking.
Dry, flushed and hot skin (especially over face and neck), fever, difficulty in micturition, a scarlet rash may appear.
Dilated pupil, photophobia, blurring of near vision, palpitation.
Excitement, psychotic behaviour, ataxia, delirium, hallucinations.
Hypotension, weak and rapid pulse, cardiovascular collapse with respiratory depression. Convulsions and coma occur only in severe poisoning.

Treatment If poison has been ingested, gastric lavage should be done with tannic acid ($KMnO_4$ is ineffective in oxidizing atropine). The patient should be kept in a dark quiet room. Cold sponging or ice bags are applied for reducing body temperature. Physostigmine 1–3 mg s.c. or i.v. antagonizes both central and peripheral effects. It may be repeated 4–6 hourly. Neostigmine is less satisfactory.

Other general measures (maintenance of blood volume, artificial respiration, diazepam to control convulsions) should be taken as appropriate.

Contraindications Atropinic drugs are absolutely contraindicated in individuals with a narrow iridocorneal angle—may precipitate acute congestive glaucoma. However, marked rise in intraocular tension is rare in patients with wide angle glaucoma.

Caution is advocated in elderly males with prostatic hypertrophy—urinary retention can occur.

Interactions

1. Absorption of most drugs is slowed because atropine delays gastric emptying. Extent of digoxin and tetracycline absorption may be increased due to longer transit time in the g.i.t.
2. Antihistaminics, tricyclic antidepressants, phenothiazines, disopyramide, pethidine have anticholinergic property—additive side effects occur with atropinic drugs.

DRUGS ACTING ON AUTONOMIC GANGLIA

Acetylcholine is the primary excitatory neurotransmitter in both sympathetic and parasympathetic ganglia.

Drugs can either stimulate or block the ganglia.

Ganglionic stimulants

Selective nicotinic agonists	*Nonselective/muscarinic agonists*
Nicotine (small dose)	Acetylcholine
Lobeline	Carbachol
Dimethyl phenyl piperazinium iodide (DMPP)	Pilocarpine
Tetramethyl ammonium (TMA)	Anticholinesterases
	MCN 343-A

Nicotine (from *Nicotiana tabacum*) is important in the context of smoking or chewing tobacco, but there is no clinical application of ganglionic stimulants, because no useful purpose can be served by stimulating both sympathetic and parasympathetic ganglia concurrently.

Nicotine transdermal has recently become available for treatment of nicotine dependence and as an aid to smoking cessation.

Ganglion blocking agents

A. *Competitive blockers*

Quaternary ammonium compounds
- Hexamethonium
- Pentolinium

Amines (secondary/tertiary)
- Mecamylamine
- Pempidine

Monosulfonium compound
- Trimethaphan camforsulfonate

B. *Persistent depolarising blockers*
- Nicotine (large dose)
- Anticholinesterases (large dose)

The competitive ganglion blockers were used in the 1950s for hypertension and peptic ulcer, but have been totally replaced now because they produce a number of intolerable side effects.

There is at present no clinical relevance of ganglion blockers.

CHAPTER

6

Drugs Acting on Autonomic Nervous System

Adrenergic and Antiadrenergic Drugs

ADRENERGIC TRANSMISSION

Adrenergic (more precisely 'Noradrenergic') transmission is restricted to the sympathetic division of the ANS. There are three closely related endogenous catecholamines (CAs).

Noradrenaline (NA) It acts as transmitter at post-ganglionic sympathetic sites (except sweat glands, hair follicles and some vasodilator fibres) and in certain areas of brain.

Adrenaline (Adr) It is secreted by adrenal medulla and may have a transmitter role in the brain.

Dopamine (DA) It is a major transmitter in basal ganglia, limbic system, CTZ, anterior pituitary, etc. and in a limited manner in the periphery.

1. *Synthesis of CAs* Catecholamines are synthesized from the amino acid phenylalanine as depicted in Fig. 6.1. Synthesis of NA occurs in all adrenergic neurones, while that of Adr occurs only in the adrenal medullary cells and probably requires high concentration of glucocorticoids through intra-adrenal portal circulation for induction of the methylating enzyme.

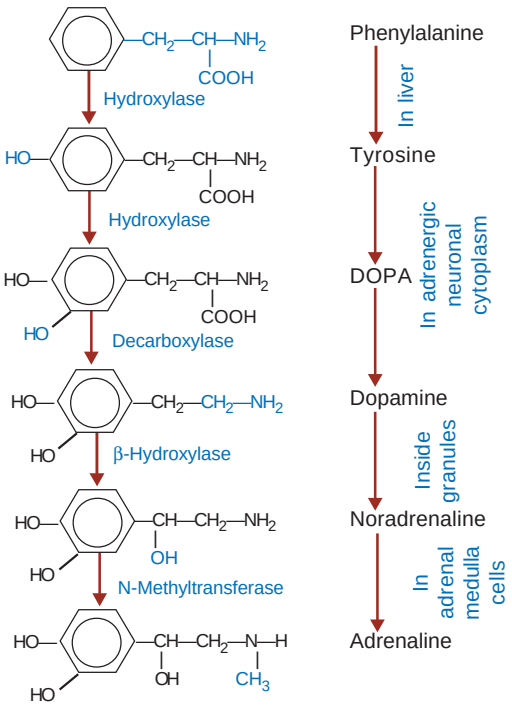


Fig. 6.1: Steps in the synthesis of catecholamines

2. *Storage of CAs* NA is stored in synaptic vesicles or 'granules' within the adrenergic nerve terminal (*see* Fig. 6.4). The granular membrane actively takes up DA from the cytoplasm and the final step of synthesis of NA takes place inside the granule which contains dopamine β-hydroxylase. NA is then stored as a complex with ATP (in a ratio of 4:1). The cytoplasmic pool of CAs is kept low by the enzyme monoamine oxidase (MAO) present on the outer surface of mitochondria.

3. *Release of CAs* The nerve impulse coupled release of CA takes place by *exocytosis* (*see* p. 68) and all the granular contents (NA or Adr, ATP, dopa-

mine β hydroxylase, chromogranin) are poured out. The release is modulated by presynaptic receptors, of which α_2 inhibitory control is dominant.

Indirectly acting sympathomimetic amines (tyramine, etc.) also induce release of NA, but they do so by displacing NA from the nerve ending binding sites and by exchange diffusion utilizing amine carrier of uptake-1 (*see* below). This process is not exocytotic and does not require Ca^{2+}.

4. *Uptake of CAs* There is a very efficient mechanism by which NA released from the nerve terminal is recaptured. This occurs in two steps—

Axonal uptake An active amine pump is present at the neuronal membrane which transports NA at a higher rate than Adr (uptake-1). The indirectly acting sympathomimetic amines also utilize this pump for entering the neurone. This uptake is the most important mechanism for terminating the postjunctional action of NA and is inhibited by cocaine, desipramine and its congeners.

Granular uptake The membrane of intracellular granules has another amine pump which transports CA from the cytoplasm to within the granule. The granular NA is constantly leaking out into the axoplasm and is recaptured by this mechanism. This carrier also takes up DA formed in the axoplasm for further synthesis to NA. Thus, it is very important in maintaining the NA content of the neurone. This uptake is inhibited by reserpine.

5. *Metabolism of CAs* The pathways of metabolism of CAs are depicted in Fig. 6.2. Part of the NA leaking out from granules into cytoplasm as well as that taken up by axonal transport is first attacked by MAO, while that which diffuses into circulation is first acted upon by catechol-o-methyl transferase (COMT) in liver and other tissues. The other enzyme can subsequently act to produce vanillylmandelic acid (VMA). The major metabolites excreted in urine are VMA and 3-methoxy-4-hydroxy phenylethylene glycol (a reduced product) along with some metanephrine, normetanephrine and 3,4 dihydroxy mandelic acid. These metabolites are mostly conjugated with glucuronic acid or sulfate before excretion in urine. However, metabolism does not play an important role in terminating the action of endogenous CAs.

6. *Adrenergic receptors* Adrenergic receptors are membrane bound G-protein coupled receptors which function primarily by increasing or decreasing the intracellular production of second messengers cAMP or IP_3/DAG. In some cases, the activated G-protein itself operates K^+ or Ca^{2+} channels, or increases prostaglandin production.

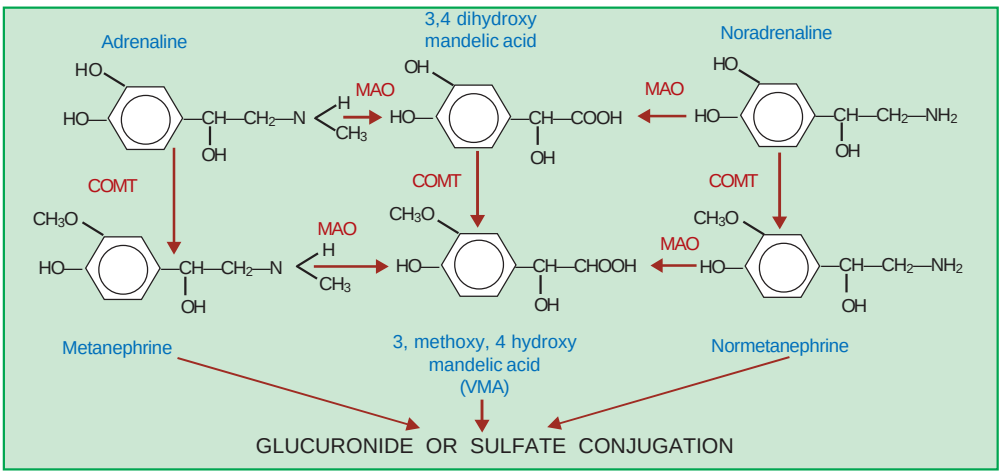


Fig. 6.2: Metabolism of catecholamines

Table 6.1: Differences between α and β adrenergic receptors

	α	β
1. Rank order of potency of agonists	Adr > NA > Iso	Iso > Adr > NA
2. Antagonist	Phenoxybenzamine	Propranolol
3. Effector pathway	$IP_3/DAG\uparrow$, cAMP ↓, K^+ channel ↑	cAMP↑, Ca^{2+} channel ↑

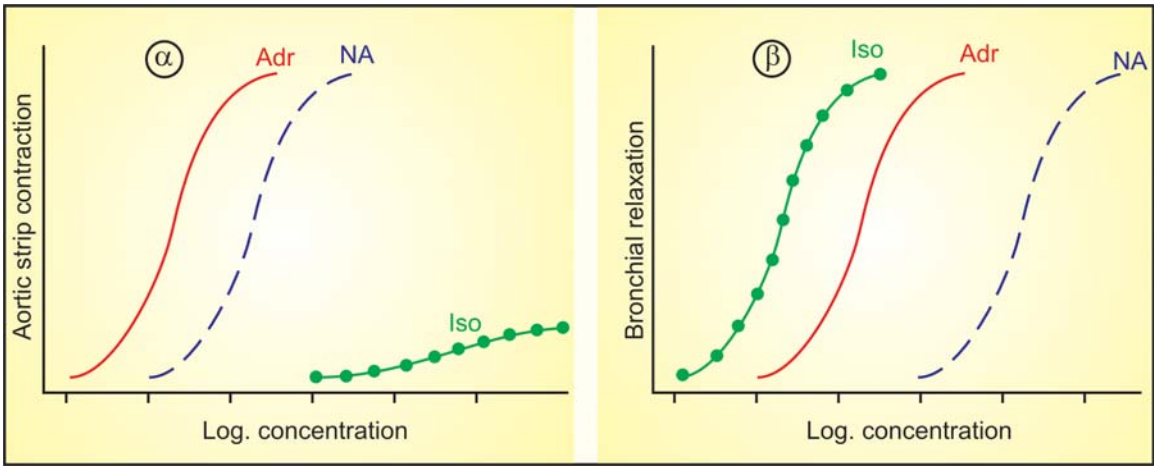


Fig. 6.3: Dose-response curves of 3 catecholamines adrenaline (Adr), noradrenaline (NA) and isoprenaline (Iso) on isolated aortic strip and isolated bronchial smooth muscle illustrating two distinct rank orders of potencies respectively for α and β adrenergic receptors

Ahlquist (1948), on the basis of two distinct rank order of potencies of adrenergic agonists (Fig. 6.3), classified adrenergic receptors into two types α and β. This classification was then confirmed by the development of selective α and β adrenergic antagonists. Important features of α and β receptors are given in Table 6.1.

On the basis of relative organ specificity of selective agonists and antagonists, the β receptors were further subdivided into β_1 (cardiac) and β_2 (bronchial, vascular, uterine) subtypes. The β_1 receptors are preferentially activated by dobutamine and blocked by metoprolol, while β_2 receptors are selectively activated by salbutamol and blocked by α-methyl propranolol.

Similarly, subtypes of α adrenoceptor have also been identified. The α_1 subtype is located only postjunctionally. Phenylephrine and prazosin respectively are its selective agonist and antagonist. The α_2 subtype is present both pre- and postjuctionally. It is selectively activated by clonidine and blocked by yohimbine.

The adrenergic neuronal mechanisms and action of drugs which modify them are depicted in Fig. 6.4. A summary of drugs acting through adrenergic neuronal mechanisms is presented in Table 6.2.

ADRENERGIC DRUGS (Sympathomimetics)

These are drugs with actions similar to that of Adr or of sympathetic stimulation.

Direct sympathomimetics They act directly as agonists on α and/or β adrenoceptors —Adr, NA, isoprenaline (Iso), phenylephrine, methoxamine, xylometazoline, salbutamol and many others.

Indirect sympathomimetics They act on adrenergic neurone to release NA which then acts on the adrenoceptors—tyramine.

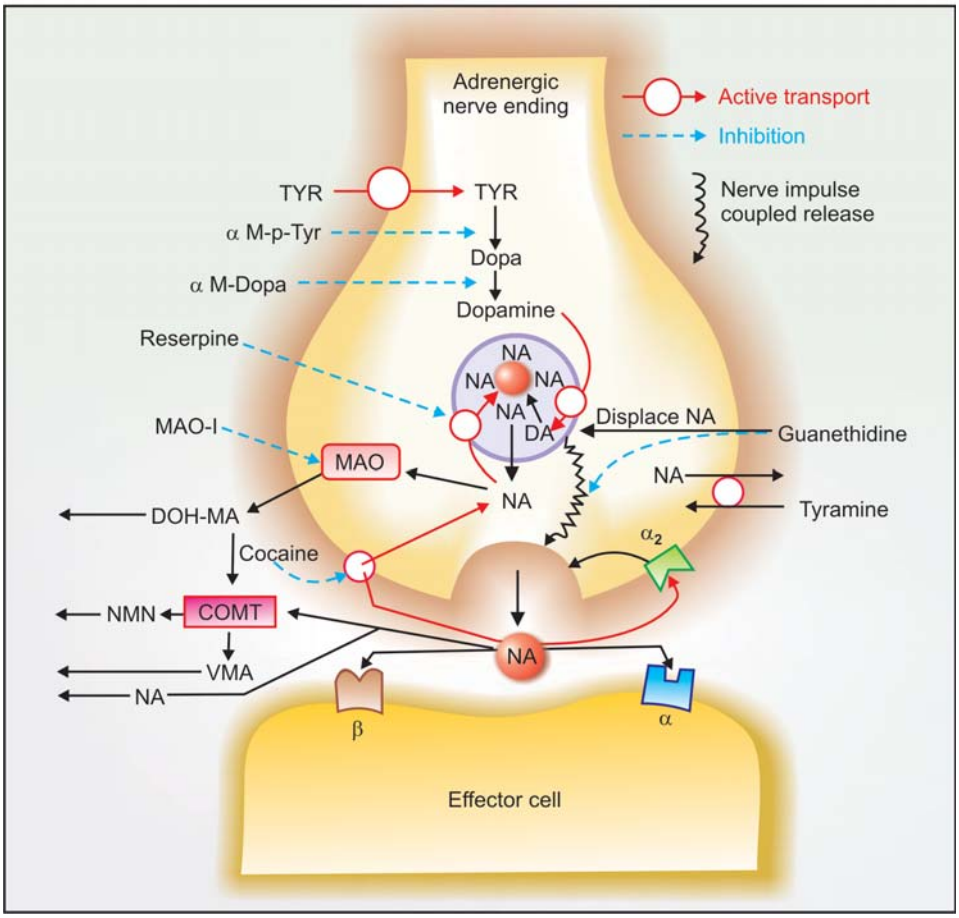


Fig.6.4: Schematic representation of adrenergic neurotransmission and its modification by drugs TYR—tyrosine; α M-p-TYR—α methyl-p-tyrosine; α M-DOPA—α methyl dopa; MAO— monoamineoxidase; MAOI—monoamine oxidase inhibitor; COMT—catechol-o-methyl transferase; DOH-MA—dihydroxy mandelic acid, NMN—nor-metanephrine; VMA—vanillyl mandelic acid

Mixed action sympathomimetics They act directly as well as indirectly—ephedrine, amphetamine, mephentermine.

ACTIONS

The peripheral actions of Adr in most tissues have been clearly differentiated into those mediated by α or β receptors depending on the predominant receptor type present in a given tissue. These are tabulated in Table 6.3. The receptor subtype, wherever defined, has been mentioned in parenthesis. The actions of a particular sympathomimetic amine depend on its relative activity at different types of adrenergic receptors.

Adr : $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$
NA: $\alpha_1 + \alpha_2 + \beta_1$ but no β_2 action
Iso: $\beta_1 + \beta_2$ but no α action

Important actions of Adr, NA and Iso are compared in Table 6.4.

Table 6.2: Summary of drug action through modification of adrenergic transmission

	Step/site	*Action*	*Drug*	*Response*
1.	Synthesis of NA	Inhibition Utilisation of same synthetic pathway	α-methyl-p-tyrosine α-methyl dopa	Depletion of NA Replacement of NA by α-methyl NA (false transmitter)
2.	Axonal uptake	Blockade	Cocaine, desipramine, guanethidine	Potentiation of NA (endo-and exogenous), inhibition of tyramine
3.	Granular uptake	Blockade	Reserpine	Depletion of NA (degraded by MAO)
4.	Nerve impulse coupled release of NA	Inhibition	Guanethidine, bretylium	Loss of transmission
5.	Granular NA	Displacement	Guanethidine	Initially sympathomimetic, depletion later
6.	Membrane NA pool	Exchange diffusion	Tyramine, ephedrine	Indirect sympathomimetic
7.	Metabolism	MAO inhibition	Nialamide tranylcypromine	Potentiation of NA (slight), —of tyramine (marked)
		COMT inhibition	Tolcapone, entacapone	Potentiation of NA (slight)
8.	Receptors	Mimicking	Phenylephrine	α_1 sympathomimetic
			Clonidine	α_2–inhibition of NA release, ↓ sympathetic outflow
			Isoprenaline	$\beta_1 + \beta_2$ —sympathomimetic
			Salbutamol	β_2—sympathomimetic
		Blockade	Phenoxybenzamine	$\alpha_1 + \alpha_2$—blockade
			Prazosin	α_1—blockade
			Yohimbine	α_2—blockade
			Propranolol	$\beta_1 + \beta_2$—blockade
			Metoprolol	β_1—blockade

The overall actions are —

1. Heart Adr increases heart rate by increasing automaticity of SA node. It also activates latent pacemakers in A-V node and Purkinje fibres; arrhythmias can occur with high doses that raise BP markedly. Certain anaesthetics (chloroform, halothane) sensitize the heart to arrhythmic action of Adr. Idioventricular rate is increased in patients with complete heart block.

Force of cardiac contraction is increased. Cardiac output and oxygen consumption of the heart are markedly enhanced.

Conduction velocity through A-V node, bundle of His, atrial and ventricular fibres is increased; partial A-V block may be overcome. Refractory period (RP) of all types of cardiac cells is reduced. All cardiac actions are predominantly β_1 receptor mediated.

When BP rises markedly, reflex bradycardia occurs due to stimulation of vagus— this is the usual response seen when NA is injected i.v.

2. Blood vessels Both vasoconstriction (α) and vasodilatation (β_2) can occur depending on the drug, its dose and vascular bed. Constriction predominates in cutaneous, mucous membrane and renal beds. Vasoconstriction occurs through both α_1 and α_2 receptors. Dilatation predominates in skeletal muscles, liver and coronaries. The direct effect on cerebral vessels is not prominent—blood flow through this bed parallels change in BP.

Table 6.3: Adrenergic responses mediated through α and β receptors

	α actions	*β actions*
1.	Constriction of arterioles and veins → rise in BP (mainly α_1)	Dilatation of arterioles and veins → fall in BP (β_2)
2.	Heart—little action, arrhythmia at high dose (α_1)	Cardiac stimulation (β_1), ↑ rate, force and conduction velocity
3.	—	Bronchodilatation (β_2)
4.	Contraction of radial muscles of iris → mydriasis (α_1), decreased aqueous secretion	No effect on iris and ciliary muscle Enhanced aqueous secretion
5.	Intestinal relaxation, contraction of sphincters	Intestinal relaxation (β_2)
6.	Bladder trigone—contraction	Detrusor—relaxation
7.	Uterus—contraction	Relaxation (β_2)
8.	Splenic capsule—contraction	Relaxation (β_2) (slight)
9.	Neuromuscular transmission facilitated, ↑ ACh release	Active state—prolonged in fast contracting muscle, abbreviated in slow contracting muscle; tremors (β_2)
10.	Insulin secretion inhibited (α_2) (dominant)	Augmented insulin (mild) and glucagon secretion (β_2)
11.	Liver—glycogenolysis (α in some species)	Liver—glycogenolysis (β_2) → hyperglycaemia Muscle—glycogenolysis (β_2) → hyperlactacidaemia Fat—lipolysis (β_3) → increased blood FFA, calorigenesis
12.	—	Renin release from kidney (β_1)
13.	Male sex organs—ejaculation	—
14.	Salivary gland—K^+ and water secretion (α_1)	Ptylin secretion
15.	—	ADH secretion from posterior pituitary (β_1)
16.	Nictitating membrane—contraction (in animals)	—

Action is most marked on arterioles; larger arteries and veins are affected at higher doses.

3. BP The effect depends on the amine, its dose and rate of administration.

- NA causes rise in systolic, diastolic and mean BP; it does not cause vasodilatation (no β_2 action), peripheral resistance increases consistently due to α action.
- Iso causes rise in systolic but marked fall in diastolic BP (β_1—cardiac stimulation, β_2—vasodilatation). The mean BP generally falls.
- Adr given by slow i.v. infusion or s.c. injection causes rise in systolic but fall in diastolic BP; peripheral resistance decreases because vascular β_2 receptors are more sensitive than α receptors. Mean BP generally rises. Pulse pressure is increased.

When an α blocker has been given, only fall in BP is seen—*vasomotor reversal of Dale.*

4. Respiration Adr and Iso but not NA are potent bronchodilators (β_2). This action is more marked when the bronchi are constricted. Adr can directly stimulate respiratory centre (RC), but this action is seldom manifest at clinically used doses.

5. Eye Mydriasis occurs due to contraction of radial muscles of iris (α_1), but this is minimal after topical application because Adr penetrates cornea poorly. The intraocular tension tends to fall, especially in wide angle glaucoma due to both reduction in aqueous formation and facilitation of outflow.

6. GIT In isolated preparations of gut relaxation occurs through activation of both α and β

receptors. In intact animals and man, peristalsis is reduced and sphincters are constricted, but the effects are brief and of no clinical import.

7. Bladder Detrusor is relaxed (β) and trigone is constricted (α): both actions tend to hinder micturition.

8. Uterus Adr can both contract or relax uterine muscle through respectively α and β receptors; effect varies with species, hormonal and gestational status. Human uterus at term of pregnancy is relaxed by Adr; while at other times, its contractions are enhanced.

9. Skeletal muscle Adr facilitates neuromuscular transmission. However, incomplete fusion of individual muscle fibre contractions along with enhanced firing of muscle spindles is responsible for the tremors produced by β_2 agonists.

10. CNS Adr, in clinically used doses, does not produce any marked CNS effects because of poor penetration in brain, but restlessness, apprehension and tremor may occur. Activation of α_2 receptors in the brainstem results in decreased sympathetic outflow → fall in BP and bradycardia.

11. Metabolic Adr produces glycogenolysis—hyperglycaemia, hyperlactacidaemia (β_2); lipolysis—rise in plasma free fatty acid (FFA), calorigenesis (β_2 + β_3) and transient hyperkalaemia followed by hypokalaemia due to direct action on liver, muscle and adipose tissue cells. In addition, metabolic effects result from reduction of insulin (α_2) and augmentation of glucagon (β_2) secretion.

Biochemical mediation of adrenergic responses

β actions The β actions are mediated through cAMP (*see* Fig. 3.4). Adr activates membrane bound enzyme *adenylyl cyclase* through a regulatory protein Gs → ATP is broken down to cAMP at the inner face. This in turn phosphorylates a number of intracellular cAMP-dependent protein kinases and initiates a series of reactions.

α actions The mediation of α actions is varied and less well defined. Vascular and other muscle contractions are mediated through IP_3/DAG production and mobilization of intracellular Ca^{2+}. In other tissues, inhibition of cAMP production and hyperpolarization through K^+ channel activation mediates the α adrenergic responses.

Table 6.4: Comparative effects of adrenaline, noradrenaline and isoprenaline

	Adr	*NA*	*Iso*
1. Heart rate	↑	↓	↑↑
2. Cardiac output	↑↑	–	↑↑
3. BP—Systolic	↑↑	↑↑	↑
Diastolic	↓↑	↑↑	↓↓
Mean	↑	↑↑	↓
4. Blood flow			
Skin and mm	↓	↓	–
Sk. muscle	↑↑	–, ↓	↑
Kidney	↓	↓	–
Liver	↑↑	–	↑
Coronary	↑	↑	↑
5. Bronchial muscle	↓↓	–	↓↓
6. Intestinal muscle	↓↓	↓	↓
7. Blood sugar	↑↑	–, ↑	↑

Administration CAs are absorbed from the intestine but are rapidly degraded by MAO and COMT present in the intestinal wall and liver. They are thus orally inactive. For systemic effects *Adrenaline (epinephrine)* is administered by s.c. or i.m. injection in a dose of 0.2–0.5 mg; action lasts 0.5–2 hours. In dental practice, it is used as a local vasoconstrictor added to lignocaine in a concentration of 1 in 200,000 to 100,000 for dental anaesthesia.

ADRENALINE 1 mg/ml inj.; in XYLOCAINE with ADRENALINE: Lignocaine 21.3 mg + Adrenaline 0.005 mg per ml inj, 30 ml vial.

Noradrenaline (*norepinephrine*, *levarterenol*) is administered only by slow i.v. infusion at the rate of 2–4 µg/min, for raising BP in emergency situations.

Adverse effects and contraindications

- Transient restlessness, palpitation, anxiety, tremor, pallor may occur after s.c./i.m. injection of Adr.
- Marked rise in BP leading to cerebral haemorrhage, ventricular tachycardia/fibrillation, angina, myocardial infarction are the hazards of large doses or inadvertant i.v. injection of Adr.

- Adr is contraindicated in hypertensive, hyperthyroid and angina patients.
- Adr mixed local anaesthetic should be used very cautiously for dental anaesthesia in patients with heart disease.
- It should not be given during anaesthesia with halothane (risk of arrhythmias) and to patients receiving β blockers (marked rise in BP can occur).

THERAPEUTIC CLASSIFICATION OF ADRENERGIC DRUGS

I. *Pressor agents*
- Noradrenaline
- Ephedrine
- Dopamine
- Phenylephrine
- Methoxamine
- Mephentermine

II. *Cardiac stimulants*
- Adrenaline
- Isoprenaline
- Dobutamine

III. *Bronchodilators*
- Isoprenaline
- Salbutamol (Albuterol)
- Terbutaline
- Salmeterol
- Formoterol

IV. *Nasal decongestants*
- Phenylephrine
- Xylometazoline
- Oxymetazoline
- Naphazoline
- Pseudoephedrine
- Phenyl propanolamine

V. *CNS stimulants*
- Amphetamine
- Dexamphetamine
- Methamphetamine

VI. *Anorectics*
- Fenfluramine
- Dexfenfluramine
- Sibutramine

VII. *Uterine relaxant and vasodilators*
- Ritodrine
- Isoxsuprine
- Salbutamol
- Terbutaline

Salient features of important adrenergic drugs are summarized below:

Dopamine (DA) It is a dopamine (D_1 and D_2) as well as adrenergic α and β_1 (but not β_2) agonist. The D_1 receptors in renal and mesenteric blood vessels are the most sensitive: i.v. infusion of low dose of DA dilates these vessels increasing g.f.r. and Na^+ excretion. Moderately high doses produce a positive inotropic effect on heart. Vasoconstriction (α_1 action) occurs only when large doses are infused. At doses normally infused i.v. (0.2–1 mg/min), it raises cardiac output and systolic BP with little effect on diastolic BP. This is useful in cardiogenic and septic shock.

Dobutamine A derivative of DA, but not a D_1 or D_2 receptor agonist. Though it acts on both α and β adrenergic receptors, the only prominent action of clinically employed doses (2.5–10 µg/kg/min i.v. infusion) is increase in force of cardiac contraction and output. It is used as an inotropic agent in pump failure accompanying myocardial infarction, cardiac surgery, and for short-term management of severe congestive heart failure.

Ephedrine It is an alkaloid obtained from *Ephedra vulgaris*. Mainly acts indirectly but has some direct action on α and β receptors also. Repeated injections produce tachyphylaxis, primarily because the neuronal pool of NA available for displacement is small. It is resistant to MAO, therefore, effective orally. It crosses to brain and causes stimulation.

Ephedrine is now occasionally used in mild chronic bronchial asthma and for hypotension during spinal anaesthesia.

Amphetamines These are synthetic compounds having the same pharmacological profile as ephedrine; orally active with long duration (4–6 hr). The CNS actions are more prominent; maximal selectivity is exhibited by dextroamphetamine and methamphetamine, which in the usual doses produce few peripheral effects.

The central effects include alertness, increased concentration and attention span, euphoria, talkativeness, increased work capacity. Fatigue is allayed. Athletic performance is improved temporarily followed by deterioration. It is one of the drugs included in the 'dope test' for athletes. The reticular activating system is stimulated resulting

in wakefulness and postponement of sleep deprivation induced physical disability. But this is short lived and may be accompanied by anxiety, restlessness, tremor, dysphoria and agitation.

Amphetamines stimulate respiratory centre, especially if it has been depressed. Hunger is suppressed as a result of inhibition of hypothalamic feeding centre. Peripheral effects on heart and BP are not significant at the usual doses, but tone of vesical sphincter is definitely increased.

Amphetamines are drugs of abuse and are capable of producing marked psychological but little or no physical dependence. Amphetamine abusers are generally teenagers seeking thrill or kick which is obtained on rapid i.v. injection. High doses produce euphoria, marked excitement which may progress to mental confusion, delirium, hallucinations and an acute psychotic state.

Repeated use is likely to produce long-lasting behavioural abnormalities; psychosis may be precipitated.

Phenylephrine It is a selective α_1 agonist, has negligible β action. It raises BP by causing vasoconstriction. Topically, it is used as a nasal decongestant and for producing mydriasis when cycloplegia is not required. It is also a constituent of orally administered nasal decongestant preparations.

Methoxamine Another selective α_1 stimulant with no β actions; occasionally used as a pressor agent.

Mephentermine It produces both cardiac stimulation and vasoconstriction by directly activating α and β adrenergic receptors as well as by releasing NA. It is used to prevent and treat hypotension due to spinal anaesthesia, shock and other hypotensive states.

SELECTIVE β_2 STIMULANTS

These include, salbutamol, terbutaline, salmeterol, formoterol and ritodrine. They cause bronchodilatation, vasodilatation and uterine relaxation, without producing significant cardiac stimulation. β_2 selectivity is only relative. Salbutamol has β_2:β_1 action ratio of about 10 . They are primarily used in bronchial asthma and as uterine relaxant to delay premature labour.

The most important side effect is muscle tremor.

NASAL DECONGESTANTS

These are α agonists which on topical application as dilute solution (0.05–0.1%) produce local vasoconstriction. The imidazoline compounds—xylometazoline and oxymetazoline are relatively selective α_2 agonist (like clonidine). They have a longer duration of action (12 hr) than ephedrine. Rise in BP can occur in hypertensives after nasal instillation.

Phenylpropanolamine (PPA) Chemically and pharmacologically similar to ephedrine; causes vasoconstriction and has some amphetamine like CNS effects. It is included in a large number of oral cold/decongestant combination remedies; but has been banned in the USA because of possible risk of haemorrhagic stroke when used as appetite suppressant in relatively larger doses.

ANORECTIC AGENTS

A number of drugs related to amphetamine have been developed which inhibit feeding centre but have little/no CNS stimulant action or abuse liability. All of them act by inhibiting the reuptake of NA/DA or 5-HT, enhancing monoaminergic transmission in the brain.

Fenfluramine and its dextroisomer *dexfenfluramine* reduce food seeking behaviour by enhancing serotonergic transmission in the hypothalamus; have no stimulant property. However, tolerance to the anorectic action develops and use beyond 3 months is not recommended. The US-FDA has prohibited their use.

Sibutramine is a newer antiobesity drug which inhibits both NA and 5-HT reuptake. It reduces appetite and may in addition stimulate thermogenesis resulting in weight loss. The safety of this drug is under review.

THERAPEUTIC USES

1. *Hypotensive states* (shock, spinal anaesthesia, hypotensive drugs) One of the pressor agents can be used along with volume replacement for neurogenic and haemorrhagic shock, also as an expedient measure to maintain cerebral circulation in other hypotensive states. Slow i.v. infusion of dopamine is more appropriate, while use of NA is practically obsolete. Adr 0.5 mg injected promptly i.m. is the drug of choice in anaphylactic shock (*see* p 59). It not only raises BP, but counteracts bronchospasm/laryngeal edema that may accompany. Because of the rapidity and profile of action, it is the only life-saving measure.

2. *Along with local anaesthetics* Adr 1 in 100,000 or 1 in 200,000 for infiltration, nerve block and spinal anaesthesia. Duration of anaesthesia is prolonged and systemic toxicity of local anaesthetic is reduced. It is routinely included in dental anaesthesia; serves to reduce bleeding as well.

3. *Control of local bleeding* From skin, mucous membranes, tooth socket, epistaxis, etc: compresses or packs of Adr 1 in 10,000, soaked in cotton can control arteriolar and capillary bleeding.

4. *Nasal decongestant* In colds, rhinitis, sinusitis, blocked eustachian tube—one of the α-agonists is used as nasal drops.

5. *Cardiac arrest* (drowning, electrocution, Stokes-Adams syndrome and other causes) Adr injected i.v. may be used to stimulate the heart along with external cardiac massage.

6. *Partial or complete A-V block* Iso may be used as temporary measure to maintain sufficient ventricular rate.

7. *Congestive heart failure* Adrenergic inotropic drugs are not useful in the routine treatment of CHF. However, controlled short-term i.v. infusion of DA/dobutamine can tide over acute cardiac decompensation during myocardial infarction, cardiac surgery and in resistant CHF.

8. *Bronchial asthma* Adrenergic drugs, especially β_2 stimulants, are the primary drugs for relief of reversible airway obstruction.

9. *Allergic disorders* Adr is life saving in laryngeal edema and anaphylaxis, and can afford quick relief in urticaria, angioedema of mouth/face, etc., because it is a physiological antagonist of histamine.

10. *Mydriatic* Phenylephrine is used to facilitate fundus examination; cycloplegia is not required. It tends to reduce intraocular tension in wide angle glaucoma. The ester prodrug of Adr dipivefrine is a second choice/adjuvant drug for open angle glaucoma.

11. *Narcolepsy* Narcolepsy is sleep occurring in fits, and is adequately controlled by amphetamines.

12. *Hyperkinetic children* (minimal brain dysfunction, attention deficit hyperkinetic disorder): Amphetamines have an apparently paradoxical effect to calm down hyperkinetic children. By increasing attention span, they improve behaviour and performance in studies.

13. *Obesity* The anorectic drugs can help the obese to tolerate a reducing diet for short periods, but do not improve the long-term outlook. Their use (for 2–3 months) may be considered in severe obesity.

14. *Uterine relaxant* Selective β_2 stimulants, especially ritodrine, infused i.v. have been successfully used to postpone labour. Isoxsuprine has been used in threatened abortion, but efficacy is doubtful.

15. *Insulin hypoglycaemia* Adr may be used as an expedient measure, but glucose should be given as soon as possible.

ANTIADRENERGIC DRUGS (ADRENERGIC RECEPTOR ANTAGONISTS)

These are drugs which antagonize the receptor action of adrenaline and related drugs. They are

competitive antagonists at α or β or both types of adrenergic receptors.

α ADRENERGIC BLOCKING AGENTS

These drugs inhibit adrenergic responses mediated through the α adrenergic receptors without affecting those mediated through β receptors.

CLASSIFICATION

I. *Nonequilibrium type*
β-*Haloalkylamines*—Phenoxybenzamine.

II. *Equilibrium type (competitive)*

A. Nonselective
(i) *Ergot alkaloids*—Ergotamine, Ergotoxine.
(ii) *Hydrogenated ergot alkaloids*—Dihydroergotamine (DHE), Dihydroergotoxine.
(iii) *Imidazolines*—Tolazoline, Phentolamine.
(iv) *Miscellaneous*—Chlorpromazine, Ketanserin.

B. α_1 selective—Prazosin, Terazosin, Doxazosin, Tamsulosin.

C. α_2 selective—Yohimbine.

GENERAL EFFECTS OF α BLOCKERS

1. Blockade of vasoconstrictor α_1 (also α_2) receptors reduces peripheral resistance and causes pooling of blood in capacitance vessels → venous return and cardiac output are reduced → fall in BP. Postural reflex is interfered with → marked hypotension occurs on standing → dizziness and syncope. Hypovolemia accentuates the hypotension. Special care must be taken to ensure that patients receiving an α blocker (e.g. prazosin for hypertension or benign prostatic hypertrophy) do not suddenly stand up after being supine on the dental chair. Also, these patients are more prone to develop hypotension if they bleed during the dental procedure. The α blockers abolish pressor action of Adr which then produces only fall in BP due to β_2 mediated vasodilatation—*vasomotor reversal of Dale*. Pressor and other actions of selective α agonists (NA, phenylephrine) are suppressed.

2. Reflex tachycardia occurs due to fall in mean arterial pressure and increased release of NA due to blockade of presynaptic α_2 receptors.

3. Nasal stuffiness and miosis result from blockade of α receptors in nasal blood vessels and in radial muscles of iris respectively.

4. Intestinal motility is increased due to partial inhibition of relaxant sympathetic influences—diarrhoea may occur.

5. Hypotension produced by α blockers can reduce renal blood flow → g.f.r. is reduced and more complete reabsorption of Na^+ and water occurs in the tubules → Na^+ retention and increase in blood volume. This is accentuated by reflex increase in renin release mediated through β_1 receptors.

6. Tone of smooth muscle in bladder trigone, sphincter and prostate is reduced by blockade of α_1 receptors (mostly of the α_{1A} subtype) → urine flow in patients with benign hypertrophy of prostate (BHP) is improved.

7. Contractions of vas deferens and related organs which result in ejaculation are coordinated through α receptors—α blockers can inhibit ejaculation; this may manifest as impotence.

The α blockers have no effect on adrenergically induced cardiac stimulation, bronchodilatation, vasodilatation and most of the metabolic changes, because these are mediated predominantly through β receptors.

Apart from these common effects, most of which manifest as side effects, many α blockers have some additional actions. Their pharmacological profile is also governed by their central effects and by the relative activity on α_1 and α_2 receptor subtypes.

Side effects that may occur with any α blocker are—palpitation, postural hypotension, nasal blockage, loose motions, fluid retention, inhibition of ejaculation and impotence.

Distinctive features of important α adrenergic blockers are given below:

Phenoxybenzamine It cyclizes spontaneously in the body giving rise to a highly reactive ethyleniminium intermediate which reacts with

α adrenoceptors and other biomolecules by forming strong covalent bonds. The α blockade develops gradually (even after i.v. injection) and lasts 3–4 days.

In isolated preparations low concentrations cause DRC of NA to shift to right without suppression of maxima (till spare receptors are available); higher concentrations progressively flatten the DRC and nonequilibrium antagonism is manifested. Increased release of NA from sympathetic nerves (due to α_2 blockade) occurs and reflex tachycardia is prominent.

The fall in BP caused by phenoxybenzamine is mainly postural. It tends to shift fluid from extravascular to vascular compartment because of relatively greater relaxation of postcapillary than precapillary vessels. Phenoxybenzamine is lipid soluble, penetrates brain and can produce CNS stimulation, nausea and vomiting on rapid i.v. injection. However, oral doses produce depression, tiredness and lethargy.

Phenoxybenzamine has been used primarily in pheochromocytoma; occasionally in secondary shock and peripheral vascular disease.

Natural and hydrogenated ergot alkaloids The amino acid alkaloids *ergotamine* and *ergotoxine* are partial agonists and antagonists at α adrenergic, serotonergic and dopaminergic receptors. The amine alkaloid *ergometrine* has no α blocking activity.

The natural ergot alkaloids produce long-lasting vasoconstriction which predominates over their α blocking action—peripheral vascular insufficiency and gangrene of toes and fingers occurs in ergotism. Hydrogenation reduces vasoconstrictor and increases α blocking activity.

The principal use is in migraine. Diagnostic use of ergotamine has been made to precipitate ECG signs of ischaemia in coronary artery disease. Dihydroergotoxine has been used as a cognition enhancer.

Phentolamine It is a rapidly acting α blocker with short duration of action (in minutes) which has been utilized for diagnosis and intraoperative management of pheochromocytoma and for control of hypertension due to clonidine withdrawal, cheese reaction, etc.

Prazosin It is first of the highly selective α_1 blockers having $\alpha_1 : \alpha_2$ selectivity ratio 1000:1. It blocks sympathetically mediated vasoconstriction and produces fall in BP which is attended by only mild tachycardia; NA release is not increased due to absence of α_2 blockade.

Prazosin dilates arterioles more than veins. Postural hypotension occurs, especially in the beginning—dizziness and fainting as 'first dose effect'. This can be minimized by starting with a low dose and taking it at bedtime.

Prazosin is primarily used as an antihypertensive. Other uses are—LVF not controlled by diuretics and digitalis, Raynaud's disease and prostatic hypertrophy—blocks α_1 receptors in bladder trigone and prostate and thus improves urine flow, reduces residual urine in bladder.

Terazosin and doxazosin are longer acting congeners of prazosin suitable for once daily dosing, particularly in BHP.

Tamsulosin is relatively uroselective due to higher affinity for α_{1A} subtype of α_1 receptors which predominate in the bladder base and prostate. Thus, it does not cause significant changes in BP or HR at doses which relieve urinary symptoms of BHP. No increase in adverse cardiovascular events, including postural hypotension has been noted. Dizziness and retrograde ejaculation are the only significant side effects. Its modified release (MR) capsule needs only once daily dosing.

Yohimbine An alkaloid from West African plant *Yohimbehe*. It is a relatively selective α_2 blocker with short duration of action. It may cause congestion of genitals and has been claimed to be an aphrodisiac. This effect is only psychological.
There are no valid indications for clinical use of yohimbine.

USES OF α BLOCKERS

1. *Pheochromocytoma* It is a tumour of adrenal medullary cells. Excess CAs are secreted which can cause intermittent or persistent hypertension. Estimation of urinary CA metabolites

(VMA, normetanephrine) is diagnostic. In addition, a pharmacological test can be performed by injecting phentolamine 5 mg i.v. A fall in BP > 35 mmHg systolic or > 25 mmHg diastolic is indicative of pheochromocytoma.

Phenoxybenzamine can be used as definitive therapy for inoperable and malignant tumours. It is also employed before and during surgical removal of the tumour. Alternatively, phentolamine drip can be instituted during the operation.

2. *Hypertension* Prazosin and other selective α_1 blockers are useful antihypertensive drugs, but the nonselective $\alpha_1 + \alpha_2$ blockers have been a failure. However, phentolamine/phenoxybenzamine are of great value in controlling episodes of rise in BP during clonidine withdrawal and cheese reaction in patients on MAO inhibitors.

3. *Secondary shock* Shock due to blood or fluid loss is accompanied by reflex vasoconstriction. If volume replacement fails to reverse this (extremities remain pale and cold, pulse pressure does not improve), therapy with an α blocker (phenoxybenzamine i.v.) can help by counteracting vasoconstriction and improving tissue perfusion, shifting blood from extravascular to vascular compartment and from pulmonary to systemic circuit.

4. *Peripheral vascular diseases* The α blockers afford symptomatic relief when vasoconstriction is prominent as in Raynaud's phenomenon, but not when vascular obstruction is organic as in Buerger's disease.

5. *Benign hypertrophy of prostate (BHP)* The urinary obstruction caused by BHP has a static component due to increased size of prostate and a dynamic component due to increased tone of bladder neck/prostate smooth muscle. Since activation of α_1 adrenoceptors in bladder trigone, prostate and prostatic urethra increases smooth muscle tone, their blockade relaxes these structures, reducing dynamic obstruction, increasing urinary flow rate and causing more complete emptying of bladder in many patients of BHP.

Terazosin, doxazosin and tamsulosin are the peferred α_1 blockers because of once daily dosing. Tamsulosin appears to cause fewer vascular side effects because of relative α_{1A} selectivity.

6. *Migraine* Ergotamine is one of the most effective drugs to abort/terminate moderate-to-severe migraine attacks.

β ADRENERGIC BLOCKING AGENTS

These drugs inhibit adrenergic responses mediated through the β receptors. All β blockers are competitive antagonists.

CLASSIFICATION

Nonselective (β_1 and β_2)

a. *Without intrinsic sympathomimetic activity*
Propranolol, Sotalol, Timolol.

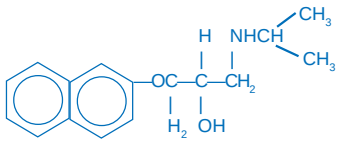
b. *With intrinsic sympathomimetic activity*
Pindolol, Oxprenolol.

c. *With additional α blocking property*
Labetalol, Carvedilol.

Cardioselective (β_1)

Metoprolol, Atenolol, Acebutolol, Bisoprolol, Esmolol, Betaxolol, Celiprolol, Nebivolol.

The pharmacology of propranolol is described as prototype.



PROPRANOLOL

PHARMACOLOGICAL ACTIONS

1. CVS

(a) Heart Propranolol decreases heart rate, force of contraction (at relatively higher doses) and cardiac output (c.o.). The effects on a normal resting subject are not appreciable, but become prominent under sympathetic overactivity (exercise, emotion).

Cardiac work and oxygen consumption are reduced as the product of heart rate and aortic

pressure decreases. Overall effect in angina patients is improvement of O_2 supply/demand status: exercise tolerance is increased.

Propranolol suppresses ectopic automaticity, especially if it has been augmented by adrenergic stimuli. The A-V conduction is delayed. At high doses, a direct depressant and membrane stabilizing (quinidine like) action is exerted, but this contributes little to the antiarrhythmic effect at usual doses. Propranolol blocks cardiac stimulant action of adrenergic drugs but not that of digoxin, Ca^{2+}, methylxanthines or glucagon.

(b) Blood vessels Propranolol blocks vasodilatation and fall in BP evoked by Iso and enhances the rise in BP caused by Adr—there is re-reversal of vasomotor reversal that is seen after α blockade. It has no direct effect on blood vessels and there is little acute change in BP. On prolonged administration, BP gradually falls in hypertensive subjects but not in normotensive. Total peripheral resistance (t.p.r.) is increased initially (due to blockade of β mediated vasodilatation) and c.o. is reduced—little change in BP. With continued treatment, resistance vessels gradually adapt to chronically reduced c.o. so that t.p.r. decreases—both systolic and diastolic BP fall. This is considered to be the most likely explanation of the antihypertensive action. Other mechanisms that may contribute are:

(i) Reduced NA release from sympathetic terminals.

(ii) Decreased renin release from kidney (β_1 mediated).

(iii) Central action reducing sympathetic outflow.

2. Respiratory tract Propranolol increases bronchial resistance by blocking β_2 receptors. The effect is hardly discernible in normal individuals because sympathetic bronchodilator tone is minimal. In asthmatics, however, the condition is consistently worsened and a severe attack may be precipitated.

3. CNS No overt central effects are produced by propranolol. However, subtle behavioural changes, forgetfulness, increased dreaming and nightmares have been reported with long-term use of relatively high doses.

4. Local anaesthetic Propranolol is as potent a local anaesthetic as lignocaine, but is not clinically used for this purpose because of its irritant property.

5. Metabolic Propranolol blocks adrenergically induced lipolysis and consequent increase in plasma free fatty acid levels. Plasma triglyceride level and LDL/HDL ratio is increased. It also inhibits glycogenolysis—recovery from insulin action is delayed. Though there is no effect on normal blood sugar level, prolonged propranolol therapy may reduce carbohydrate tolerance by decreasing insulin release.

6. Skeletal muscle Propranolol inhibits adrenergically provoked tremor. This is a peripheral action exerted directly on muscle fibre through β_2 receptors.

7. Eye Instillation of β blockers reduces secretion of aqueous humor: i.o.t. is lowered. There is no consistent effect on pupil size or accommodation.

PHARMACOKINETICS

Propranolol is well absorbed after oral administration, but has low bioavailability due to high first pass metabolism in liver. Oral: parenteral dose ratio of up to 40:1 has been found.

Metabolism of propranolol is dependent on hepatic blood flow. Chronic use of propranolol itself decreases hepatic blood flow—oral bioavailability is increased and its t½ is prolonged. Metabolites of propranolol, one of which is active, are excreted in urine.

INTERACTIONS

1. Additive depression of sinus node and A-V conduction with digitalis and verapamil—cardiac arrest can occur.
2. Propranolol delays recovery from hypoglycaemia due to insulin and oral antidiabetics.

Warning signs of hypoglycaemia mediated through sympathetic stimulation (tachycardia, tremor) are suppressed.
3. Phenylephrine, ephedrine and other α agonists present in cold remedies can cause marked rise in BP in β blocked subjects.
4. Indomethacin and other NSAIDs attenuate the antihypertensive action of β blockers.
5. Cimetidine inhibits propranolol metabolism.
6. Propranolol retards lignocaine metabolism by reducing hepatic blood flow.

ADVERSE EFFECTS AND CONTRAINDICATIONS

1. Propranolol can accentuate myocardial insufficiency and worsen CHF. However, when compensation has been restored, careful addition of a β_1 blocker is now established therapy to prolong survival.
2. Bradycardia: resting HR may be reduced to 60/min or less.
3. Propranolol worsens chronic obstructive lung disease; can precipitate life-threatening attack of bronchial asthma: contraindicated in asthmatics.
4. Propranolol exacerbates variant (Prinzmetal's) angina due to unopposed α mediated coronary constriction.
5. Carbohydrate tolerance may be impaired in prediabetics.
6. Plasma lipid profile is altered on long-term use.
7. Withdrawal of propranolol after chronic use should be gradual, otherwise rebound hypertension, worsening of angina and even sudden death can occur.
8. Propranolol is contraindicated in partial and complete heart block: arrest may occur.
9. Tiredness and reduced exercise capacity.
10. Cold hands and feet due to blockade of vasodilator β_2 receptors.
11. Side effects not overtly due to β blockade are—g.i.t. upset, lack of drive, nightmares, forgetfulness, rarely hallucinations. Male patients more frequently complain of sexual distress.

OTHER β BLOCKERS

A number of β blockers have been developed having some special features. The associated properties with their significance can be summarized as:

Cardioselectivity (in metoprolol, atenolol, acebutolol, bisoprolol, nebivolol).
These drugs are more potent in blocking cardiac (β_1) than bronchial (β_2) receptors. Their features are:
1. Lower propensity to cause bronchoconstriction.
2. Less interference with carbohydrate metabolism.
3. Lower incidence of cold hands and feet.
4. No/less deleterious effect on blood lipid profile.
5. Ineffective in suppressing essential tremor.
6. Less liable to impair exercise capacity.

Partial agonistic (intrinsic sympathomimetic) action (in pindolol, oxprenolol). They themselves activate β_1 and/or β_2 receptors submaximally.
1. Bradycardia and depression of contractility at rest are not prominent.
2. Withdrawal is less likely to exacerbate hypertension or angina.
3. Not effective in migraine prophylaxis—they dilate cerebral vessels.
4. Less suitable for secondary prophylaxis of MI.

Salient features of important β blockers are given below:

1. Sotalol Nonselective β blocker that has additional K^+ channel blocking and class III antiarrhythmic property.

2. Timolol It is a β blocker used topically in the eye for glaucoma.

Betaxolol and Levobunolol are other β blockers employed topically for glaucoma.

3. Pindolol A potent β blocker with prominent intrinsic sympathomimetic activity.

4. Metoprolol It is the prototype of cardioselective (β_1) blockers. Its potency to block cardiac

stimulation is similar to propranolol, but nearly 50 times higher dose is needed to block Iso induced vasodilatation. It is less likely to worsen asthma and it may be preferred in diabetics receiving insulin or oral hypoglycaemics.

5. Atenolol A relatively selective β_1 blocker having low lipid solubility. It is incompletely absorbed orally, but first pass metabolism is not significant. Because of longer duration of action, once daily dose is often sufficient. It is one of the most commonly used β blockers for hypertension and angina.

6. Esmolol It is an ultrashort acting β_1 blocker devoid of partial agonistic or membrane stabilizing actions. It is inactivated by esterases in blood; plasma t½ is < 10 min; action lasts 15–20 min after terminating i.v. infusion—degree of β blockade can be titrated by regulating rate of infusion.

It has been used to terminate supraventricular tachycardia, episodic atrial fibrillation or flutter, arrhythmia during anaesthesia, to reduce HR and BP during and after cardiac surgery, and in early treatment of myocardial infarction.

7. Nebivolol This cardioselective β blocker also acts as a nitric oxide (NO) donor: produces vasodilatation and has the potential to improve endothelial function.

USES

1. *Hypertension* β blockers are relatively mild antihypertensives. All agents, irrespective of associated properties, are nearly equally effective. They are one of the first choice drugs because of good patient acceptability (*see* Ch. 11).

2. *Angina pectoris* All β blockers benefit angina of effort. Taken on a regular schedule, they decrease frequency of attacks and increase exercise tolerance (*see* Ch. 11).

3. *Cardiac arrhythmias* β blockers suppress extrasystoles and tachycardias, especially those mediated adrenergically (during anaesthesia, digitalis induced)—may be used i.v. for this purpose. Esmolol is an alternative drug for paroxysmal supraventricular tachycardia (*see* Ch. 12).

4. *Myocardial infarction (MI)* In relation to MI, β blockers are used for two purposes:
(a) Secondary prophylaxis of MI: there is now firm evidence of benefit. Long-term use after recovery from MI has been found to decrease subsequent mortality by 20%.
(b) Myocardial salvage during evolution of MI: administered i.v. within 4–6 hours of an attack followed by continued oral therapy. β blockers—
(i) May limit infarct size by reducing O_2 consumption—marginal tissue which is partially ischaemic may survive.
(ii) May prevent arrhythmias including ventricular fibrillation.

However, β blockers can be given to only those patients not in shock or cardiac failure. In megatrials such therapy has been found to reduce mortality by 20–25%.

5. *Congestive heart failure* Although β blockers can worsen heart failure, several studies have reported beneficial haemodynamic effects of low doses of β_1 blockers in selected patients with dilated cardiomyopathy. Introduced gradually and maintained for long term, these drugs retard the progression of CHF and prolong life. The benefit may result from antagonism of deleterious effects of sympathetic overactivity on myocardium. Certain β_1 blockers used appropriately along with other measures under expert supervision is now considered standard therapy for most mild-to-moderate CHF patients.

6. *Dissecting aortic aneurysm* β blockers help by reducing cardiac contractile force and aortic pulsation.

7. *Pheochromocytoma* β blockers may be added to α blockers to control tachycardia and arrhythmia.

8. *Thyrotoxicosis* Propranolol rapidly controls symptoms (palpitation, nervousness, tremor,

fixed stare, severe myopathy and sweating) without significantly affecting thyroid status. It is used preoperatively and while awaiting response to antithyroid drugs/radioactive iodine.

9. *Migraine* Propranolol is the most effective drug for chronic prophylaxis of migraine (*see* p. 107).

10. *Anxiety* Propranolol exerts an apparent antianxiety effect, especially under conditions which provoke nervousness and panic, e.g. examination, unaccustomed public appearance, etc. This is probably due to blockade of peripheral manifestations of anxiety (palpitation, tremor) which have a reinforcing effect on anxiety.

11. *Essential tremor* Nonselective β blockers have an established place in treating essential tremor.

12. *Glaucoma* Timolol and other ocular β blockers are first choice drugs for chronic simple (wide angle) glaucoma; also used as adjuvant in angle closure glaucoma.

13. *Hypertrophic obstructive cardiomyopathy* The subaortic region is hypertrophic. β blockers improve c.o. in these patients during exercise, by reducing left ventricular outflow obstruction.

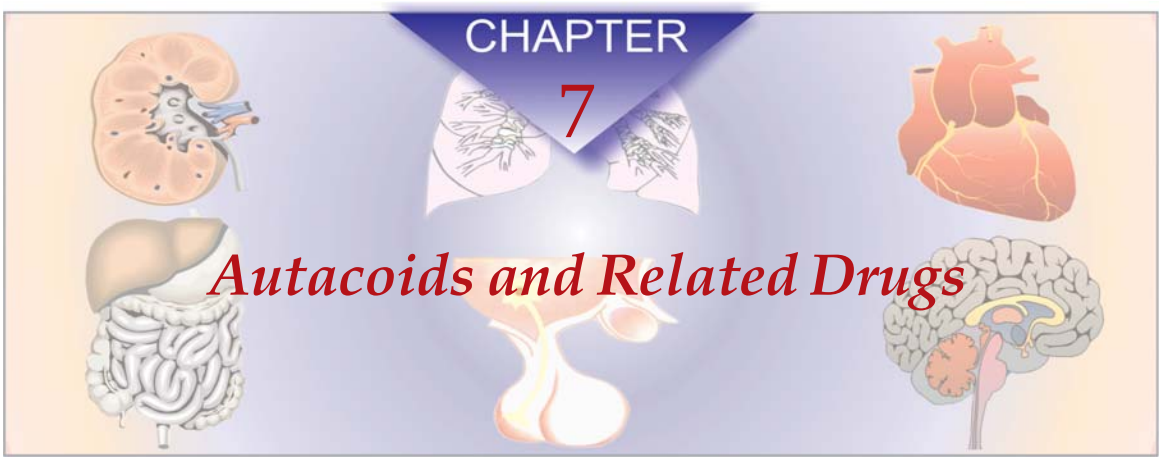
α + β ADRENERGIC BLOCKERS

Labetalol It is the first adrenergic antagonist capable of blocking both α and β receptors. The β blocking potency is about 1/3rd that of propranolol, while the α blocking potency is about 1/10th of phentolamine.

Labetalol is 5 times more potent in blocking β than α receptors. As such, effects of a low dose resemble those of propranolol alone; while at high doses, they are like a combination of propranolol and phenoxybenzamine. It causes fall in BP which is attended by no change or slight decrease in heart rate.

Labetalol is orally effective but undergoes considerable first pass metabolism. It is a moderately potent hypotensive and is specially useful in pheochromocytoma, clonidine withdrawal; can also be used in essential hypertension. Most important side effect is postural hypotension, though other side effects of α and β blockers can also occur.

Carvedilol It is a β_1 + β_2 + α_1 adrenoceptor blocker; produces vasodilatation due to α_1 blockade as well as direct action, and has antioxidant property. It has been used in hypertension and is the β blocker especially employed as cardioprotective in CHF.



Autacoid This term is derived from Greek: *autos*—self, *akos*—healing substance or remedy. These are diverse substances produced by a *wide variety of cells* in the body, having intense biological activity, but generally *act locally* (e.g. within inflammatory pockets) at the site of synthesis and release.

They have also been called 'local hormones'. However, they differ from 'hormones' in two important ways—hormones are produced by *specific cells*, and are transported through circulation to act on *distant target tissues*.

Autacoids are involved in a number of physiological and pathological processes (especially reaction to injury and immunological insult) and even serve as transmitters or modulators in the nervous system, but their role at many sites is not precisely known. A number of useful drugs act by modifying their action or metabolism. The classical autacoids are—

Amine autacoids Histamine, 5-Hydroxytryptamine (Serotonin).

Lipid-derived autacoids Prostaglandins, Leukotrienes, Platelet activating factor.

Peptide autacoids Plasma kinins (Bradykinin, Kallidin), Angiotensin.

In addition, cytokines (interleukins, TNFα, GM-CSF, etc.) and several peptides like gastrin, somatostatin, vasoactive intestinal peptide and many others may be considered as autacoids.

HISTAMINE

Histamine, meaning 'tissue amine' (*histos*—tissue) is almost ubiquitously present in animal tissues and in certain plants, e.g. stinging nettle.

Histamine is present mostly within storage granules of *mast cells*. Tissues rich in histamine are skin, gastric and intestinal mucosa, lungs, liver and placenta. Nonmast cell histamine occurs in brain, epidermis, gastric mucosa and growing regions. Turnover of mast cell histamine is slow, while that of nonmast cell histamine is fast. Histamine is also present in blood, most body secretions, venoms and pathological fluids.

Synthesis, storage and destruction Histamine is β imidazolylethylamine. It is synthesized locally from the amino acid histidine and degraded rapidly by oxidation and methylation (Fig. 7.1). Histamine is inactive orally because liver degrades all histamine that is absorbed from the intestines.

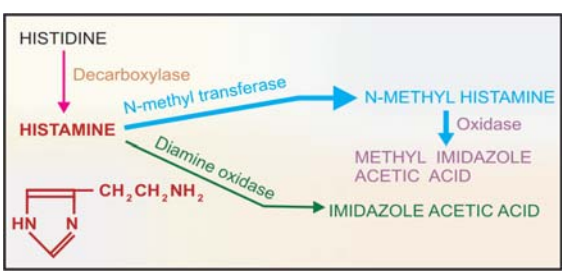


Fig. 7.1: Synthesis and degradation of histamine

Table 7.1: Distinctive features of H_1 and H_2 histaminergic receptors

	H_1	H_2
1. Selective agonists (relative selectivity H_1: H_2)	2-Methyl histamine (8:1) 2-Pyridylethylamine(30:1) 2-Thiazolyl ethylamine (90: 1)	4-Methyl histamine (1:170) Dimaprit (1:2000) Impromidine (1:10,000)
2. Selective antagonists (relative selectivity H_1: H_2)	Mepyramine (6000:1) Chlorpheniramine (15000:1)	Cimetidine (1: 500) Ranitidine (1 : >500)
3. Receptor type	G-protein coupled	G-protein coupled
4. Effector pathway	PIP_2 hydrolysis → IP_3/DAG : Release of Ca^{2+} from intracellular stores; Protein Kinase-C activation	Adenylyl cyclase activation — cAMP↑ — phosphorylation of specific proteins
5. Distribution in body: actions mediated	a) Smooth muscle (intestine, airway, uterus) — contraction b) Blood vessels i) Endothelium: Release of EDRF, PGI_2 — vasodilatation. widening of gap junctions — increased capillary permeability ii) Smooth muscle — vasoconstriction. c) Afferent nerve endings — stimulation d) Ganglionic cell — stimulation. e) Adrenal medulla — release of CAs. f) Brain—transmitter.	a) Gastric glands — acid secretion b) Blood vessels (smooth muscle) — dilatation c) Heart Atria: +ive chronotropy Ventricles: +ive inotropy d) Uterus (rat)—relaxation e) Brain — transmitter

PIP_2 — Phosphatidyl inositol bisphosphate; IP_3 — Inositol trisphosphate; DAG — Diacylglycerols: EDRF— Endothelium dependent relaxing factor: PGI_2 — Prostacyclin; CAs — Catecholamines: cAMP —Cyclic 3', 5' adenosine monophosphate; ACh — acetylcholine

Histamine receptors Analogous to adrenergic α and β receptors, histaminergic receptors are classified into H_1 and H_2; and a third H_3 receptor, which serves primarily as an autoreceptor controlling histamine release from neurones in brain has been lately identified, but is not of clinical importance. The important features of H_1 and H_2 histamine receptors are given in Table 7.1.

PHARMACOLOGICAL ACTIONS

1. Blood vessels Histamine causes marked dilatation of smaller blood vessels, including arterioles, capillaries and venules. On s.c. injection flushing, especially in the blush area, heat, increased heart rate and cardiac output, with little or no fall in BP are produced. Rapid i.v. injection causes fall in BP which has an early short-lasting H_1 and a slow but more persistent H_2 component. Dilatation of cranial vessels causes pulsatile headache.

Like ACh and many other autacoids, vasodilatation caused by histamine is partly (H_1 component) indirect, mediated through 'endothelium-dependent relaxing factor' (EDRF): the receptor being located on the endothelial cells. H_2 receptors mediating vasodilatation are located directly on the vascular smooth muscle. Histamine also causes increased capillary permeability due to separation of endothelial cells → exudation of plasma. This is primarily a H_1 response.

Injected intradermally, it elicits the *triple response* consisting of:

Red spot: due to intense capillary dilatation.
Wheal: due to exudation of fluid from capillaries and venules.

Flare: i.e. redness in the surrounding area due to arteriolar dilatation mediated by axon reflex.

2. Heart Direct effects of histamine on *in situ* heart are not prominent, but the isolated heart is stimulated.

3. Visceral smooth muscle Histamine causes bronchoconstriction; guineapigs and patients of asthma are highly sensitive. Large doses cause abdominal cramps and colic by increasing intestinal contractions. Other visceral smooth muscles are not much affected.

4. Glands Histamine causes marked increase in gastric secretion—primarily of acid but also of pepsin (*see* Ch. 18). This is a direct action exerted on parietal cells through H_2 receptors and is mediated by increased cAMP generation, which in turn activates the membrane proton pump (H^+ K^+ ATPase).

5. Sensory nerve endings Itching occurs when histamine is injected i.v. or intracutaneously. Higher concentrations injected more deeply cause pain.

6. Autonomic ganglia and adrenal medulla These are stimulated and release of Adr occurs, which can cause a secondary rise in BP.

7. CNS Histamine does not penetrate blood-brain barrier—no central effects are seen on i.v. injection. However, intracerebroventricular administration produces rise in BP, cardiac stimulation, behavioural arousal, hypothermia, vomiting and ADH release.

PATHOPHYSIOLOGICAL ROLES

1. *Gastric secretion* Histamine has dominant physiological role in mediating secretion of HCl in the stomach (*see* Fig. 18.1). Histamine is released locally under the influence of all stimuli that evoke gastric secretion (feeding, vagal stimulation, cholinergic drugs and gastrin) and activates the proton pump (K^+H^+ ATPase) through H_2 receptors to secrete HCl.

2. *Allergic phenomena* Released from mast cells following AG : AB reaction (involving IgE type of reaginic antibodies), histamine is causative in urticaria, angioedema, bronchoconstriction and anaphylactic shock. The H_1 antagonists are effective in controlling these manifestations to a considerable extent, except asthma and to a lesser extent anaphylactic fall in BP in which leukotrienes (especially LTD_4) and PAF appear to be more important. Histamine is not involved in delayed or retarded type of allergic reactions.

3. *As transmitter* Histamine is believed to be the afferent transmitter which initiates the sensation of itch and pain at sensory nerve endings.

In the brain, it is involved in maintaining wakefulness; (H_1 antihistaminics owe their sedative action to blockade of this function) and appears to regulate many other functions.

4. *Inflammation* Histamine has been implicated as a mediator of vasodilatation and other changes that occur during inflammation. It may also regulate microcirculation according to local needs.

5. *Headache* Histamine has been implicated in certain vascular headaches, but there is no conclusive evidence.

Histamine has no therapeutic use.

H_1 ANTAGONISTS (Conventional antihistaminics)

These drugs competitively antagonize actions of histamine at the H_1 receptors.

Pharmacological actions

Qualitatively all H_1 antihistaminics have similar actions, but there are quantitative differences, especially in the sedative property.

1. *Antagonism of histamine* They effectively block histamine induced bronchoconstriction, contraction of intestinal and other smooth muscle and triple response—especially wheal, flare and itch. Fall in BP produced by low doses of hista-

Table 7.2: Clinical classification, doses and preparations of H_1 antihistaminics

	Drug	*Dose and route*	*Preparations*
I.	*HIGHLY SEDATIVE*		
	Diphenhydramine	25–50 mg oral	BENADRYL 25 mg cap., 12.5 mg/5 ml syr.
	Dimenhydrinate	25–50 mg oral,	DRAMAMINE 16 mg/5 ml syr, 50 mg tab
	Promethazine	25–50 mg oral, i.m. (1 mg/kg)	PHENERGAN 10, 25 mg tab., 5 mg/ml elixer, 25 mg/ml inj
	Hydroxyzine	25–50 mg oral, i.m.	ATARAX 10, 25 mg tab., 10 mg/5 ml syr, 6 mg/ml drops, 25 mg/ml inj.
II.	*MODERATELY SEDATIVE*		
	Pheniramine	20–50 mg oral, i.m.	AVIL 25 mg, 50 mg tab, 15 mg/5 ml syr, 22.5 mg/ml inj.
	Cyproheptadine	4 mg oral	PRACTIN, CIPLACTIN 4 mg tab., 2 mg/5 ml syrup,
	Meclizine	25–50 mg oral	In DILIGAN 12.5 mg + niacin 50 mg tab
	Cinnarizine	25–50 mg oral	STUGERON, VERTIGON 25 and 75 mg tab.
III.	*MILD SEDATIVE*		
	Chlorpheniramine	2–4 mg (0.1 mg/kg) oral, i.m.	PIRITON 4 mg tab, POLARAMINE 2 mg tab, 0.5 mg/ 5 ml syr
	Triprolidine	2.5–5 mg oral	ACTIDIL 2.5 mg tab.
	Mebhydroline	100–300 mg oral	INCIDAL 50 mg (base) tab.
	Cyclizine	50 mg oral	MAREZINE 50 mg tab.
IV.	*SECOND GENERATION ANTIHISTAMINICS*		
	Fexofenadine	120–180 mg oral	ALLEGRA, ALTIVA, FEXO 120, 180 mg tab
	Astemizole	10 mg oral	STEMIZOLE, HISTALONG, STEMIZ, 5 mg, 10 mg tab., 1 mg/ml susp.
	Loratadine	10 mg oral	LORFAST, LORIDIN, LORMEG, 10 mg tab, 1 mg/ml susp.
	Desloratadine	5 mg oral	DESLOR 5 mg tab
	Cetirizine	10 mg oral	ALERID, CETZINE, ZIRTIN, SIZON 10 mg tab, 5 mg/5 ml syr.
	Azelastine	4 mg oral 0.28 mg intranasal	AZEP NASAL SPRAY 0.14 mg per puff nasal spray
	Mizolastine	10 mg oral	ELINA 10 mg tab
	Ebastine	10 mg oral	EBAST 10 mg tab

mine is blocked, but additional H_2 antagonists are required for complete blockade of higher doses. Action of histamine on gastric secretion is singularly not affected by these drugs.

2. *Antiallergic action* Many manifestations of immediate hypersensitivity (type I reactions) are suppressed. Urticaria, itching and angioedema are well controlled. Anaphylactic fall in BP is only partially prevented. Asthma in man is practically unaffected.

3. *CNS* The older antihistamines produce variable degree of CNS depression. This appears to depend on the compound's ability to penetrate blood-brain barrier and its affinity for the central (compared to peripheral) H_1 receptors. Individual susceptibility to different agents varies consi-

derably, but an overall grading of the sedative property is presented in Table 7.2. Some individuals also experience stimulant effects like restlessness and insomnia. Excitement and convulsions are frequently seen at toxic doses. The second generation antihistaminics are practically nonsedating.

Certain (*see* below) H_1 antihistamines are effective in preventing motion sickness. Promethazine also controls vomiting of pregnancy and other causes.

Promethazine and a few other antihistaminics reduce tremor, rigidity and sialorrhoea of parkinsonism. Anticholinergic and sedative properties underlie the benefit. Some H_1 antihistamines are used as antitussives (*see* Ch. 19).

4. *Anticholinergic action* Many H_1 blockers in addition antagonize muscarinic actions of ACh. The anticholinergic action can be graded as:

High	*Low*	*Minimal/Absent*
Promethazine	Chlorpheniramine	Fexofenadine
Diphenhydramine	Hydroxyzine	Astemizole
Dimenhydrinate	Triprolidine	Loratadine
Pheniramine	Cyclizine	Cetirizine
Cyproheptadine		Mizolastine

5. *Local anaesthetic* Some drugs have strong while others have weak membrane stabilizing property. However, they are not used clinically as local anaesthetic because they cause irritation when injected s.c.

Membrane stabilizing activity also confers antiarrhythmic property to these compounds.

6. *BP* Most antihistaminics cause a fall in BP on i.v. injection (direct smooth muscle relaxation). However, this is not evident on oral administration.

Pharmacokinetics The classical H_1 antihistaminics are well absorbed from oral and parenteral routes, metabolized in the liver and excreted in urine. They are widely distributed in the body and enter brain. The newer compounds penetrate brain poorly. Duration of action of most agents is 4–6 hours, except astemizole, loratadine, cetirizine and fexofenadine which act for 12–24 hours or more. On repeated use, many antihistamines induce their own metabolism.

Side effects and toxicity Side effects with first generation H_1 antihistaminics are frequent, but are generally mild. Individuals show marked differences in susceptibility to side effects with different drugs. Some tolerance to side effects develops on repeated use.

Sedation, diminished alertness and concentration, light headedness, motor incoordination, fatigue and tendency to fall asleep are the most common. Objective testing shows impairment of psychomotor performance. Patients should be cautioned not to operate motor vehicles or machinery requiring constant attention. Alcohol synergises in producing these effects as do other CNS depressants. Few individuals become restless, nervous and are unable to sleep. Second generation compounds are largely free of CNS effects.

Dryness of mouth, alteration of bowel movement, urinary hesitancy and blurring of vision can be ascribed to anticholinergic property.

Epigastric distress and headache are also common.

Local application can cause contact dermatitis.

SECOND GENERATION ANTIHISTAMINICS

The second generation antihistaminics (SGAs) may be defined as those H_1 receptor blockers marketed after 1980 which have one or more of the following properties:

- Higher H_1 selectivitiy: no anticholinergic side effects.
- Absence of CNS depressant property.
- Additional antiallergic mechanisms apart from histamine blockade.

These newer drugs have the advantage of not impairing psychomotor performance (driving, etc. need not be contraindicated), produce no subjective effects, no sleepiness, do not potentiate alcohol or benzodiazepines. Some patients do complain of sedation, but incidence is similar to placebo. However, they have a narrow spectrum of therapeutic usefulness which is limited by the

extent of involvement of histamine (acting through H_1 receptors) in the disease state. Their principal indications are:

(i) Allergic rhinitis and conjunctivitis, hay fever, pollinosis—control sneezing, runny but not blocked nose, and red, watering, itchy eyes.
(ii) Urticaria, dermographism, atopic eczema.
(iii) Acute allergic reactions to drugs and foods.

They have poor antipruritic, antiemetic and antitussive actions.

A life-threatening adverse effect due to overdose or drug interaction has occurred with some SGAs. Terfenadine, the first SGA introduced clinically, was found to cause polymorphic ventricular tachycardia (*Torsades de pointes*) in a few patients. The risk was markedly increased in liver disease or when erythromycin, clarithromycin, ketoconazole or itraconazole (inhibitors of CYP 3A4) were given concurrently. This adverse effect occurs due to blockade of cardiac K^+ channels by high concentrations of terfenadine (but not by its active carboxy metabolite). Similar incidences have been reported with astemizole and are possible with ebastine, but not with other SGAs. Terfenadine has been withdrawn by the manufacturers.

Fexofenadine It is the active metabolite of terfenadine that does not block delayed rectifier K^+ channels in the heart—does not prolong QTc interval. Therefore, it has been introduced as a substitute of terfenadine free of arrhythmogenic potential.

Astemizole It has slow onset (2–4 hr) and long duration (2–5 days) of action. An active metabolite is produced whose t½ is 12–19 days. Astemizole is better used for maintenance therapy and is not suitable for rapid control of symptoms. In perennial rhinitis it has shown good efficacy. However, it shares the ventricular tachycardia producing potential of terfenadine.

Loratadine Another long-acting selective peripheral H_1 antagonist which lacks CNS depressant effects and is faster acting than astemizole. Good efficacy has been reported in urticaria and atopic dermatitis.

Cetirizine This nonsedating antihistamine in addition inhibits release of histamine and cytotoxic mediators from platelets as well as eosinophil chemotaxis during the secondary phase of the allergic response. Thus, it may benefit allergic disorders by other actions as well. It is indicated in upper respiratory allergies, pollinosis, urticaria and atopic dermatitis; also used as adjuvant in seasonal asthma.

Azelastine This newer H_1 blocker has good topical activity. Given by nasal spray for seasonal and perennial allergic rhinitis it provides quick symptomatic relief lasting 12 hr. Stinging in the nose and altered taste perception are the local side effects.

USES

The uses of H_1 antihistaminics are based on their ability to block certain effects of histamine released endogeneously, as well as on sedative and anticholinergic properties.

1. *Allergic disorders* They do not suppress AG: AB reaction, but block the effects of released histamine—are only palliative. They effectively control certain immediate type of allergies, e.g. itching, urticaria, seasonal hay fever, allergic conjunctivitis and angioedema of lips, eyelids, etc. However, their action is slow—Adr alone is life saving in laryngeal angioedema. Similarly, they cannot be relied upon in anaphylactic shock and have a secondary place to Adr. Benefits are less marked in perennial vasomotor rhinitis, atopic dermatitis and chronic urticarias.
Certain newer compounds like cetirizine have adjuvant role in seasonal asthma.

Type I hypersensitivity reactions to drugs (except asthma and anaphylaxis) are suppressed. Some skin rashes also respond.

2. *Other conditions involving histamine* They afford symptomatic relief in insect bite and ivy poisoning. Abnormal dermographism is suppressed. They have prophylactic value in blood/saline infusion induced rigor.

3. *Pruritides* Though relief is often incomplete, older antihistaminics remain the first choice drugs for idiopathic pruritus.

4. *Common cold* Antihistaminics do not affect the course of the illness but may afford symptomatic relief by anticholinergic (reduce rhinorrhoea) and sedative actions. The newer nonsedating antihistamines are less effective in this respect.

5. *Motion sickness* Promethazine, diphenhydramine, dimenhydrinate and cyclizine have prophylactic value in milder types of motion sickness; should be taken one hour before starting journey. Promethazine can also be used in morning sickness, drug induced and postoperative vomiting.

6. *Vertigo* Cinnarizine is the H_1 antihistamine having additional anticholinergic, anti-5-HT, sedative and vasodilator properties which has been widely used in vertigo. It inhibits vestibular sensory nuclei in the inner ear, possibly by reducing stimulated influx of Ca^{2+} from endolymph into the vestibular sensory cells.

7. *Preanaesthetic medication* Promethazine has been used, especially in children, for its anticholinergic and sedative properties.

8. *Cough* Antihistaminics like chlorpheniramine, diphenhydramine, promethazine are constituents of many popular cough remedies. They have no selective cough suppressant action, but may afford symptomatic relief by sedative and anticholinergic action.

9. *Parkinsonism* Promethazine and some others afford mild symptomatic relief in early cases—based on anticholinergic and sedative property.

10. *Acute muscle dystonia* Caused by antiemetic-antipsychotic drugs is promptly relieved by parenteral promethazine or hydroxyzine. This is again based on central anticholinergic action of the drugs.

11. *As sedative, hypnotic, anxiolytic* Antihistamines with CNS depressant action have been used as sedative and to induce sleep, especially in children. They are not as dependable as benzodiazepines.

H_2 antagonists They are primarily used in peptic ulcer and other gastric hypersecretory states (*see* Ch. 18).

5-HYDROXYTRYPTAMINE (5-HT, Serotonin)

Serotonin was the name given to the vasoconstrictor substance which appeared in serum when blood clotted, and was shown to be *5-hydroxytryptamine* (5-HT). About 90% of body's content of 5-HT is localized in the intestines; most of the rest is in platelets and brain. It is also found in wasp and scorpion sting and widely distributed in invertebrates and plants (banana, pear, pineapple, tomato, stinging nettle, cowhage).

Synthesis, storage and destruction

5-HT is β-aminoethyl-5-hydroxyindole. It is synthesized from the amino acid tryptophan and degraded primarily by MAO and to a small extent by a dehydrogenase (Fig. 7.2).

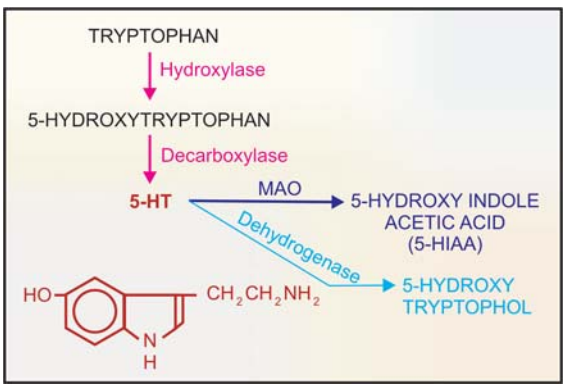


Fig. 7.2: Synthesis and degradation of 5-hydroxytryptamine (5-HT)

Like NA, 5-HT is actively taken up by an amine pump which operates at the membrane of platelets (therefore, 5-HT does not circulate in free form in plasma) and serotonergic nerve endings and is inhibited by tricyclic antidepressants. Platelets do not synthesize but acquire 5-HT by uptake during passage through intestinal blood vessels. Again, like CAs, 5-HT is stored within storage granules and its uptake at the granular membrane is inhibited by reserpine.

Serotonergic (5-HT) receptors

Four families of 5-HT receptors (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_{4-7}) comprising of 14 receptor subtypes have so far been recognized. However, only some of these have been functionally correlated or their selective agonists/antagonists defined. Knowledge of subtypes of 5-HT receptors has assumed importance because some newly developed therapeutically useful drugs can only be described as 5-HT receptor subtype selective agonists or antagonists.

Important 5-HT receptor subtypes

5-HT_1: Autoreceptors; inhibit serotonergic neural activity in brain.
5-HT_{1A}—present in raphe nuclei and hippocampus; buspirone appears to exert antianxiety action through these receptors.
5-$HT_{1B/1D}$—Constricts cranial blood vessels and inhibits release of inflammatory neuropeptides in them; sumatriptan controls migraine through these receptors.

5-HT_{2A}: Most important postjunctional receptor mediating direct actions of 5-HT like vascular and visceral smooth muscle contraction, platelet aggregation, neuronal activation in brain; ketanserin blocks these receptors.

5-HT_3: Depolarizes neurones by gating cation channels; elicits reflex effects of 5-HT—emesis, gut peristalsis, bradycardia, transient hypotension, apnoea, pain, itch; ondansetron acts as antiemetic by blocking these receptors.

5-HT_4: Mediate intestinal secretion, augmentation of peristalsis. Renzapride is a selective 5-HT_4 agonist.

All 5-HT receptors (except 5-HT_3) are G protein coupled receptors which function through decreasing (5-HT_1) or increasing (5-HT_4, 5-HT_6, 5-HT_7) cAMP production or by generating IP_3/DAG (5-HT_2) as second messengers. The 5-HT_3 is a ligand gated cation (Na^+, K^+) channel which on activation elicits fast depolarization.

Actions

5-HT is a potent depolarizer of nerve endings. It thus exerts direct as well as reflex and indirect effects. Tachyphylaxis is common with repeated doses of 5-HT. The overall effects, therefore, are often variable; important ones are:

1. Constriction of larger arteries and veins, but dilatation of arterioles: variable and phasic effect on BP.
2. Isolated heart is stimulated, but in the intact animal bradycardia due to coronary chemoreflex predominates.
3. Enhanced peristalsis and secretion in gut → diarrhoea.
4. Inhibition of gastric acid and pepsin secretion; augmentation of mucus production: ulceroprotective.
5. Activation of afferent nerve endings—tingling or pricking sensation, pain; cardiovascular and respiratory reflexes are elicited.
6. Proaggregatory action on platelets.

Pathophysiological roles ascribed to 5-HT are:

1. Neurotransmitter in brain, especially raphe nuclei, substantia nigra, limbic system, cortex, etc; involved in sleep, temperature regulation, cognitive function, behavior and mood, vomiting and pain perception.
2. Regulation of gut peristalsis by 5-HT containing neurones on enteric plexuses and enterochromaffin cells.
3. Precursor of melatonin in pineal gland: regulation of biological clock.
4. Control of anterior pituitary hormone function by hypothalamus.
5. Nausea and vomiting, especially that evoked by cancer chemotherapy/radiotherapy.
6. Migraine: probably involved in initiating constriction of cranial vessels and inducing neurogenic inflammation of vessel wall.

7. Haemostasis by promoting platelet aggregation and blood vessel retraction.
8. Vasospastic disorders like Raynaud's phenomenon and variant angina.
9. Carcinoid syndrome: mediates bowel hypermotility and bronchoconstriction.

5-HT ANTAGONISTS

The ability to antagonize at least some actions of 5-HT is found in many classes of drugs, e.g. ergot derivatives (ergotamine, LSD, 2-bromo LSD, methysergide), adrenergic α blockers (phenoxybenzamine), antihistaminics (cyproheptadine, cinnarizine), chlorpromazine, morphine, etc., but these are nonselective and interact with several other receptors as well. Drugs that have been used as 5-HT antagonists are:

1. Cyproheptadine It primarily blocks 5-HT_{2A} receptors and has additional H_1 antihistaminic, anticholinergic and sedative properties. Like other antihistaminics, it has been used in allergies and is a good antipruritic. It increases appetite and has been recommended in children and poor eaters to promote weight gain.

The anti-5-HT activity of cyproheptadine has been utilized in controlling intestinal manifestations of carcinoid and postgastrectomy dumping syndromes.

2. Methysergide Methysergide is a potent 5-$HT_{2A/2C}$ and weak 5-HT_1 antagonist. It has been used for migraine prophylaxis, carcinoid and postgastrectomy dumping syndrome.

3. Ketanserin It has 5-HT_2 receptor blocking property with negligible action on 5-HT_1, 5-HT_3 and 5-HT_4 receptors and no partial agonistic activity.

Ketanserin is an effective antihypertensive, but α_1 adrenergic blockade appears to be causative rather than 5-HT_{2A} blockade.

4. Clozapine In addition to being a dopaminergic antagonist (weaker than the typical neuroleptics), this atypical antipsychotic is a 5-$HT_{2A/2C}$ blocker (*see* Ch. 10).

5. Risperidone This atypical antipsychotic is a combined 5-HT_{2A} + dopamine D2 antagonist, similar to clozapine.

6. Ondansetron It is the prototype of the new class of selective 5-HT_3 antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of highly emetic anticancer drugs and radiotherapy.

ERGOT ALKALOIDS

Ergot is a fungus *Claviceps purpurea* which grows on rye, millet and some other grains. Epidemics of ergot poisoning (ergotism), due to consumption of contaminated grains, have been recorded from the beginning of history. It still occurs in epidemic and sporadic forms. Dry gangrene of hands and feet which become black (as if burnt) is the most prominent feature. Miscarriages occur in women and cattle. A convulsive type is also described.

Ergot contains a host of pharmacologically active substances—alkaloids, LSD, histamine, ACh, tyramine and other amines, sterols, etc.

Ergot alkaloids are tetracyclic indole containing compounds which may be considered as derivatives of *lysergic acid*. They are divided into—

(a) *Amine alkaloid* Ergometrine (Ergonovine): which is oxytocic.
(b) *Amino acid alkaloids* Ergotamine, Ergotoxine (mixture of ergocristine + ergocornine + ergocryptine): that are vasoconstrictor and α adrenergic blocker.

The ergot alkaloid-related compounds have diverse pharmacological properties. They act as agonists, partial agonists and antagonists on certain subtypes of α adrenergic, serotonergic and dopaminergic receptors: activity differing depending on the tissue.

Ergotamine It acts as a partial agonist and antagonist at α adrenergic and all subtypes of 5-HT_1 and 5-HT_2 receptors, produces sustained vasoconstriction, visceral smooth muscle contraction, vasomotor centre depression and antagonizes the action of NA and 5-HT on smooth muscles. It is a potent emetic (through CTZ) and moderately potent oxytocic.

Dihydroergotamine (DHE) Hydrogenation of ergotamine reduces serotonergic and α-adrener-

gic agonistic actions, but enhances α-receptor blocking property. Consequently, DHE is a less potent vasoconstrictor.

Dihydroergotoxine (Codergocrine) This hydrogenated mixture of ergotoxine group of alkaloids is a more potent α blocker and a very weak vasoconstrictor. It has been advocated for treatment of dementia.

Bromocriptine The 2 bromo derivative of ergocryptine is a relatively selective dopamine D2 agonist on pituitary lactotropes (inhibits prolactin release), in striatum (antiparkinsonian) and in CTZ (emetic—but less than ergotamine).

Ergometrine (Ergonovine) This amine ergot alkaloid has a very weak agonistic and practically no antagonistic action on α adrenergic receptors: vasoconstriction is not significant. Partial agonistic action on 5-HT receptors has been demonstrated in uterus, placental and umbilical blood vessels. The most prominent action is contraction of myometrium; used exclusively in obstetrics (*see* Ch. 15).

DRUG THERAPY OF MIGRAINE

Migraine is a mysterious disorder characterized by pulsating headache, usually restricted to one side, which comes in attacks lasting 4–48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, vertigo, loose motions and other symptoms. Two major types are—*migraine with aura* (classical migraine) in which headache is preceded by visual or other neurological symptoms, and *migraine without aura* (common migraine). Pulsatile dilatation of certain large cranial vessels is the immediate cause of pain. The pathogenic mechanisms are not well understood. Some triggering event appears to produce neurogenic inflammation of the affected blood vessel wall which is amplified by retrograde transmission in the afferent nerves and release of mediators like 5-HT, neurokinin, substance P, calcitonin gene-related peptide (CGRP), nitric oxide, etc.

Changes in blood/urinary levels of 5-HT and its metabolites during migraine attack, its precipitation by 5-HT releasers and efficacy of drugs having actions in the serotonergic system to prevent/abort/terminate migraine attacks suggests a pivotal role of 5-HT in this disorder.

Drug therapy of migraine has to be individualized: severity and frequency of attacks and response of individual patients to various drugs determine the choice. The strategy mostly adopted is summarized in the box.

Mild migraine Cases having fewer than one attack per month of throbbing but tolerable headache lasting up to 8 hours which does not incapacitate the individual may be classified as mild migraine.

(i) *Simple analgesics* like paracetamol (500 mg) or aspirin (300–600 mg) taken at the first indication of an attack and repeated 4–6 hourly abort and suppress most mild attacks.

(ii) *Nonsteroidal antiinflammatory drugs (NSAIDs) and their combinations* Drugs like ibuprofen (400–800 mg 8 hourly), diclofenac (50 mg 8 hourly), mephenamic acid (500 mg 8 hourly), either alone or combined with paracetamol/codeine/diazepam/diphenhydramine/caffeine are found more satisfactory by some patients. Drugs are taken only till the attack passes off. Taken in the prodromal stage they also have a prophylactic effect.

(iii) *Antiemetics* Metoclopramide (10 mg oral/i.m.) is frequently used. Domperidone (10–20 mg

Severity		Drug therapy
Mild	:	Simple analgesics/NSAIDs or their combinations (± antiemetic)
Moderate	:	NSAIDs combinations/ergot alkaloids/sumatriptan (+ antiemetic)
Severe	:	Ergot alkaloids/sumatriptan (+ antiemetic)
	+ Prophylaxis	• Propranolol/other β blockers • Amitriptyline/other tricyclic antidepressants • Flunarizine/other Ca^{2+} channel blockers • Methysergide/Cyproheptadine

oral) and prochlorperazine (10–25 mg oral/i.m.) are also effective.

Moderate migraine Migraine may be labelled as moderate when the throbbing headache is more intense, lasts for 6–24 hours, nausea/vomiting and other features are more prominent and the patient is functionally impaired.

Simple analgesics are usually not effective, but stronger NSAIDs or their combinations mentioned above are beneficial in many cases. The remaining are treated with an ergot preparation or sumatriptan. Antiemetics are almost regularly needed. Prophylactic therapy is advised only when attacks are more frequent than 2 to 3 per month.

Severe migraine These patients suffer more than 2 to 3 attacks per month of severe throbbing headache lasting 12–48 hours, often accompanied by vertigo, vomiting and other symptoms; the subject is grossly incapacitated during the attack.

Analgesics/NSAIDs and their combinations usually do not afford adequate relief—specific drugs like ergot alkaloids/sumatriptan have to be prescribed along with antiemetics. Prophylactic regimens lasting 6 months or more are recommended.

Ergotamine It is the most effective ergot alkaloid for migraine. Given early in attack, relief is often dramatic and lower doses suffice, but when pain has become severe—larger doses are needed and control may be achieved only after a few hours.

Ergotamine probably acts by constricting the dilated cranial vessels. It has also been shown to reduce neurogenic inflammation and leakage of plasma in duramater that occurs due to retrograde stimulation of perivascular afferent nerves. These actions appear to be mediated through partial agonism at 5-$HT_{1B/1D}$ receptors in and around cranial vessels.

Dihydroergotamine (DHE) It is nearly as effective as ergotamine and preferred for parenteral administration because injected DHE is less hazardous. Orally, it is a safer alternative to ergotamine in patients who respond to this drug.

Ergot alkaloids should be discontinued when relief is obtained. They have no prophylactic value. *Caffeine* 100 mg taken with ergotamine enhances its absorption from oral and rectal routes and adds to the cranial vasoconstricting action.

Sumatriptan This novel selective 5-$HT_{1B/1D}$ receptor agonist does not interact with 5-HT_2, 5-HT_3, 5-$HT_{4\text{-}7}$, α or β adrenergic, dopaminergic, cholinergic or GABA receptors. Administered at the onset of an attack of migraine sumatriptan is as effective and better tolerated than ergotamine. It tends to suppress nausea and vomiting of migraine, while ergotamine accentuates these symptoms. The antimigraine activity of sumatriptan has been ascribed to 5-$HT_{1B/1D}$ receptor mediated constriction of dilated cranial extracerebral blood vessels, especially the arteriovenous shunts in the carotid artery, which express 5-$HT_{1B/1D}$ receptors. Like ergotamine, the triptans have been found to suppress neurogenic inflammation of cranial vessels.

Side effects to sumatriptan are usually mild. Tightness in head and chest, feeling of heat and other paresthesias in limbs, dizziness, weakness are short lasting but dose-related side effects. Bradycardia, coronary vasospasm and risk of myocardial infarction are the serious but infrequent adverse effects.

It is contraindicated in patients with ischaemic heart disease, hypertension, epilepsy, hepatic or renal impairment and during pregnancy.

Prophylaxis of migraine

Regular medication to reduce the frequency and/or severity of attacks is recommended for moderate-to-severe migraine when more than 2 to 3 attacks occur per month. Diverse classes of drugs are used but none is effective in all cases, and none abolishes the attacks totally.

(i) *β-Adrenergic blockers* Propranolol is the most commonly used drug: reduces frequency as well as severity of attacks in up to 70% patients.

Effect is generally seen in 4 weeks and is sustained during prolonged therapy.

(ii) *Tricyclic antidepressants* Many tricyclic compounds, of which amitriptyline has been most extensively tried, reduce migraine attacks. It is effective in many patients but produces more side effects than propranolol.

(iii) *Calcium channel blockers* Flunarizine is claimed to be a cerebro-selective Ca^{2+} channel blocker which may benefit migraine by reducing intracellular Ca^{2+} overload due to brain hypoxia and other causes. It may reduce frequency of attacks, but effect on intensity and duration of attacks is less marked. Verapamil also has some prophylactic value in migraine.

The 5-HT antagonists methysergide and cyproheptadine have less impressive prophylactic effect in migraine and produce more side effects than propranolol.

PROSTAGLANDINS AND LEUKOTRIENES (Eicosanoids)

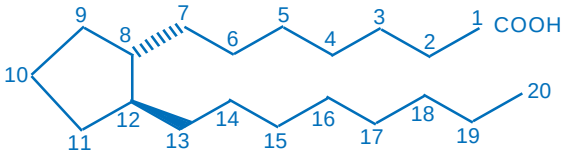
Prostaglandins (PGs) and Leukotrienes (LTs) are biologically active derivatives of 20 carbon atom polyunsaturated essential fatty acids that are released from cell membrane phospholipids. They are the major lipid-derived autacoids.

In the 1930s, human semen was found to contract isolated uterine and other smooth muscle strips and to cause fall in BP in animals. The active principle was termed 'prostaglandin', thinking that it was derived from prostate. Only in 1960s, it was shown to be a mixture of closely related compounds, the chemical structures were elucidated and widespread distribution was revealed. In 1970s, it became clear that aspirin-like drugs act by inhibiting PG synthesis, and that in addition to the classical PGs (Es and Fs), thromboxane (TX), prostacyclin (PGI) and leukotrienes (LTs) were of great biological importance. Bergstrom, Samuelsson and Vane got the Nobel prize in 1982 for their work on PGs and LTs.

CHEMISTRY, BIOSYNTHESIS AND DEGRADATION

Chemically, PGs may be considered to be derivatives of *prostanoic acid*, though prostanoic acid does not naturally occur in the body. It has a five membered ring and two side chains projecting in opposite directions at right angle to the plane of the ring. There are many series of PGs designated A, B, C,..., I, and thromboxanes (TXs) depending on the ring structure and the substituents on it. Each series has members with subscript 1, 2, 3 indicating the number of double bonds in the side chains.

Leukotrienes are so named because they were first obtained from leukocytes (*leuko*) and have 3 conjugated double bonds (*triene*). They have also been similarly designated A, B, C,..., F and given subscripts 1, 2, 3, 4.



PROSTANOIC ACID

In the body PGs, TXs and LTs are all derived from *5,8,11,14 eicosa tetraenoic acid (arachidonic acid)*. During PG, TX and prostacyclin synthesis, 2 of the 4 double bonds of arachidonic acid get saturated in the process of cyclization, leaving 2 double bonds in the side chain. Thus, subscript 2 PGs are most important in man, e.g. PGE_2, $PGF_{2\alpha}$, PGI_2, TXA_2. No cyclization or reduction of double bonds occurs during LT synthesis—the LTs of biological importance are LTB_4, LTC_4, LTD_4.

Eicosanoids are the most universally distributed autacoids in the body. Practically, every cell and tissue is capable of synthesizing one or more types of PGs or LTs. The pathways of biosynthesis of eicosanoids are summarized in Fig. 7.3.

There are no preformed stores of PGs and LTs. They are synthesized locally at rates governed by the release of arachidonic acid from membrane lipids in response to appropriate stimuli. These stimuli activate hydrolases, including phospholipase A.

The *cyclooxygenase* (COX) pathway generates eicosanoids with a ring structure (PGs, TXs, prostacyclin) while *lipoxygenase* (LOX) produces

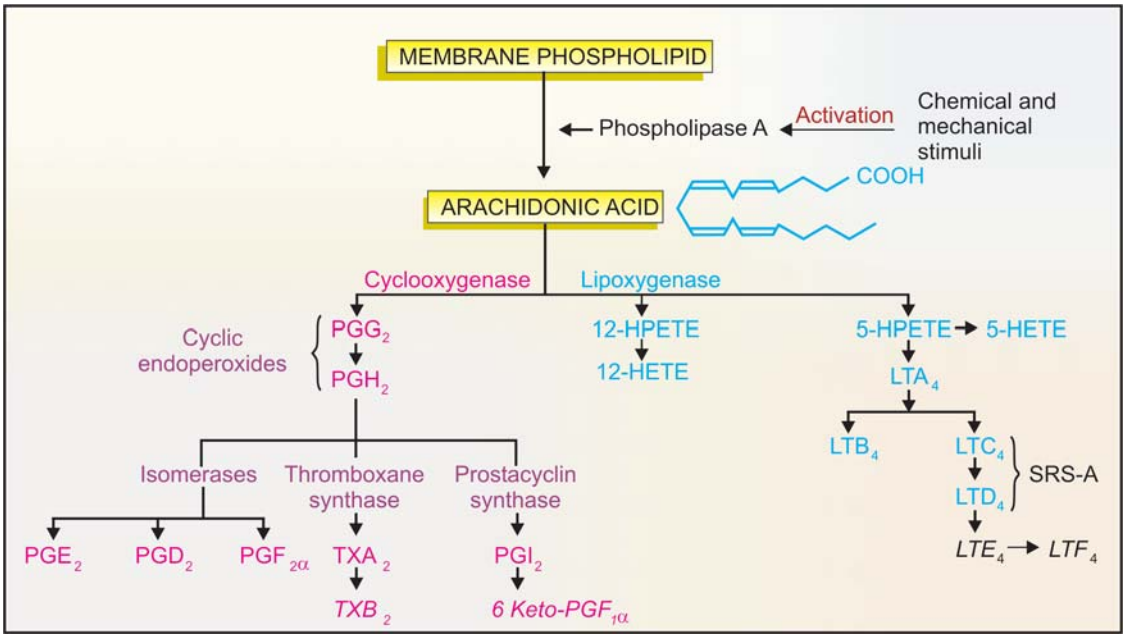


Fig. 7.3: Biosynthesis of prostaglandins (PG) and leukotrienes (LT). Less active metabolites are shown in italics
TX—Thromboxane, PGI—Prostacyclin; HPETE—Hydroperoxy eicosatetraenoic acid (Hydroperoxy arachidonic acid); HETE—Hydroxyeicosatetraenoic acid (Hydroxy arachidonic acid); SRS-A—Slow-reacting substance of anaphylaxis

open chain compounds (LTs). All tissues have COX—can form cyclic endoperoxides PGG_2 and PGH_2 which are unstable compounds. Further course in a particular tissue depends on the type of isomerases or other enzymes present in it. PGE_2 and $PGF_{2\alpha}$ are the primary prostaglandins. Lung and spleen can synthesize the whole range of COX products. Platelets primarily synthesize TXA_2 which is chemically unstable, spontaneously changes to TXB_2. Endothelium mainly generates prostacyclin (PGI_2) that is also chemically unstable and rapidly converts to 6-keto $PGF_{1\alpha}$.

Cyclooxygenase is now known to exist in two isoforms COX-1 and COX-2. While both isoforms catalyse the same reactions, COX-1 is a constitutive enzyme in most cells—its activity is not changed once the cell is fully grown. On the other hand, COX-2 normally present in insignificant amounts is inducible by cytokines, growth factors and other stimuli during the inflammatory response. It is believed that eicosanoids produced by COX-1 participate in physiological (house keeping) functions such as secretion of mucus for protection of gastric mucosa, haemostasis and maintenance of renal function, while those produced by COX-2 lead to inflammatory and other pathological changes. However, certain sites in kidney and brain constitutively express COX-2 which may play physiological role.

Lipoxygenase pathway appears to operate mainly in the lung, WBC and platelets. Its most important products are the LTs, (generated by 5-LOX) particularly LTB_4 (potent chemotactic) and LTC_4, LTD_4 which together constitute the 'slow reacting substance of anaphylaxis' (SRS-A).

Inhibition of synthesis Synthesis of COX products can be inhibited by nonsteroidal antiinflammatory drugs (NSAIDs). Aspirin acetylates COX at a serine residue and causes irreversible inhibition, while other NSAIDs are competitive and reversible inhibitors. Most

NSAIDs are nonselective COX-1 and COX-2 inhibitors, but some newer ones like celecoxib, rofecoxib are selective for COX-2.

NSAIDs do not inhibit the production of LTs: this may even be increased since all the arachidonic acid becomes available to the LOX pathway.

Glucocorticosteroids inhibit the release of arachidonic acid from membrane lipids (by stimulating production of proteins called *annexins* or *lipocortins* which inhibit phospholipase A_2) — indirectly reduce production of all eicosanoids— PGs, TXs and LTs. Moreover, they inhibit the induction of COX-2 by cytokines at the site of inflammation.

Degradation of arachidonates occurs rapidly in most tissues, but fastest in the lungs. Most PGs, TXA_2 and prostacyclin have plasma t½ of a few seconds to a few minutes. First a specific carrier mediated uptake into cells occurs, the side chains are then oxidized and double bonds are reduced in a stepwise manner to yield inactive metabolites. Metabolites are excreted in urine. PGI_2 is catabolized mainly in the kidney.

PROSTAGLANDINS, THROMBOXANES AND PROSTACYCLIN

Actions

The cyclic eicosanoids produce a wide variety of actions depending upon the particular PG (or TX or PGI), species on which tested, tissue, hormonal status and other factors. PGs differ in their potency to produce a given action and different PGs sometimes have opposite effects. Even the same PG may have opposite effects under different circumstances. The actions of important PGs, PGI_2 and TXA_2 are summarized in Table 7.3.

Patho-physiological roles

Since virtually all cells and tissues are capable of forming PGs, they have been implicated as mediators or modulators of a number of physiological processes and pathological states.

1. PGI_2 is probably involved in the regulation of local vascular tone as a dilator.
2. PGE_2 and PGI_2 are believed to be continuously produced locally in the ductus arteriosus during foetal life—keep it patent; at birth their synthesis is inhibited and closure occurs. Aspirin and indomethacin have been found to induce closure when it fails to occur spontaneously. These PGs may also be important in maintaining placental blood flow.
3. PGs, along with LTs and other autacoids may mediate vasodilatation and exudation at the site of inflammation.
4. TXA_2 (produced by platelets) and PGI_2 (produced by vascular endothelium) probably constitute a mutually antagonistic system: preventing aggregation of platelets while in circulation and inducing aggregation on injury, when plugging and thrombosis are needed.

Aspirin interferes with haemostasis by inhibiting platelet aggregation which is due to TXA_2 production. Before it is deacetylated in liver, aspirin acetylates COX in platelets while they are in portal circulation. Further, platelets are unable to regenerate fresh COX (lack nucleus: do not synthesize protein), while vessel wall is able to do so (fresh enzyme is synthesized within hours). Thus, in low doses, aspirin selectively inhibits TXA_2 production and has antithrombotic effect lasting > 3 days.

5. PGs produced by foetal tissues at term probably mediate initiation and progression of labour. Aspirin has been found to delay the initiation of labour and also prolongs its duration.
6. Because PGs are present in high concentration in semen and can be rapidly absorbed when lodged in the vagina at coitus, it is believed that they so coordinate movements of the female genital tract that transport of sperms and fertilization is facilitated.
7. Dysmenorrhoea in many women is associated with increased PG synthesis by the endometrium. This apparently induces uncoordinated uterine contractions which compress blood vessels → uterine ischaemia → pain. Aspirin group of drugs are highly effective in relieving dysmenorrhoea in most women.

Table 7.3: A summary of the actions of major prostaglandins, prostacyclin and thromboxane

	Organ	*Prostaglandin E_2 (PGE_2)*	*Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)*	*Prostacyclin (PGI_2)*	*Thromboxane A_2 (TXA_2)*
1.	Blood vessels	Vasodilatation, ↓ BP	Vasodilatation (mostly), larger veins constrict, little effect on BP	Vasodilatation (marked and widespread), ↓↓ BP	Vasoconstriction
2.	Heart	Weak inotropic, reflex cardiac stimulation	Weak inotropic	—	—
3.	Platelets	Variable effect	—	Antiaggregatory	Aggregation and release reaction
4.	Uterus	Contraction (*in vivo*), relaxes nongravid human uterus *in vitro*, softening of cervix	Contraction (*in vivo* and *in vitro*), softening of cervix	—	—
5.	Bronchi	Dilatation, inhibit histamine release	Constriction	Dilatation (mild), inhibit histamine release	Constriction
6.	Stomach	↓ acid secretion, ↑ mucus production	—	↓ acid secretion (weak), mucosal vasodilatation	—
7.	Intestine	Contracts longitudinal & relaxes circular muscles, ↑ peristalsis, ↑ Cl^- & water secretion	Spasmogenic, ↑ fluid & electrolyte secretion (weak)	Weak spasmogenic, inhibit toxin-induced fluid secretion	Weak spasmogenic
8.	Kidney	Natriuresis, ↓ Cl^- reabsorption, inhibit ADH action, vasodilatation, renin release	—	Natriuresis, vasodilatation, renin release	Vasoconstriction
9.	CNS	Pyrogenic, variety of effects on i.c.v. inj.			
10.	Release of NA	↑ or ↓	↑ or ↓		
11.	Afferent nerves	Sensitize to noxious stimuli → tenderness	—	Same as PGE_2	—
12.	Endocrine system	Release of ant. pituitary hormones, steroids, insulin; TSH-like action	Release of gonadotropins & prolactin, luteolysis (in animals)	—	—
13.	Metabolism	Antilipolytic, insulin-like action, mobilization of bone Ca^{2+}	—	—	—

8. Asthma may be due to an imbalance between constrictor PGs (F_{2a}, PGD_2, TXA_2) and LTs on one hand and dilator ones (PGE_2, PGI_2) on the other. In few individuals aspirin-like drugs consistently induce asthma. However, in allergic human asthma, LTs are more important and COX inhibitors are without any effect in most patients.
9. PGs may be involved in mediating toxin induced increased fluid movement in secretory diarrhoeas. PGs appear to play a role in the growth of colonic polyps and cancer. Association of low incidence of colon cancer with regular intake of aspirin is now established.
10. PGs (especially PGI_2) appear to be involved in the regulation of gastric mucosal blood flow and PGE_2 enhances gastric mucus production. They may be functioning as natural ulcer protectives. The ulcerogenic action of NSAIDs may be due to loss of this protective influence.
11. PGs appear to function as intrarenal regulators of blood flow as well as tubular reabsorption in kidney. The NSAIDs tend to retain salt and water. The diuretic action of furosemide is blunted by indomethacin—indicating a facilitatory role of PGs by increasing renal blood flow and/or augmenting inhibition of tubular reabsorption.
12. PGE_2 may mediate bacterial or other pyrogen-induced fever and malaise at the level of hypothalamus. Aspirin and other inhibitors of PG synthesis are antipyretic.
13. PGs may be functioning as neuromodulators in the brain by regulating neuronal excitability. They may also modulate sympathetic neurotransmission in the periphery.
14. PGs (especially E_2 and I_2) sensitize afferent nerve endings to pain inducing chemical and mechanical stimuli (Fig. 7.4). They irritate mucous membranes and produce long lasting dull pain on intradermal injection.

PGs appear to serve as algesic agents during inflammation. They cause tenderness and amplify the action of other algesics. Inhibition of PG synthesis is a major antiinflammatory mechanism.

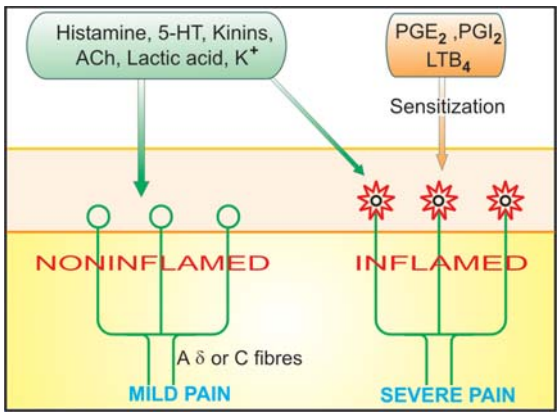


Fig. 7.4: Sensitization of nociceptors (pain receptors) to mediators of pain by prostaglandins at the inflammatory site

LEUKOTRIENES

The straight chain lipoxygenase products of arachidonic acid are produced by a more limited number of tissues (LTB_4 mainly by neutrophils; LTC_4 and LTD_4—the cysteinyl LTs—mainly by macrophages) but probably they are pathophysiologically as important as PGs.

1. CVS and blood LTC_4 and LTD_4 injected i.v. evoke a brief rise in BP followed by a more prolonged fall. The fall in BP is not due to vasodilatation because no relaxant action has been seen on blood vessels. It is probably a result of coronary constriction induced decrease in cardiac output and reduction in circulating volume due to increased capillary permeability. These LTs markedly increase capillary permeability and are more potent than histamine in causing local edema formation.

LTB_4 is highly chemotactic for neutrophils and monocytes. Migration of neutrophils through capillaries and their clumping at sites of inflammation in tissues is also promoted by LTB_4.

Role LTs are important mediators of inflammation. They are produced (along with PGs) locally at the site of injury. While LTC_4 and D_4 cause exudation of plasma, LTB_4 attracts the inflammatory cells which reinforce the reaction.

5-HPETE and 5-HETE may facilitate local release of histamine from mast cells.

2. Smooth muscle LTC_4 and D_4 contract most smooth muscles. They are potent bronchoconstrictors and induce spastic contraction of g.i.t. at low concentrations.

They also increase mucus secretion in the airways.

Role The cysteinyl LTs (C_4 and D_4) are the most important mediators of human allergic asthma. They are released along with PGs and other autacoids during AG: AB reaction in the lungs. In comparison to other mediators, they are more potent and are metabolized slowly in the lungs, exert a long lasting action. LTs may also be responsible for abdominal colics during systemic anaphylaxis.

3. Afferent nerves Like PGE_2 and I_2, the LTB_4 also sensitizes afferents carrying pain impulses—contributes to pain and tenderness of inflammation.

PROSTANOID RECEPTORS

PGs, TX and prostacyclin act on their own specific receptors located on cell membrane. Five major types of prostanoid receptors have been designated, each after the natural PG for which it has the greatest affinity. This has been supported by receptor cloning. All prostanoid receptors are G-protein coupled receptors which utilize the IP_3/DAG or cAMP transducer mechanisms. Some selective antagonists of prostanoid receptors have been produced. The prostanoid receptors are:

DP Has greatest affinity for PGD_2, but PGE_2 also acts on it.

EP Has greatest affinity for PGE_2; *enprostil* is a selective agonist. It has been subdivided into EP_1 which causes smooth muscle contraction through IP_3/DAG pathway and EP_2 which mediates smooth muscle relaxation by increasing cAMP.

FP Has greatest affinity for $PGF_{2\alpha}$; *fluprostenol* is a selective agonist. The most prominent effect of activation of this receptor is smooth muscle contraction mediated through IP_3/DAG formation.

IP Has greatest affinity for PGI_2; PGE also acts on it and *cicaprost* is a selective agonist. It functions by activating adenylyl cyclase in platelets (inhibiting aggregation) and smooth muscles (relaxation).

TP Has greatest affinity for TXA_2; PGH_2 also acts on it. It utilizes IP_3/DAG as second messengers which mediate platelet aggregation and smooth muscle contraction.

LEUKOTRIENE RECEPTORS

Separate receptors for LTB_4 and for the cysteinyl LTs (LTC_4, LTD_4) have been defined. Two subtypes *cys*LT_1 and *cys* LT_2 of the cysteinyl LT receptor have been cloned. All LT receptors function through the IP_3/DAG transducer mechanism. Many *cys*LT_1 receptor antagonists, *viz. Montelukast, Zafirlukast,* etc. are now valuable drugs for bronchial asthma (*see* Ch 19).

USES

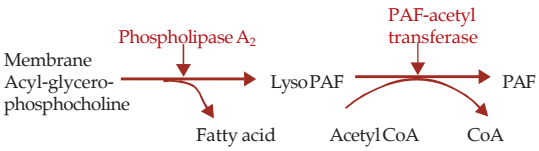
Clinical use of PGs and their analogues is rather restricted because of limited availability, short lasting action, cost, side effects and other practical considerations. Their approved indications are:

1. Abortion, especially during the 2nd trimester; PGE_2 or $PGF_{2\alpha}$ may be injected intra-or extra-amniotically.
2. Induction/augmentation of labour: intravaginal PGE_2 or $PGE_{2\alpha}$ are alternative to oxytocin, but less reliable.
3. Cervical priming: low doses of PGE_2 applied in cervical canal/vagina make the cervix soft and more compliant for abortion/delivery.
4. Postpartum haemorrhage: carboprost (15-methyl $PGF_{2\alpha}$) i.v. is an alternative to ergometrine/oxytocin.
5. Peptic ulcer: Misoprostol (PGE_1 analogue) can be used to heal NSAID-associated peptic ulcer.
6. Glaucoma: Topical latanoprost ($PGF_{2\alpha}$ analogue) is an adjunctive drug.
7. To maintain patency of ductus arteriosus in neonates with congenital heart disease: alprostadil (PGE_1) i.v. infusion.
8. To avoid platelet damage during haemodialysis/cardiopulmonary bypass.

PLATELET ACTIVATING FACTOR (PAF)

Like eicosanoids, platelet activating factor (PAF) is a cell membrane-derived polar lipid with intense biological activity; discovered in 1970s and now recognized to be an important signal molecule. PAF is acetyl-glyceryl ether-phosphoryl choline.

Synthesis and degradation PAF is synthesized from precursor phospholipids present in cell membrane by the following reactions:



The second step is rate limiting. Antigen-antibody reaction and a variety of mediators stimulate PAF synthesis in a Ca^{2+} dependent manner on demand: there are no preformed stores of PAF. In contrast to eicosanoids, the types of cells which synthesize PAF is quite limited—mainly WBC, platelets, vascular endothelium and kidney cells.

PAF is degraded by reversal of the above reactions and the product is incorporated back into the membrane.

Actions PAF has potent actions on many tissues/organs.

Platelets Aggregation and release reaction; also releases TXA_2; i.v. injection results in intravascular thrombosis.

WBC PAF is chemotactic to neutrophils, eosinophils and monocytes. It stimulates neutrophils to aggregate, to stick to vascular endothelium and migrate across it to the site of infection. It also prompts release of lysosomal enzymes and LTs and generation of superoxide radical by the polymorphs.

Blood vessels Vasodilatation occurs mediated by release of EDRF → fall in BP on i.v. injection.

PAF is the most potent agent known to increase vascular permeability. Wheal and flare occur at the site of intradermal injection.

Visceral smooth muscle Contraction occurs by direct action as well as through release of LTC_4, TXA_2 and PGs. Aerosolized PAF is a potent bronchoconstrictor. In addition, it produces mucosal edema, secretion and a delayed and long-lasting bronchial hyper-responsiveness. It also stimulates intestinal and uterine smooth muscle.

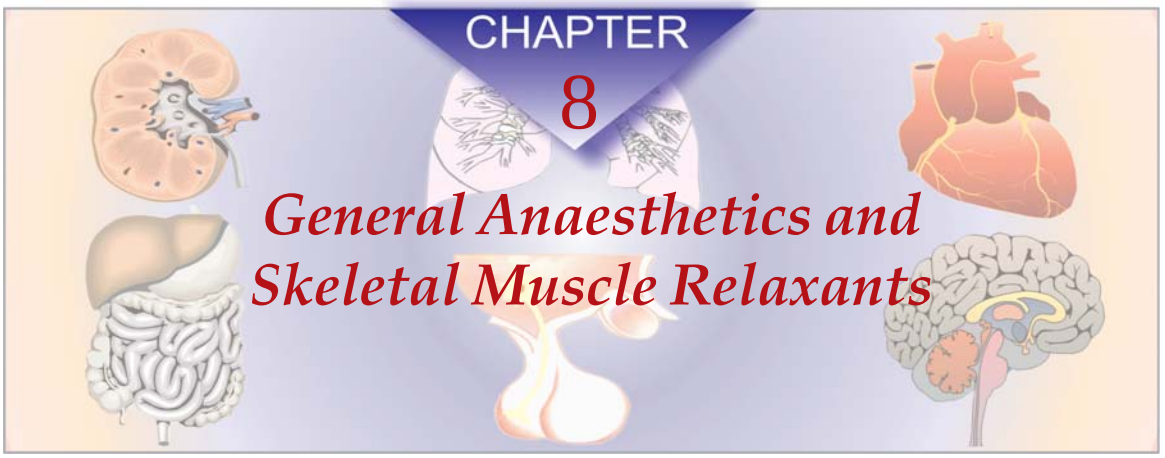
Stomach Ulcerogenic: erosions and mucosal bleeding occur shortly after i.v. injection of PAF. The gastric smooth muscle contracts.

Mechanism of action Membrane bound specific PAF receptors have been identified. The PAF receptor is a G-protein coupled receptor which exerts most of the actions through intracellular messengers IP_3/DAG → Ca^{2+} release.

PAF antagonists A number of natural and synthetic PAF receptor antagonists have been investigated. Important among these are ginkgolide B (from a Chinese plant), and some structural analogues of PAF. The PAF antagonists have manyfold therapeutic potentials but none has been found worth marketing. Alprazolam and triazolam antagonize some actions of PAF.

Pathophysiological roles PAF has been implicated in many physiological processes and pathological states, especially those involving cell-to-cell interaction. These are:

1. Inflammation
2. Bronchial asthma
3. Anaphylactic (and other) shock conditions
4. Haemostasis and thrombosis
5. Rupture of mature graafian follicle and implantation
6. Labour
7. Ischaemic states of brain, heart and g.i.t., including g.i. ulceration.



CHAPTER 8

General Anaesthetics and Skeletal Muscle Relaxants

GENERAL ANAESTHETICS

General anaesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness. The cardinal features of general anaesthesia are:

- Loss of all sensation, especially pain
- Sleep (unconsciousness) and amnesia
- Immobility and muscle relaxation
- Abolition of reflexes.

In the modern practice of balanced anaesthesia, these modalities are achieved by using combination of drugs, each drug for a especific purpose. Anaesthesia has developed as a highly specialized science in itself. In dental practice, general anaesthesia is employed occasionally; is administered and managed by a qualified anaesthetist, and not by the dental surgeon himself.

Mechanism of general anaesthesia

The mechanism of action of GAs is not precisely known. A wide variety of chemical agents produce general anaesthesia. Therefore, GA action had been related to some common physicochemical property of the drugs. Mayer and Overton (1901) pointed out a direct parallelism between lipid/water partition coefficient of the GAs and their anaesthetic potency.

Minimal alveolar concentration (MAC) is the lowest concentration of the anaesthetic in pulmonary alveoli needed to produce immobility in response to a painful stimulus (surgical incision) in 50% individuals. It is accepted as a valid measure of potency of inhalational GAs because it remains fairly constant for a given species even under varying conditions.

The MAC of a number of GAs shows excellent correlation with their oil/gas partition coefficient. However, this only reflects capacity of the anaesthetic to enter into CNS and attain sufficient concentration in neuronal membrane, but not the mechanism by which anaesthesia is produced.

Recent evidence favours a direct interaction of the GA molecules with hydrophobic domains of membrane proteins or the lipid-protein interface.

Different anaesthetics may be acting through different molecular mechanisms and various components of the anaesthetic state involve action at discrete loci in the cerebrospinal axis. The principal locus of causation of unconsciousness appears to be in the thalamus or reticular activating system, amnesia may result from action in hippocampus, while spinal cord is the likely seat of immobility on surgical stimulation.

Recent findings show that ligand gated ion channels (but not voltage sensitive ion channels) are the major targets of anaesthetic action. The $GABA_A$ receptor gated Cl^- channel is the most important of these. Many inhalational anaesthetics, barbiturates, benzodiazepines and propofol potentiate the action of inhibitory transmitter GABA to open Cl^- channels. Each of the above anaesthetics appears to interact with its own specific binding site on the $GABA_A$ receptor-Cl^- channel complex, but none binds to the GABA binding site as such. Action of glycine (another inhibitory transmitter which also activates Cl^- channels) in the spinal cord and medulla is augmented by barbiturates, propofol and many inhalational anaesthetics. This action may block responsiveness to painful stimuli resulting in immobility of the anaesthetic state. Certain fluorinated anaesthetics and barbiturates, in addition, inhibit neuronal cation channel gated by nicotinic cholinergic receptor.

On the other hand, N_2O and ketamine do not affect GABA or glycine gated Cl^- channels. Rather they selectively inhibit the excitatory NMDA type of glutamate receptor. This receptor gates mainly Ca^{2+} selective cation channels in the neurones and their inhibition appears to be the primary mechanism of anaesthetic action of ketamine as well as N_2O. The volatile anaesthetics have little action on this receptor.

Unlike local anaesthetics which act primarily by blocking axonal conduction, the GAs appear to act by depressing synaptic transmission.

Stages of anaesthesia

GAs cause an irregularly descending depression of CNS, i.e. the higher functions are lost first and progressively lower areas of the brain are involved, but in the spinal cord lower segments are affected somewhat earlier than the higher segments. The vital centres located in the medulla are paralysed the last as the depth of anaesthesia increases. Guedel (1920) described four stages with *ether* anaesthesia.

I. *Stage of analgesia* From beginning of anaesthetic inhalation to loss of consciousness; pain is progressively abolished; some minor procedures can be performed, but it is difficult to maintain.

II. *Stage of delirium* From loss of consciousness to beginning of regular respiration; excitement, struggling, breath-holding, jerky breathing, sympathetic stimulation occur. No procedure can be carried out. This stage is inconspicuous in modern anaesthesia.

III. *Surgical anaesthesia* From onset of regular respiration to cessation of spontaneous breathing. This stage has been divided into 4 planes as anaesthesia becomes light to deep. Most dental/surgical procedures are carried out at plane 1 or 2.

IV. *Medullary paralysis* From cessation of breathing to failure of circulation and death; never attempted.

These clear-cut stages are not seen now-a-days with the use of faster acting GAs, premedication and employment of many drugs together. The precise sequence of events differs somewhat with anaesthetics other than ether.

The modern anaesthetist has to depend on several other observations to gauge the depth of anaesthesia.

- If eyelash reflex is present and patient is making swallowing movements—Stage II has not been reached.
- Incision of the skin causes reflex increase in respiration, BP rise or other effects; insertion of endotracheal tube is resisted and induces coughing, vomiting, laryngospasm; tears appear in eye; passive inflation of lungs is resisted—anaesthesia is light.
- Fall in BP, cardiac and respiratory depression are signs of deep anaesthesia.

In the present-day practice, anaesthesia is generally kept light; adequate analgesia, amnesia and muscle relaxation are produced by the use of intravenous drugs. Concentrations of inhalational anaesthetics exceeding 1.2 MAC are rarely used.

Pharmacokinetics of inhalational anaesthetics

Inhalational anaesthetics are gases or vapours that diffuse rapidly across pulmonary alveoli and tissue barriers. The depth of anaesthesia depends on the potency of the agent (MAC is an index of potency) and its partial pressure (PP) in the brain, while induction and recovery depend on the rate of change of PP in the brain. Transfer of the anaesthetic between lung and brain depends on a series of tension gradients which may be summarized as—

Alveoli ⇌ Blood ⇌ Brain

Factors affecting the PP of anaesthetic attained in brain are—

1. *PP of anaesthetic in the inspired gas* This is proportional to its concentration in the inspired gas mixture. Higher the inspired tension more anaesthetic will be transferred to the blood hastening induction.

2. *Pulmonary ventilation* It governs delivery of the GA to the alveoli. Hyperventilation will bring in more anaesthetic per minute and quicken induction.

3. *Alveolar exchange* The GAs diffuse freely across alveoli, but if alveolar ventilation and perfusion are mismatched (as occurs in emphysema and other lung diseases) the attainment of equilibrium between alveoli and blood will be delayed. Induction and recovery both are slowed.

4. *Solubility of anaesthetic in blood* This is the most important property determining induction and recovery. Large amount of an anaesthetic that is highly soluble in blood (ether) must dissolve before its PP is raised. The rise as well as fall of PP in blood and consequently induction as well as recovery are slow. Drugs with low blood solubility, e.g. N_2O, sevoflurane, desflurane induce quickly.

5. *Solubility of anaesthetic in tissues* Relative solubility of anaesthetic in blood and tissues determines its concentration in tissues at equilibrium. Most of GAs are equally soluble in lean tissues as in blood but more soluble in fatty tissue. Anaesthetics with higher lipid solubility (halothane) continue to enter adipose tissue for hours and also leave it slowly.

6. *Cerebral blood flow* Brain is a highly perfused organ; as such GAs are quickly delivered to it. This can be hastened by CO_2 inhalation which causes cerebral vasodilatation—induction and recovery are accelerated.

Elimination When anaesthetic administration is discontinued, gradients are reversed and the channel of absorption (pulmonary epithelium) becomes the channel of elimination. Same factors which govern induction also govern recovery. Anaesthetics, in general, persist for long periods in adipose tissue because of their high lipid solubility and low blood flow through fatty tissues. Muscles occupy an intermediate position between brain and adipose tissue. Most GAs are eliminated unchanged. Metabolism is significant only for halothane which is about 20% metabolized in liver.

Second gas effect and diffusion hypoxia In the initial part of induction, diffusion gradient from alveoli to blood is high and larger quantity of anaesthetic is entering blood. If the inhaled concentration of anaesthetic is high, substantial loss of alveolar gas volume will occur and the gas mixture will be sucked in, independent of ventilatory exchange—gas flow will be higher than tidal volume. This is significant only with N_2O since it is given at 70–80% concentration. Though it has low solubility in blood, about 1 litre/min of N_2O enters blood in the first few minutes—gas flow is 1 litre/min higher than minute volume. If another potent anaesthetic, e.g. halothane (1–2%) is being given at the same time, it also will be delivered to blood at a rate 1 litre/min higher than minute volume and induction will be faster—*second gas effect.*

The reverse occurs when N_2O is discontinued after prolonged anaesthesia—N_2O having low blood solubility rapidly diffuses into alveoli and dilutes the alveolar air—PP of oxygen in alveoli is reduced. The resulting hypoxia, called *diffusion hypoxia*, is not of much consequence if cardiopulmonary reserve is normal, but may be dangerous if it is low. This can be prevented by continuing 100% O_2 inhalation for a few minutes after discontinuing N_2O, instead of straight away switching over to air. Diffusion hypoxia is not significant with other anaesthetics because they are administered at low concentrations (0.2–4%) and cannot dilute alveolar air by more than 1–2%.

Table 8.1: Physical and anaesthetic properties of inhalational anaesthetics

	Anaesthetic	*Boiling point (°C)*	*Inflammability*	*Irritancy (odour)*	*Oil: Gas partition coefficient**	*Blood: Gas partition coefficient**	*MAC (%)*	*Induction*	*Muscle relaxation*
1.	Ether	35	Infl. + Explo.	+++ (Pungent)	65	12.1	1.9	Slow	V. good
2.	Halothane	50	Noninfl.	– (Pleasant)	224	2.3	0.75	Interm.	Fair
3.	Isoflurane	48	Noninfl.	± (Not pleasant)	99	1.4	1.2	Fast	Good
4.	Desflurane	24	Noninfl.	+ (Unpleasant)	19	0.42	6.0	Fast	Good
5.	Sevoflurane	59	Noninfl.	– (Pleasant)	50	0.68	2.0	Fast	Good
6.	Nitrous oxide	Gas	Noninfl.	–	1.4	0.47	105	Fast	Poor

*At 37°C
MAC—Minimal alveolar concentration; Infl.—Inflammable; Explo.—Explosive; Interm.—Intermediate

Properties of an ideal anaesthetic

A. *For the patient* It should be pleasant, non-irritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects.

B. *For the surgeon* It should provide adequate analgesia, immobility and muscle relaxation. It should be noninflammable and nonexplosive so that cautery may be used.

C. *For the anaesthetist* Its administration should be easy, controllable and versatile.

- Margin of safety should be wide—no fall in BP. Heart, liver and other organs should not be affected.
- It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
- Rapid adjustments in depth of anaesthesia should be possible.
- It should be cheap, stable and easily stored.
- It should not react with rubber tubing or soda lime.

Most inhalational anaesthetics have a steep concentration-response curve: increasing the concentration only by 1/3rd over MAC makes almost all individuals immobile (at MAC only 50% are immobilized), and 2–4 MAC is often lethal.

The important physical and anaesthetic properties of inhalational anaesthetics are presented in Table 8.1.

CLASSIFICATION

Inhalational

Gas
Nitrous oxide

Liquids
Ether
Halothane
Isoflurane
Desflurane
Sevoflurane

Intravenous

Inducing agents
Thiopentone sod.
Propofol

Slower acting drugs
Benzodiazepines
Diazepam
Lorazepam
Midazolam
Dissociative anaesthesia
Ketamine
Opioid analgesia
Fentanyl

INHALATIONAL ANAESTHETICS

1. Nitrous oxide (N_2O) It is a colourless, odourless, heavier than air, noninflammable gas supplied under pressure in steel cylinders. It is nonirritating but low potency anaesthetic; unconsciousness cannot be produced in all individuals without concomittent hypoxia: MAC is 105% implying that even pure N_2O cannot produce adequate anaesthesia at 1 atmosphere pressure.

Nitrous oxide is a good analgesic but poor muscle relaxant. Onset of N_2O action is quick and smooth (but thiopentone is often used for induction), recovery is rapid. Second gas effect and diffusion hypoxia occur with N_2O only. Post-anaesthetic nausea is not marked.

Nitrous oxide is generally used as a carrier and adjuvant to other anaesthetics. A mixture of 70% N_2O + 25–30% O_2 + 0.2–2% another potent anaesthetic is employed for most surgical procedures.

As the sole agent, N_2O (50%) has been used with O_2 for obstetric analgesia. In dental practice N_2O is now used to provide 'conscious sedation' for allaying anxiety and apprehension (*See* p. 123). It is nontoxic to liver, kidney and brain. It is cheap and very commonly used.

2. Ether (Diethyl ether) It is a highly volatile liquid, produces irritating vapours which are inflammable and explosive. Ether is a potent anaesthetic, produces good analgesia and marked muscle relaxation —dose of competitive neuromuscular blockers should be reduced to about 1/3rd.

It is highly soluble in blood—induction is prolonged and unpleasant with struggling, breath-holding, salivation and marked respiratory secretions (atropine must be given as premedication to prevent the patient from drowning in his own secretions). Recovery is slow; post-anaesthetic nausea, vomiting and retching are marked.

Ether is not used now in developed countries because of its unpleasant and inflammable properties. However, it is still used in developing countries, particularly in peripheral areas because it is—cheap, can be given by open drop method without the need for any equipment, and is relatively safe even in inexperienced hands.

3. Halothane (FLUOTHANE) It is a volatile liquid with sweet odour, nonirritant and noninflammable. Solubility in blood is intermediate—induction is reasonably quick and pleasant.

It is a potent anaesthetic. For induction 2–4% and for maintenance 0.5–1% is delivered by the use of a special vaporizer. It is not a good analgesic or muscle relaxant; however, it potentiates competitive neuromuscular blockers.

Halothane causes direct depression of myocardial contractility. Cardiac output is reduced with deepening anaesthesia. BP starts falling early and parallels the depth. Heart rate is often reduced by direct depression of SA nodal automaticity and lack of baroreceptor activation even when BP falls. It tends to sensitize the heart to the arrhythmogenic action of Adr. Halothane causes relatively greater depression of respiration; breathing is shallow and rapid. Ventilatory support with added oxygen is frequently required.

Pharyngeal and laryngeal reflexes are abolished early and coughing is suppressed while bronchi dilate—preferred for asthmatics. It inhibits intestinal and uterine contractions.

Hepatitis occurs in susceptible individuals (approximately 1 in 10,000) especially after repeated use. A genetically determined reaction *malignant hyperthermia* occurs rarely. It is due to intracellular release of Ca^{2+} from sarcoplasmic reticulum causing persistent muscle contraction and increased heat production.

About 20% of halothane that enters blood is metabolized in the liver, the rest is exhaled out. Recovery from halothane anaesthesia is smooth and reasonably quick; shivering may occur but nausea and vomiting are rare. Psychomotor performance and mental ability remain depressed for several hours after regaining consciousness.

Halothane is currently one of the most popular anaesthetics because of nonirritant, noninflammable, pleasant and rapid action.

4. Isoflurane (SOFANE) This potent fluorinated anaesthetic has properties similar to halothane, but is less soluble in blood—produces rapid induction and recovery. Fall in BP is like halothane, but it tends to increase heart rate. Isoflurane does not sensitize the heart to adrenergic arrhythmias.

Respiratory depression is prominent and assistance is usually needed to avoid hypercarbia. Secretions are slightly increased. Renal and hepatic toxicity has not been encountered. Postanaesthetic nausea and vomiting is low.

Though slightly irritant, isoflurane has many advantages, i.e. better adjustment of depth of anaesthesia and low toxicity. It does not provoke seizures and is preferred for neurosurgery. In many hospitals it has become the routine anaesthetic, but cost is a constraint.

5. Desflurane It is a recently developed all fluorinated congener of isoflurane which has gained popularity as an anaesthetic for outpatient surgery in western countries. Its distinctive properties are high volatility, lower oil: gas partition coefficient and very low solubility in blood as well as tissues because of which induction and recovery are very fast. Depth of anaesthesia changes rapidly with change in inhaled concentration. Postanaesthetic cognitive and motor impairment is shortlived—patient can be discharged a few hours after surgery.

Desflurane is less potent than isoflurane; higher concentration has to be used for induction—irritates air passage—may induce coughing, breath-holding and laryngospasm because of somewhat pungent odour making it difficult to use for induction. Degree of respiratory depression, muscle relaxation, vasodilatation and fall in BP, as well as maintained cardiac contractility and coronary circulation are like isoflurane. Desflurane can serve as a good alternative to isoflurane for routine surgery as well, especially prolonged operations.

6. Sevoflurane It is the latest polyfluorinated anaesthetic with properties intermediate between isoflurane and desflurane. Solubility in blood and tissues as well as potency are less than isoflurane but more than desflurane. Induction and emergence from anaesthesia are fast and rapid changes in depth can be achieved. Absence of pungency makes it pleasant and administrable through face mask. Unlike desflurane, it poses no problem in induction; acceptability is good even by pediatric patients. Recovery is smooth; orientation, cognitive and motor functions are regained almost as quickly as with desflurane. Sevoflurane is suitable for both outpatient and inpatient surgery, but its high cost and need for high flow open system makes it very expensive to use.

INTRAVENOUS ANAESTHETICS

INDUCING AGENTS

These are drugs which on i.v. injection produce loss of consciousness in one arm-brain circulation time (~11 sec); are generally used for induction because of rapidity of onset of action. Anaesthesia is then usually maintained by an inhalational agent. They also serve to reduce the amount of maintenance anaesthetic. Supplemented with analgesics and muscle relaxants, they can also be used as the sole anaesthetic.

1. Thiopentone sod It is an ultrashort acting thiobarbiturate, highly soluble in water yielding a very alkaline solution, which must be prepared freshly before injection. Extravasation of the solution or inadvertent intraarterial injection produces intense pain—necrosis and gangrene may occur.

Injected i.v. (3–5 mg/kg) it produces unconsciousness in 15–20 sec. Its undissociated form has high lipid solubility—enters brain almost instantaneously. Initial distribution depends on organ blood flow—brain gets large amounts.

However, as other less vascular tissues (muscle, fat) gradually take up the drug, blood concentration falls and it back diffuses from the brain; consciousness is regained in 8–12 min (t½ of distribution phase is 3 min).

On repeated injection, the extracerebral sites are gradually filled up—lower doses produce anaesthesia which lasts longer. Its ultimate disposal occurs mainly by hepatic metabolism (elimination t½ is 7–12 hr). Residual CNS depression may persist for > 12 hr. The patient should not be allowed to leave the hospital without an attendant before this time.

Thiopentone is a poor analgesic. Painful procedures should not be carried out under its influence unless an opioid or N_2O has been given; otherwise, the patient may struggle, shout and show reflex changes in BP and respiration.

It is a weak muscle relaxant. BP falls immediately after injection mainly due to vasodilatation, but recovers rapidly.

Thiopentone is the commonest inducing agent used. It can be employed as the sole anaesthetic for short operations that are not painful.

Adverse effects Laryngospasm occurs generally when respiratory secretions or other irritants are present, or when intubation is attempted while anaesthesia is light. It can be prevented by atropine premedication.

Shivering and delirium may occur during recovery. Postanaesthetic nausea and vomiting are uncommon.

2. Propofol It is an oily liquid employed as a 1% emulsion for i.v. induction and short duration anaesthesia. Unconsciousness after propofol injection occurs in 15–45 sec and lasts ~10 min. Propofol distributes rapidly (distribution t½ 2–4 min). Elimination t½ (100 min) is much shorter than that of thiopentone due to rapid metabolism.

Intermittent injection or continuous infusion of propofol has been used for total i.v. anaesthesia when supplemented by fentanyl. It lacks airway irritancy and is particularly suited for outpatient surgery because residual impairment is less marked and incidence of postoperative nausea and vomiting is low. Excitatory effects and involuntary movements are noted in few patients. Induction apnoea lasting ~1 min is common. Fall in BP due primarily to vasodilatation occurs consistently and is occasionally severe, but short lasting. Bradycardia is also frequent.

In subanaesthetic doses (2.4 mg/kg/hr) it has been used for sedating intubated patients in intensive care units.

SLOWER ACTING DRUGS

1. Benzodiazepines (BZDs) In addition to preanaesthetic medication, BZDs are now frequently used for inducing, maintaining and supplementing anaesthesia as well as for conscious sedation. Relatively large doses (diazepam 0.2–0.5 mg/kg or equivalent) injected i.v. produce sedation, amnesia and then unconsciousness in 5–10 min. If no other anaesthetic or opioid is given, the patient becomes responsive in 1 hr or so due to redistribution of the drug (distribution t½ of diazepam is 15 min), but amnesia persists for 2–3 hr and sedation for 6 hr or more. BZDs are poor analgesics : an opioid or N_2O is usually added if the procedure is painful.

By themselves, BZDs do not markedly depress respiration, cardiac contractility or BP; but when opioids are also given, these functions are considerably compromised. They do not provoke postoperative nausea or vomiting. Involuntary movements are not stimulated.

BZDs are now the preferred drugs for endoscopies, cardiac catheterization, angiographies, conscious sedation during local/regional anaesthesia for dental procedures, fracture setting, etc. They are a frequent component of balanced anaesthesia employing several drugs. The anaesthetic action of BZDs can be rapidly reversed by flumazenil 0.5–2 mg i.v.

Diazepam 0.2–0.5 mg/kg by slow undiluted injection in a running i.v. drip: this technique reduces the burning sensation in the vein and incidence of thromboflebitis.

Lorazepam Three times more potent, slower acting and less irritating than diazepam. It distributes more gradually—awakening may be delayed. Amnesia is more profound.

Midazolam Water soluble, nonirritating to veins, faster and shorter acting and 3 times more potent than diazepam. It is being preferred over diazepam for anaesthetic use and for sedation of dental patients, intubated and mechanically ventilated patients, etc.

2. Ketamine It induces a so- called '*dissociative anaesthesia*'—profound analgesia, immobility, amnesia with light sleep and feeling of dissociation from one's own body and the surroundings. The primary site of action is in the cortex and subcortical areas; not in the reticular activating system.

Respiration is not depressed, airway reflexes are maintained and muscle tone increases. Heart rate, cardiac output and BP are elevated due to sympathetic stimulation. The above effects are produced within a min and recovery starts after 10–15 min, but the patient remains amnesic for 1–2 hr. Emergence delirium, hallucinations and involuntary movements occur in up to 50% patients, but injection is not painful. Children tolerate the drug better. Its elimination t½ is 3–4 hr.

Ketamine has been employed for dental and other operations on the head and neck, in patients who have bled, in asthmatics (relieves bronchospasm), in those who do not want to lose consciousness and for short operations. It is good for repeated use; particularly suitable for burn dressing. Combined with diazepam, it has found use in angiographies, cardiac catheterization and trauma surgery. It may be dangerous for hypertensives and in ischaemic heart disease, but is good for hypovolemic patients.

3. Fentanyl This short acting (30–50 min) potent opioid analgesic related to pethidine is generally given i.v. at the beginning of painful surgical procedures. It is frequently used to supplement anaesthetics in balanced anaesthesia. This permits use of lower anaesthetic concentrations with better haemodynamic stability. Combined with benzodiazepines, it can obviate the need for inhaled anaesthetics for diagnostic, endoscopic, angiographic, dental and other minor procedures in poor risk patients, as well as for burn dressing.

After i.v. fentanyl (2–4 µg/kg) the patient remains drowsy but conscious and his co-operation can be commanded. Respiratory depression is marked, but predictable; the patient may be encouraged to breathe and assistance may be provided. Heart rate decreases, because fentanyl stimulates vagus. Fall in BP is slight and heart is not sensitized to Adr.

Nausea, vomiting and itching often occur during recovery. The opioid antagonist naloxone can be used to counteract persisting respiratory depression and mental clouding.

COMPLICATIONS OF GENERAL ANAESTHESIA

A. *During anaesthesia*

1. Respiratory depression and hypercarbia.
2. Salivation, respiratory secretions—less now as nonirritant anaesthetics are mostly used.
3. Cardiac arrhythmias, asystole.
4. Fall in BP.
5. Aspiration of gastric contents: acid pneumonitis.
6. Laryngospasm and asphyxia.
7. Awareness: dreadful perception and recall of events during surgery—by use of light anaesthesia + analgesics and muscle relaxants.
8. Delirium, convulsions, excitatory effects.
9. Fire and explosion—rare now due to use of non-inflammable agents.

B. *After anaesthesia*

1. Nausea and vomiting.
2. Persisting sedation: impaired psychomotor function.
3. Pneumonia, atelectasis.
4. Organ toxicities: liver, kidney damage.
5. Nerve palsies—due to faulty positioning.

6. Emergence delirium.
7. Cognitive defects: prolonged excess cognitive decline has been observed in some patients, especially the elderly.

DRUG INTERACTIONS

1. Patients on antihypertensives given general anaesthetics—BP may fall markedly.
2. Neuroleptics, opioids, clonidine and monoamine oxidase inhibitors potentiate anaesthetics.
3. Halothane sensitizes heart to Adr.
4. If a patient on corticosteroids is to be anaesthetized, give 100 mg hydrocortisone intraoperatively because anaesthesia is a stress—can precipitate adrenal insufficiency.
5. Insulin need of a diabetic is increased during GA: switch over to plain insulin even if the patient is on oral hypoglycaemics.

CONSCIOUS SEDATION

In place of general anaesthesia 'conscious sedation' can be employed, supplemented with local anaesthesia, to carry out dental procedures/surgery in apprehensive children (or adults) and in medically compromised patients. It allows operative procedure to be performed with minimal physiologic and psychologic stress. *Conscious sedation* is a technique in which drugs are used to produce a state of CNS depression (but not unconsciousness) enabling surgical procedure to be carried out while maintaining communication with the patient who is able to respond to commands and maintain a patent airway throughout. The difference between conscious sedation and anaesthesia is one of degree. The protective airway and other reflexes are not lost during conscious sedation; therefore, it is safer. However, by itself, it is not able to suppress pain of dental procedure; local anaesthetic must be injected in addition. Drugs used for conscious sedation are:

1. *Nitrous oxide* The patient is made to breathe 100 oxygen through a nose piece or hood and N_2O is added in 10% increments (to a maximum of 50% rarely 70%) till the desired level of sedation assessed by constant verbal contact is obtained. This is maintained till the procedure is performed. Thereafter, N_2O is switched off but 100% O_2 is continued for next 5 min. The patient is generally roadworthy in 30–60 min.

2. *Diazepam* It is injected i.v. in small (1–2 mg) repeated doses or by slow infusion until the desired level of sedation is produced indicated by relaxation, indifference, slurring of speech, ptosis, etc. Further injection is stopped, after which this state lasts for about 1 hour and psychomotor impairment persists for 6–24 hours; an escort is needed to take back the patient home. Flumazenil can be used to reverse the sedation, but repeated doses are needed.

   Midazolam (i.v.) is a shorter acting alternative to diazepam. Oral diazepam administered 1 hr before is also used with the limitation that level of sedation cannot be titrated. The patient remains sedated (not roadworthy) for several hours.

3. *Propofol* Because of brief action, it has to be administered by continuous i.v. infusion regulated by infusion pump throughout the procedure. However, level of sedation can be altered during the procedure and recovery is relatively quick, permitting early discharge of the patient.

   Intramuscular promethazine (especially in children) and i.v. fentanyl have also been used to produce conscious sedation.

PREANAESTHETIC MEDICATION

Preanaesthetic medication refers to the use of drugs before anaesthesia to make it more pleasant and safe. The aims are:

1. Relief of anxiety and apprehension preoperatively and to facilitate smooth induction.
2. Amnesia for pre- and postoperative events.
3. Supplement analgesic action of anaesthetics and potentiate them so that less anaesthetic is needed.

4. Decrease secretions and vagal stimulation caused by anaesthetics.
5. Antiemetic effect extending to the postoperative period.
6. Decrease acidity and volume of gastric juice so that it is less damaging if aspirated.

Different drugs achieve different purposes. One or more drugs may be used in a patient depending on the needs.

1. Opioids Morphine or pethidine, i.m. allay anxiety and apprehension of the operation, produce pre- and postoperative analgesia, smoothen induction, and supplement poor analgesic (thiopentone, halothane) or weak (N_2O) anaesthetics but have disadvantages as well.

Use of opioids is now mostly restricted to those having preoperative pain.

2. Sedative-antianxiety drugs Benzodiazepines like diazepam or lorazepam have become popular drugs for preanaesthetic medication because they produce tranquility and smoothen induction with little respiratory depression. They counteract CNS toxicity of local anaesthetics.

Promethazine is an antihistaminic with sedative, antiemetic and anticholinergic properties. It causes little respiratory depression and has been used particularly in children.

3. Anticholinergics Atropine or hyoscine (0.6 mg i.m./i.v.) have been used, primarily to reduce salivary and bronchial secretions. Need for their use is now less compelling because of the increasing employment of nonirritant anaesthetics. However, they must be given before hand when *ether* is used. The main aim of their use now is to prevent vagal bradycardia, hypotension and prophylaxis of laryngospasm.

Glycopyrrolate This quaternary atropine substitute is a potent antisecretory and antibradycardiac drug; acts rapidly and is less likely to produce central effects (*see* Ch. 5).

4. Neuroleptics Chlorpromazine, triflupromazine or haloperidol i.m. are infrequently used in premedication. They allay anxiety and have antiemetic action. However, they potentiate respiratory depression and hypotension caused by the anaesthetics and delay recovery.

5. H_2 blockers Patients undergoing prolonged operations and obese patients are at increased risk of gastric regurgitation and aspiration pneumonia. Ranitidine or famotidine benefit by raising pH of gastric juice; may also reduce its volume and thus chances of regurgitation. Prevention of stress ulcers is another advantage.

The proton pump inhibitor omeprazole/ pantoprazole is an alternative.

6. Antiemetics *Metoclopramide* injected preoperatively is effective in reducing postoperative vomiting. By enhancing gastric emptying and tone of LES, it reduces the chances of reflux and its aspiration.

Domperidone and *Ondansetron* (5-HT_3 antagonist) can be used as alternatives.

SKELETAL MUSCLE RELAXANTS

Skeletal muscle relaxants are drugs that act peripherally at neuromuscular junction/ muscle fibre itself or centrally in the cerebrospinal axis to reduce muscle tone and/or cause paralysis.

The neuromuscular blocking agents are used in conjunction with general anaesthetics to provide muscle relaxation for surgery, while centrally acting muscle relaxants are used primarily for painful muscle spasms and spastic neurological diseases.

PERIPHERALLY ACTING MUSCLE RELAXANTS

I. Neuromuscular Blocking Agents

A. Nondepolarizing (Competitive) blockers

1. *Long acting*: d-Tubocurarine, Pancuronium, Doxacurium, Pipecuronium.

2. *Intermediate acting:* Vecuronium, Atracurium, Rocuronium.
3. *Short acting:* Mivacurium.

B. Depolarizing blockers

Succinylcholine (SCh., Suxamethonium), Decamethonium (C-10)

II. Directly Acting Agents

Dantrolene sodium, Quinine

NEUROMUSCULAR BLOCKING AGENTS

Curare It is the generic name for certain plant extracts used by south American tribals as arrow poison for game hunting. The animals got paralysed even if not killed by the arrow. Natural sources of curare are *Strychnos toxifera, Chondrodendron tomentosum* and related plants. Muscle paralysing active principles of these are tubocurarine, toxiferins, etc.

MECHANISM OF ACTION

The site to action of both competitive and depolarizing blockers is the endplate of skeletal muscle fibres.

Competitive block (Nondepolarizing block)

This is produced by curare and related drugs.

The competitive blockers have affinity for the nicotinic (N_M) cholinergic receptors at the muscle endplate but have no intrinsic activity. The N_M receptor has been isolated and studied in detail. It is a protein with 5 subunits (α2 β ε or γ and δ) which are arranged like a rosette surrounding the Na^+ channel (*see* Fig. 3.2). The two α subunits carry 2 ACh binding sites; these have negatively charged groups which combine with the cationic head of ACh → opening of Na^+ channel. Most of the competitive blockers have two or more quaternary N^+ atoms which provide the necessary attraction to the same site, but the bulk of the antagonist molecule does not allow conformational changes in the subunits needed for opening the channel. ACh released from motor nerve endings is not able to combine with its receptors to generate endplate potential (EPP)

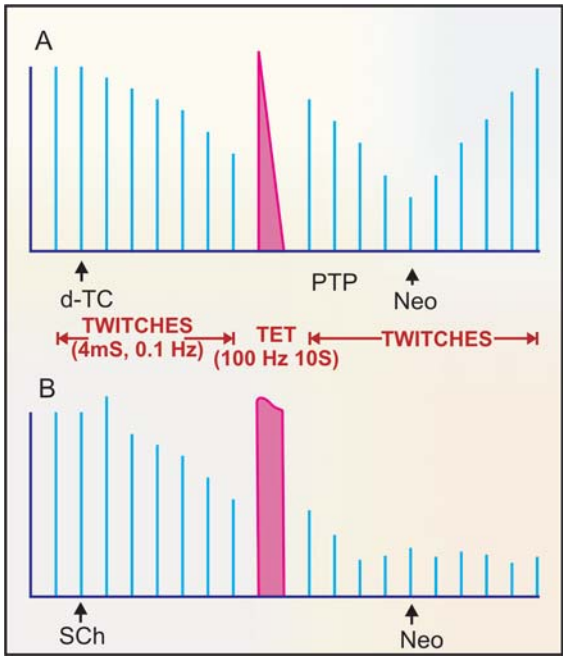


Fig. 8.1: Illustration of characteristics of competitive (A) and depolarizing (B) neuromuscular blockade in sciatic nerve-gastrocnemius muscle of cat

A. Tubocurarine (d-TC) produces progressive decrease in twitch tension; tetanic stimulation (TET) produces poorly sustained contracture, which is followed by post-tetanic potentiation (PTP); Neostigmine (Neo) restores the twitch contractions.

B. Succinylcholine (SCh) produces initial augmentation of twitches followed by progressive block; tetanus is well sustained, but there is no PTP; block is not reversed (rather worsened) by neostigmine.

and muscle fails to contract in response to nerve impulse. The antagonism is surmountable by increasing the concentration of ACh *in vitro* and by anticholinesterases *in vivo*.

Depolarizing block Decamethonium and SCh have affinity as well as submaximal intrinsic activity at the N_M cholinoceptors. They depolarize muscle endplates by opening Na^+ channels (just as ACh does) and initially produce twitching and fasciculations. These drugs do not dissociate rapidly from the receptor → induce prolonged partial depolarization of the region around muscle endplate → Na^+ channels get inactivated (because transmembrane potential

Table 8.2: Features of competitive and typical depolarizing block

	Competitive block (d-TC)	*Depolarizing block (C-10)*
1. Paralysis in man	Flaccid	Fasciculations → flaccid
2. Paralysis in chick	Flaccid	Spastic
3. Effect on isolated frog's rectus muscle	No contraction, Antagonism of ACh	Contraction
4. Species sensitivity	Rat > Rabbit > Cat	Cat > Rabbit > Rat
5. Human neonates	More sensitive	Relatively resistant
6. Tetanic stimulation during partial block	Poorly sustained contraction	Well-sustained contraction
7. Neostigmine	Antagonises block	No effect
8. Ether anaesthesia	Synergistic	No effect
9. Order of paralysis	Fingers, eyes → limbs → neck, face → trunk → respiratory	Neck, limbs → face, jaw, eyes, pharynx → trunk → respiratory
10. Effect of lowering temperature	Reduces block	Intensifies block
11. Effect of cathodal current to endplate	Lessens block	Enhances block

drops to about –50 mV) → ACh released from motor nerve endings is unable to generate propagated muscle action potential (MAP) → flaccid paralysis in mammals. In other words, a zone of inexcitability is created round the endplate preventing activation of muscle fibre. In birds, the area of depolarization is more extensive and spastic paralysis occurs.

Depolarizing blockers also have 2 quaternary N^+ atoms but the molecule is long, slender and flexible. The features of classical depolarizing block differ markedly from that of nondepolarizing block (*see* Fig. 8.1 and Table 8.2).

In many species, e.g. dog, rabbit, rat, monkey, in slow contracting soleus muscle of cat, and under certain conditions in man the classical depolarizing block described above (phase I block) is followed by phase II block, which is due to desensitization of N_M receptor to ACh, and superficially resembles nondepolarizing block in features. SCh readily produces phase II block in patients with atypical or deficient pseudocholinesterase.

ACTIONS

1. *Skeletal muscles* Intravenous injection of nondepolarizing blockers rapidly produces muscle weakness followed by flaccid paralysis. Small fast response muscles (fingers, extraocular) are affected first; paralysis spreads to hands, feet—arm, leg, neck, face—trunk—finally intercostal muscles—diaphragm: respiration stops. Recovery occurs in the reverse sequence; diaphragmatic contractions resume first.

Depolarizing blockers typically produce fasciculations lasting a few seconds before inducing flaccid paralysis, but fasciculations are not prominent in well-anaesthetized patients. Though the sequence in which muscles are involved is somewhat different from the competitive blockers (Table 8.2), the action of SCh develops with such rapidity that this is not appreciated. Apnoea generally occurs within 45–90 sec, but lasts only 2–5 min; recovery is rapid.

2. *Autonomic ganglia* Because the cholinergic receptors in autonomic ganglia are nicotinic (though of a different subclass N_N), competitive neuromuscular blockers produce some degree of ganglionic blockade. SCh may cause ganglionic stimulation.

3. *Histamine release* d-TC releases histamine from mast cells resulting in hypotension, flushing, bronchospasm and increased respiratory

Table 8.3: Comparative properties of neuromuscular blocking drugs

Drug	Dose£ (mg/kg)	Onset* (min)	Duration@ (min)	Hist. release	Gang. block	Vagal block
LONG ACTING						
1. d-Tubocurarine	0.2–0.4	4–6	30–60	+++	++	±
2. Pancuronium	0.04–0.1	4–6	40–80	±	±, St.	+
3. Doxacurium	0.03–0.08	4–8	60–120	+	–	–
4. Pipecuronium	0.05–0.08	2–4	50–100	±	–	–
INTERMEDIATE ACTING						
5. Vecuronium	0.08–0.1	2–4	30–60	±	–	±
6. Atracurium	0.3–0.6	2–4	20–35	+	–	–
7. Rocuronium	0.6–0.9	1–2	25–40	–	–	±
SHORT ACTING						
8. Mivacurium	0.07–0.15	2–4	12–20	+	–	–
9. Succinylcholine	0.5–0.8	1–1.5	3–6	++	St.	St.

£Initial paralysing dose for opioid/nitrous oxide/oxygen anaesthesia. In patients anaesthetised with ether/halothane/isoflurane, the dose may be ⅛–½ of the figure given.
*Time to maximal block after i.v. injection.
@Duration of surgical grade relaxation after usual clinical doses; time to 95% recovery of muscle twitch is nearly double of the figure given (especially for long-acting drugs). Duration is also dose dependent.
St. — Stimulation

secretions. Histamine releasing potential of other neuromuscular blockers is graded in Table 8.3.

4. C.V.S.

d-Tubocurarine produces a significant fall in BP. This is due to—

(a) ganglionic blockade,
(b) histamine release, and
(c) reduced venous return—a result of paralysis of limb and respiratory muscles.

Heart rate may increase due to vagal ganglionic blockade. Pancuronium and vecuronium also tend to cause tachycardia. All newer nondepolarizing drugs have negligible effects on BP and HR.

Cardiovascular effects of SCh are variable. BP occasionally falls on account of its muscarinic action causing vasodilatation.

5. G.I.T. The ganglion blocking activity of competitive blockers may enhance postoperative paralytic ileus after abdominal operations.

6. C.N.S. All neuromuscular blockers are quaternary compounds—do not cross blood-brain barrier—no CNS effects.

PHARMACOKINETICS

All neuromuscular blockers are quaternary compounds—not absorbed orally. They are practically always given i.v. Muscles with higher blood flow receive more drug and are affected earlier. Redistribution to non-muscular tissues plays a significant role in the termination of action of a single dose. They do not cross placenta or penetrate brain. d-TC, pancuronium, doxacurium and pipecuronium are partly metabolized while vecuronium, atracurium, rocuronium and mivacurium are largely metabolized in the body. Atracurium is inactivated in plasma by spontaneous nonenzymatic degradation (Hofmann elimination) in addition to that by cholinesterases. The unchanged drug is excreted in urine as well as in bile.

SCh is rapidly hydrolysed by plasma pseudocholinesterase—action lasts for 3 to 5 min. Some patients have genetically determined abnormality (low affinity for SCh) or deficiency of pseudocholinesterase. In them, SCh causes

dominant phase II blockade resulting in muscle paralysis and apnoea lasting for hours.

INTERACTIONS

1. *Thiopentone sod* and SCh solutions should not be mixed in the same syringe—react chemically.
2. *General anaesthetics* potentiate competitive blockers.
3. *Anticholinesterases* reverse the action of competitive blockers. Neostigmine 0.5–2 mg i.v. is almost routinely used after pancuronium and other long acting blockers to hasten recovery at the end of operation.
4. *Antibiotics* Aminoglycoside antibiotics reduce ACh release from prejunctional nerve endings by competing with Ca^{2+}. They interfere with mobilization of ACh containing vesicles from a central location to near the terminal membrane, and have a weak stabilizing action on the postjunctional membrane. In clinically used doses they do not by themselves produce muscle relaxation but potentiate competitive blockers. Tetracyclines (by chelating Ca^{2+}) polypeptide antibiotics, clindamycin and lincomycin also synergise with competitive blockers.
5. *Calcium channel blockers* Verapamil and others potentiate both competitive and depolarizing neuromuscular blockers.
6. *Diuretics* produce hypokalaemia which enhances competitive block.
7. *Diazepam*, *propranolol* and *quinidine* intensify competitive block, while high dose of corticosteroids reduce it.

TOXICITY

1. Respiratory paralysis and prolonged apnoea is the most important problem.
2. Flushing can occasionally occur with atracurium and mivacurium.
3. Fall in BP and cardiovascular collapse can occur, specially in hypovolemic patients.
4. Cardiac arrhythmias and even arrest have occurred, especially with SCh.
5. Precipitation of asthma with histamine releasing neuromuscular blockers.
6. Postoperative muscle soreness after SCh.

USES

1. The most important use of neuromuscular blockers is as adjuvants to general anaesthesia; adequate muscle relaxation can be achieved at lighter planes. They are specially valuable in abdominal and thoracic surgery. In dentistry they may be needed for setting of mandibular fractures.

Succinylcholine is employed for brief procedures, e.g. endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures and to treat laryngospasm, etc.

2. Convulsions and trauma from electroconvulsive therapy can be avoided by the use of muscle relaxants.
3. Severe cases of tetanus and status epilepticus, may be paralysed by a neuromuscular blocker (repeated doses of a competitive blocker) and maintained on intermittent positive pressure respiration.

DIRECTLY ACTING MUSCLE RELAXANTS

Dantrolene This muscle relaxant is chemically and pharmacologically entirely different from neuromuscular blockers. It does not affect neuromuscular transmission or MAP, but uncouples contraction from depolarization of the muscle membrane; depolarization triggered release of Ca^{2+} from sarcoplasmic reticulum is reduced.

Used orally dantrolene reduces spasticity in upper motor neurone disorders, hemiplegia, paraplegia, cerebral palsy and multiple sclerosis.

Used i.v. it is the drug of choice for malignant hyperthermia which is due to persistent release of Ca^{2+} from sarcoplasmic reticulum (induced by fluorinated anaesthetics and SCh in genetically susceptible individuals).

Muscular weakness is the dose limiting side effect. Troublesome diarrhoea is another problem. Long-term use can cause serious liver toxicity.

Quinine This antimalarial drug increases refractory period and decreases excitability of motor endplates. Muscle tone in myotonia congenita is reduced. Taken at bed time it may abolish nocturnal leg cramps in some patients.

CENTRALLY ACTING MUSCLE RELAXANTS

These are drugs which reduce skeletal muscle tone by a selective action in the cerebrospinal axis, without altering consciousness. They selectively depress spinal and supraspinal polysynaptic reflexes involved in the regulation of muscle tone without significantly affecting monosynaptically mediated stretch reflex. Polysynaptic pathways in the ascending reticular formation which are involved in the maintenance of wakefullness are also depressed, though to a lesser extent. All centrally acting muscle relaxants do have some sedative property and they overlap with anti-anxiety drugs. They have no effect on neuromuscular transmission and on muscle fibres, but reduce decerebrate rigidity, upper motor neurone spasticity and hyperreflexia. Prominent differences between centrally and peripherally acting muscle relaxants are listed in Table 8.4.

CLASSIFICATION

(i) *Mephenesin group* — Mephenesin, Carisoprodol, Chlorzoxazone, Chlormezanone, Methocarbamol.

(ii) *Benzodiazepines* — Diazepam and others.

(iii) *GABA derivative* — Baclofen.

(iv) *Central α_2 agonist* — Tizanidine.

Mephenesin was the first drug found to reduce muscle tone by depressing spinal internuncial neurones, which modulate polysynaptic reflexes that maintain muscle tone. It is not used clinically because of toxicity. Its congeners like *carisoprodol, chlorzoxazone, chlormezanone* and *methocarbamol* have low toxicity and are used for musculoskeletal disorders associated with muscle spasm. They are often combined with NSAIDs. However, clinical efficacy of none of the above drugs as muscle relaxant is well established. Gastric irritation and sedation are the most important side effects.

Diazepam (*see* Ch. 9) is the prototype of benzodiazepines (BZDs) which act in the brain on specific receptors enhancing GABAergic transmission. It reduces muscle tone by supra-spinal rather than spinal action. Sedation limits the dose which can be used for reducing muscle tone but gastric tolerance is very good. It is particularly valuable in spinal injuries and tetanus. Combined with analgesics, it is popular for rheumatic disorders associated with muscle spasm.

Baclofen It is an analogue of the inhibitory transmitter GABA; acts as selective $GABA_B$ receptor agonist.

The GABA receptors have been divided into:

$GABA_A$ receptor Intrinsic ion channel receptor—increases Cl^- conductance; blocked by bicuculline; facilitated by BZDs.

$GABA_B$ receptor G-protein coupled receptor; hyperpolarizes neurones by increasing K^+ conductance and altering Ca^{2+} flux; bicuculline insensitive.

Baclofen does not affect Cl^- transport and its actions are not antagonized by bicuculline.

The primary site of action of baclofen is in the spinal cord where it depresses both polysynaptic and monosynaptic reflexes. As such, it

Table 8.4: Comparative features of centrally acting and peripherally acting muscle relaxants

Centrally acting	*Peripherally acting*
1. Decrease muscle tone without reducing voluntary power	Cause muscle paralysis, voluntary movements lost
2. Selectively inhibit polysynaptic reflexes in CNS	Block neuromuscular transmission
3. Cause some CNS depression	No effect on CNS
4. Given orally, sometimes parenterally	Practically always given i.v.
5. Used in chronic spastic conditions, acute muscle spasms, tetanus	Used for short-term purposes (surgical operations)

does produce muscle weakness. It reduces spasticity in many neurological disorders like multiple sclerosis, amyotropic lateral sclerosis, spinal injuries and flexor spasms but is relatively ineffective in stroke, cerebral palsy, rheumatic and traumatic muscle spasms and parkinsonism.

Tizanidine This recently introduced clonidine congener is a central α_2 adrenergic agonist—inhibits release of excitatory amino acids in spinal interneurones. Facilitation of inhibitory transmitter glycine has also been demonstrated. It inhibits polysynaptic reflexes; reduces muscle tone and frequency of muscle spasms without reducing muscle strength.

It is indicated in spasticity due to neurological disorders and in painful muscle spasms of spinal origin. Side effects are dry-mouth, drowsiness, night-time insomnia and hallucinations. Dose-dependent elevation of liver test values has been noted.

Uses of centrally acting muscle relaxants

1. *Acute muscle spasms* Overstretching of a muscle, sprain, tearing of ligaments and tendons, dislocation, fibrositis, bursitis, etc. cause painful spasm of muscles. The mephenesin like and BZD muscle relaxants are often combined with analgesics. They may help to relieve trismus occurring after a dental procedure. However, efficacy of these drugs is not impressive.

2. *Torticollis*, *lumbago*, *backache*, *neuralgias* respond in the same way as acute muscle spasms.

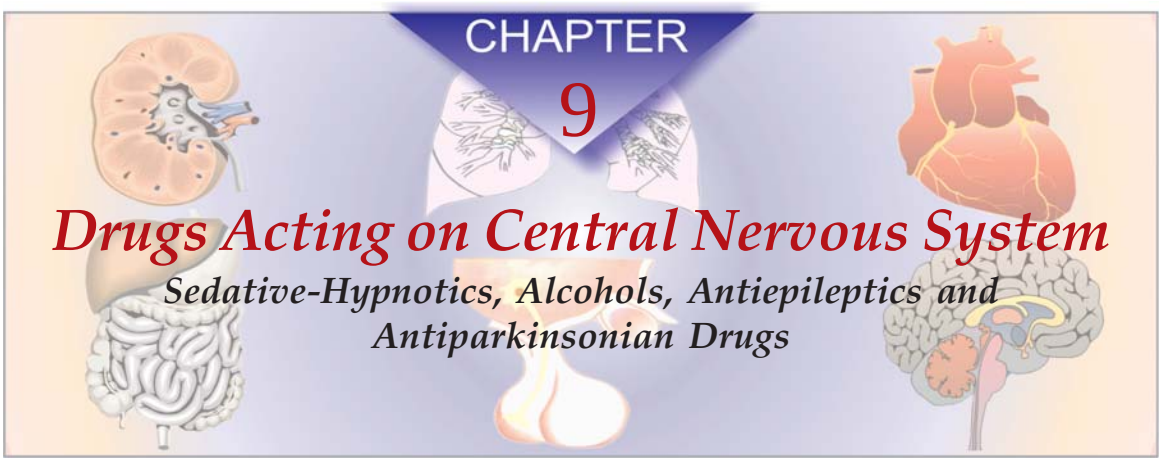
3. *Anxiety and tension* associated with increased tone of muscles.

4. *Spastic neurological diseases* like hemiplegia, paraplegia, spinal injuries, multiple sclerosis, and cerebral palsy are somewhat benefited by baclofen, diazepam, tizanidine and dantrolene.

5. *Tetanus* Most commonly diazepam is infused i.v. and the dose is titrated by the response. Methocarbamol is an alternative.

6. *Electroconvulsive therapy* Diazepam may be used to suppress convulsions.

7. *Orthopaedic manipulations* may be performed under the influence of diazepam or methocarbamol given i.v.



CHAPTER 9

Drugs Acting on Central Nervous System

Sedative-Hypnotics, Alcohols, Antiepileptics and Antiparkinsonian Drugs

SEDATIVE-HYPNOTICS

Sedative A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced. Sedation refers to decreased responsiveness to any level of stimulation; is associated with some decrease in motor activity and ideation.

Hypnotic A drug that induces and/or maintains sleep, similar to normal arousable sleep. This is not to be confused with 'hypnosis' meaning a trans like state in which the subject becomes passive and highly suggestible.

The sedatives and hypnotics are more or less general CNS depressants with somewhat differing time-action and dose-action relationships. However, there is considerable overlap; a hypnotic at lower dose may act as sedative. Thus, sedation—hypnosis—general anaesthesia may be regarded as increasing grades of CNS depression. Hypnotics given in high doses can produce general anaesthesia. However, benzodiazepines (BZDs) cannot be considered nonselective or general CNS depressants like barbiturates.

Treatment of insomnia is the most important use of this class of drugs.

Sleep

The duration and pattern of sleep varies considerably among individuals. Age has an important effect on quantity and depth of sleep. It has been recognized that sleep is an architectured cyclic process in which the subject passes from stage 0 (awake) to stage 4 (cerebral sleep) through stage 1 (dozing), stage 2 (unequivocal sleep) and stage 3 (deep sleep transition) of non-rapid eye movement (N-REM) sleep interspersed with REM (paradoxical) sleep (Fig. 9.1). About 20–30% of sleep time is spent in REM, while stage 2 occupies the major part of NREM sleep. Dreams and nightmares occur during REM sleep. The cyclic pattern of sleep stages, particularly REM, is considered to be essential for sleep to be refreshing.

CLASSIFICATION

1. *Barbiturates* For practical reasons divided into—

Long acting	Phenobarbitone
Short acting	Pentobarbitone
Ultrashort acting	Thiopentone sod.

2. *Benzodiazepines* May be divided according to primary use—

Hypnotic	*Antianxiety*
Diazepam	Diazepam
Flurazepam	Chlordiazepoxide
Nitrazepam	Oxazepam
Temazepam	Lorazepam
Triazolam	Alprazolam
Midazolam	*Anticonvulsant*
	Diazepam
	Clonazepam
	Clobazam

3. *Newer nonbenzodiazepine hypnotics*

Zopiclone	Zolpidem

Chloral hydrate, Triclophos, Paraldehyde, Methaqualone and Meprobamate are historical sedative-hypnotics no longer used.

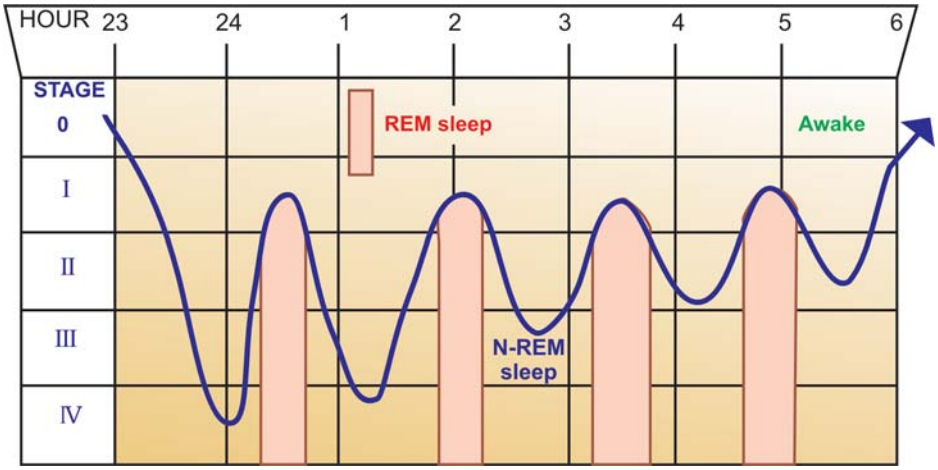


Fig. 9.1: A normal sleep cycle

In addition, some antihistaminics (promethazine, diphenhydramine), some neuroleptic/antidepressants (chlorpromazine, amitriptyline), some anticholinergic (hyoscine) and opioids (morphine, pethidine) have significant sedative action, but are not reliable for treatment of insomnia.

BARBITURATES

Barbiturates have been popular hypnotics and sedatives of the last century up to 1960s but are not used now. However, they are described first as they are the prototype of CNS depressants.

Barbiturates are substituted derivatives of barbituric acid (malonyl urea). They have variable lipid solubility, the more soluble ones are more potent and shorter acting. They are insoluble in water but their sodium salts dissolve yielding highly alkaline solution.

Pharmacological actions

Barbiturates are general depressants for all excitable cells, the CNS is most sensitive where the effect is almost global, but certain areas are more susceptible. They produce dose-dependent effects:

sedation → sleep → anaesthesia → coma.

Hypnotic dose shortens the time taken to fall asleep and increases sleep duration. The sleep is arousable, but the subject may feel confused and unsteady if waken early. REM and stage 3, 4 sleep are decreased; REM-NREM sleep cycle is disrupted. The effects on sleep become progressively less marked if the drug is given every night consecutively. A rebound increase in REM sleep and nightmares is often noted when the drug is discontinued after a few days of use. Hangover (dizziness, distortions of mood, irritability and lethargy) may occur in the morning after a nightly dose.

Sedative dose (smaller dose of a longer acting barbiturate) given at daytime can produce drowsiness, reduction in anxiety and excitability. However, barbiturates do not have selective anti-anxiety action. They can impair learning, short-term memory and judgement, and have no analgesic action; small doses may even cause hyperalgesia. An attempt to put a patient in severe pain to sleep with a barbiturate alone may result in restlessness, mental confusion, even convulsion. Euphoria may be experienced by addicts.

Barbiturates have anticonvulsant property. The 5-phenyl substituted agents (phenobarbitone) have higher anticonvulsant : sedative ratio, i.e. they have specific anticonvulsant action.

Barbiturates depress all areas of the CNS, but the reticular activating system is most sensitive;

its depression is primarily responsible for inability to maintain wakefulness.

Mechanism of action Barbiturates appear to act primarily at the GABA : BZD receptor–Cl^- channel complex (*see* Fig. 9.2) and potentiate GABAergic inhibition by increasing the lifetime of Cl^- channel opening induced by GABA. They do not bind to the BZD receptor, but bind to another site on the same macromolecular complex to exert the GABA-facilitatory action. At high concentrations, barbiturates directly increase Cl^- conductance (GABA-mimetic action; contrast BZDs which have only GABA-facilitatory action) and inhibit Ca^{2+} dependent release of neurotransmitters. In addition, they depress glutamate-induced neuronal depolarization through AMPA receptors. At very high concentrations, barbiturates depress Na^+ and K^+ channels also.

Respiration is depressed by relatively higher doses. Barbiturates do not have selective antitussive action.

Hypnotic doses of barbiturates produce a slight decrease in BP and heart rate: magnitude of change not differing from that during normal sleep. Toxic doses produce marked fall in BP due to ganglionic blockade, vasomotor centre depression and direct decrease in cardiac contractility. However, the dose producing cardiac arrest is about 3 times larger than that causing respiratory failure.

Tone and motility of bowel is decreased slightly by hypnotic doses; more profoundly during intoxication.

Barbiturates tend to reduce urine flow by decreasing BP and increasing ADH release.

Pharmacokinetics

Barbiturates are well absorbed from the g.i. tract. They are widely distributed in the body. The rate of entry into CNS is dependent on lipid solubility: highly lipid soluble thiopentone has practically instantaneous entry while less lipid soluble ones (pentobarbitone) take longer; phenobarbitone enters very slowly. Plasma protein binding varies with the compound, e.g. thiopentone 75%, phenobarbitone 20%.

Three processes are involved in termination of action of barbiturates: the relative importance of each varies with the compound.

(a) *Redistribution* It is important in the case of highly lipid soluble thiopentone and other ultrashort acting barbiturates. After their i.v. injection, consciousness is regained in 8–12 min due to redistribution (*see* Ch. 2), while the ultimate disposal occurs by metabolism (t½ of elimination phase is 9 hours).

(b) *Metabolism* Drugs with intermediate lipid solubility (short acting barbiturates) are primarily metabolized in liver by oxidation, dealkylation and conjugation. Their plasma t½ ranges from 12–40 hours.

(c) *Excretion* Barbiturates with low lipid solubility (long acting agents) are significantly excreted unchanged in urine. The t½ of phenobarbitone is 80–120 hours. Alkalinization of urine increases ionization and excretion. This is most significant in the case of long acting agents.

Barbiturates induce hepatic microsomal enzymes and increase the rate of their own metabolism as well as that of many other drugs.

Uses

Except for phenobarbitone in epilepsy and thiopentone in anaesthesia barbiturates are seldom used now. They are occasionally employed as adjuvants in psychosomatic disorders.

Adverse effects

Side effects Hangover, mental confusion, impaired performance and traffic accidents.

Idiosyncrasy In an occasional patient barbiturates produce excitement.

Hypersensitivity Rashes, swelling of eyelids, lips, etc.

Tolerance and dependence Both cellular and pharmacokinetic tolerance develops on repeated use.

Psychological as well as physical dependence occurs and barbiturates have considerable abuse liability—one of their major disadvantages. Withdrawal symptoms are—excitement, hallucinations, delirium, convulsions; deaths have occurred.

Acute barbiturate poisoning

Manifestations are due to excessive CNS depression—patient is flabby and comatose with shallow and failing respiration, fall in BP and cardiovascular collapse, renal shut down, pulmonary complications, bullous eruptions.

Lethal dose depends on lipid solubility. It is 2–3 g for the more lipid soluble agents (short acting barbiturates) and 5–10 g for less lipid soluble phenobarbitone.

Treatment

Gastric lavage; supportive measures such as patent airway, assisted respiration, oxygen, maintenance of blood volume by fluid infusion and use of vasopressors.

Forced alkaline diuresis: with mannitol and sodium bicarbonate in the case of long acting barbiturates only. Haemodialysis and haemoperfusion is highly effective in removing long acting as well as short acting barbiturates.

There is no specific antidote for barbiturates. The approach is to keep the patient alive till the poison has been eliminated.

Interactions

1. Barbiturates induce the metabolism of many drugs and reduce their effectiveness—warfarin, steroids (including contraceptives), tolbutamide, griseofulvin, chloramphenicol, theophylline.
2. Additive action with other CNS depressants —alcohol, antihistamines, opioids, etc.
3. Sodium valproate increases plasma concentration of phenobarbitone.
4. Phenobarbitone competitively inhibits as well as induces phenytoin and imipramine metabolism: complex interaction.
5. Phenobarbitone decreases absorption of griseofulvin from the g.i.t.

BENZODIAZEPINES (BZDs)

Chlordiazepoxide and diazepam were introduced around 1960 as antianxiety drugs. Since then, this class has proliferated and has gained popularity over barbiturates as hypnotic and sedative as well, because—

1. BZDs have a high therapeutic index. Ingestion of even 50 hypnotic doses does not usually endanger life.
2. Hypnotic doses do not affect respiration or cardiovascular functions.
3. BZDs have practically no action on other body systems. Only on i.v. injection the BP falls and cardiac contractility decreases.
4. BZDs cause less distortion of sleep architecture.
5. BZDs do not alter disposition of other drugs by microsomal enzyme induction.
6. They have lower abuse liability: tolerance is mild, psychological and physical dependence and withdrawal syndrome are less marked.
7. A specific BZD antagonist *flumazenil* has been developed which can be used in case of poisoning.

CNS actions The overall action of all BZDs is qualitatively similar, but there are prominent differences in selectivity and time course of action: different members are used for different purposes. In contrast to barbiturates, they are not general depressants, but exert relatively selective anxiolytic, hypnotic, muscle relaxant and anticonvulsant effects. Even when apparently anaesthetic dose of diazepam is administered i.v., some degree of awareness is maintained.

They hasten onset of *sleep*, reduce intermittent awakening and increase total sleep time. Time spent in stage 2 is increased while that in stage 3 and 4 is decreased. They tend to shorten REM phase, but effect is less marked than with barbiturates. Most subjects wake up with a feeling of refreshing sleep. Some degree of tolerance develops to the action of BZDs on sleep after repeated nightly use.

Given i.v., diazepam causes analgesia. In contrast to barbiturates, BZDs do not produce hyperalgesia.

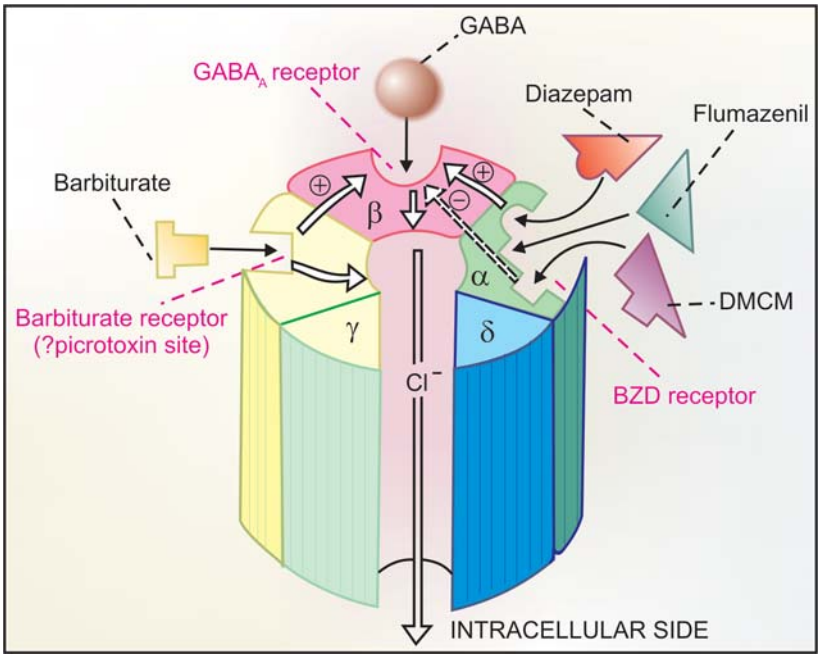


Fig. 9.2: Schematic depiction of GABA$_A$-benzodiazepine receptor-chloride channel complex
The chloride channel is gated by the primary ligand GABA. The benzodiazepine (BZD) receptor modulates GABA$_A$ receptor in either direction : agonists like diazepam facilitate, while inverse agonists like DMCM hinder GABA mediated Cl$^-$ channel opening, and BZD antagonist flumazenil blocks the action of both. The barbiturate receptor, located elsewhere, also facilitates GABA and is capable of opening Cl$^-$ channel directly as well. Bicuculline blocks GABA$_A$ receptor, while picrotoxine blocks the Cl$^-$ channel directly

Other actions Diazepam decreases nocturnal gastric secretion and prevents stress ulcers. BZDs do not significantly affect bowel movement.

Site and mechanism of action

Benzodiazepines act preferentially on midbrain ascending reticular formation (which maintains wakefulness) and on limbic system (thought and mental functions). Muscle relaxation is produced by a primary medullary site of action and ataxia is due to action on cerebellum.

BZDs act by enhancing presynaptic/post-synaptic inhibition through a specific BZD receptor which is an integral part of the GABA$_A$ receptor–Cl$^-$ channel complex. The subunits of this complex form a pentameric transmembrane anion channel (Fig. 9.2) gated by the primary ligand (GABA), and modulated by secondary ligands which include BZDs. The modulatory BZD receptor increases the frequency of Cl$^-$ channel opening induced by submaximal concentrations of GABA. The GABA$_A$ antagonist bicuculline antagonizes BZD action in a non-competitive manner. It is noteworthy that the BZDs do not themselves increase Cl$^-$ conductance; have only GABA facilitatory but no GABA mimetic action. This probably explains the lower ceiling CNS depressant effect of BZDs.

In fact, the BZD receptor appears to be capable of fine tuning GABA action in either direction. While the BZD-agonists enhance GABA induced hyperpolarization (due to influx of Cl$^-$ ions), and decrease firing rate of neurones, other compounds called *BZD-inverse agonists* like dimethoxyethyl-carbomethoxy-β-carboline (DMCM) inhibit GABA action and are convulsants. The competitive BZD-antagonist flumazenil blocks the sedative action of BZDs as well as the convulsant action of DMCM.

Table 9.1: Some pharmacokinetic and clinical features of benzodiazepines used as hypnotics

	Drug	t½ (hr)*	Redistribution$	Hypnotic dose (mg)	Clinical indications
I.	LONG ACTING				
	Flurazepam	50–100	–	15–30	Chronic insomnia, short-term insomnia
	Diazepam	30–60	+	5–10	with anxiety; Frequent nocturnal awakening;
	Nitrazepam	30	±	5–10	Night before operation or dental procedure
II.	SHORT ACTING				
	Temazepam	8–12	+	10–20	Individuals who react unfavourably to
	Triazolam	2–3	-	0.125–0.25	unfamiliar surroundings or unusual timings
	Midazolam	2	-	7.5	of sleep. Sleep onset difficulties.

* t½ of elimination phase, including that of active metabolite

$ + indicates that redistribution contributes to termination of action of single dose

Pharmacokinetics

There are marked pharmacokinetic differences among BZDs because they differ in lipid solubility by > 50-fold. Oral absorption of some is rapid while that of others is slow. Absorption from i.m. sites is irregular except for lorazepam. Plasma protein binding also varies markedly (flurazepam 10% to diazepam 99%). BZDs are widely distributed in the body. The more lipid soluble members enter brain rapidly and have a two phase plasma concentration decay curve; first due to distribution and later due to elimination. A relatively short duration of action is obtained with single dose of a drug that is rapidly redistributed, even though it may have a long elimination t½. Using the elimination t½ alone to predict duration of action may be misleading. However, elimination t½ determines duration of action in case of drugs whose elimination is by far the dominant feature or when the drug is given repeatedly.

Benzodiazepines are metabolized in liver by dealkylation and hydroxylation to many metabolites, some of which may be active. The biological effect half-life of these drugs may be longer than the plasma t½ of the administered compound. Some BZDs (e.g. diazepam) undergo enterohepatic circulation. BZDs and their phase I metabolites are excreted in urine as glucuronide conjugates. BZDs cross placenta and are secreted in milk.

Drugs with a long t½ or those which generate active metabolites cumulate on nightly use; their action may then extend into the next day. Some features of BZDs used as hypnotic are given in Table 9.1.

Adverse effects

Benzodiazepines are relatively safe drugs. Side effects of hypnotic doses are dizziness, vertigo, ataxia, disorientation, amnesia, prolongation of reaction time—impairment of psychomotor skills (should not drive). Hangover is less common. Weakness, blurring of vision, dry mouth and urinary incontinence are sometimes complained. Like any hypnotic, BZDs can aggravate sleep apnoea.

Tolerance to the sedative effects develops gradually, but there is little tendency to increase the dose. Cross tolerance to alcohol and other CNS depressants occurs.

The dependence producing liability of BZDs is low. They are seldom abused alone. Drug abusers find them rather bland (except rapidly absorbed midazolam) and prefer other CNS depressants. Withdrawal syndrome is generally mild. Drug seeking behaviour is not prominent. Anxiety, insomnia, restlessness, malaise, loss of appetite, bad dreams is all that occurs in most cases. Agitation, panic reaction, tremors and delirium are occasional; convulsions are rare.

Interactions

BZDs synergise with alcohol and other CNS depressants leading to excessive impairment. Concurrent use with sod. valproate has provoked psychotic symptoms.

Drug interactions due to microsomal enzyme induction are not significant.

Action of BZDs can be prolonged by CYP 3A4 inhibitors like ketoconazole, erythromycin and others. Cimetidine, isoniazid and oral contraceptives also retard BZD metabolism.

NON-BENZODIAZEPINE HYPNOTICS

Zopiclone This newer cyclopyrrolone hypnotic is an agonist at $GABA_A$ receptor and potentiates GABA by binding to a site other than that for BZDs. Its effects on sleep resemble those of BZDs, but it does not alter REM sleep and tends to prolong stages 3 and 4. It is reported not to disturb sleep architecture or produce hangover or withdrawal phenomena: has been used to weanoff insomniacs taking regular BZD medication.

Zopiclone is indicated for short-term treatment of insomnia.

Zolpidem An imidazopyridine which preferentially acts on ω_1 subtype of BZD receptors that are important in mediating hypnotic effect of BZDs. Only some BZD like actions but not others are prominent. Hypnotic effect is pronounced, but anticonvulsant, muscle relaxant and antianxiety effects are not evident. Its advantages are: relative lack of effect on sleep stages; minimal residual daytime sedation or fading of hypnotic action on repeated nightly use; no/little rebound insomnia on discontinuation; near absence of tolerance or physical dependence and low abuse potential combined with safety in overdose like BZDs.

Because of short t½ (2.5 hr), it can also be taken later in night when attempt to fall asleep spontaneously has failed.

USES

Currently, BZDs are one of the most frequently prescribed drugs. They have also been combined with many other categories of drugs with a view to improve efficacy by relieving attendant anxiety.

1. As hypnotic When indicated, BZDs are the hypnotic of choice and the newer non-BZD compounds zopiclone or zolpidem are also being used.

Insomnia arises under a variety of circumstances. It could be a long term (months-years), short term (weeks) or transient (a day or two, mostly situational) problem.

Dentists are likely to need to prescribe a hypnotic either to ensure sleep night before the dental procedure in an apprehensive patient, or to supplement analgesics before and after dental surgery. A longer acting BZD, like diazepam, is mostly preferred. Because of rapid onset of action oral zolpidem can be given to anxious patients in the dentist's office before carrying out the dental procedure.

2. Other uses

- As anxiolytic and for daytime sedation
- As anticonvulsant, especially emergency control of status epilepticus, febrile convulsions, tetanus, etc.
- As centrally acting muscle relaxant
- For preanaesthetic medication, i.v. anaesthesia or conscious sedation.
- Alcohol withdrawal in dependent subjects.
- Along with analgesics, NSAIDs, spasmolytics, antiulcer and many other drugs.

BENZODIAZEPINE ANTAGONIST

Flumazenil It is a BZD analogue which has little intrinsic activity (practically no effect on normal subjects), but competes with BZD agonists as well as inverse agonists for the BZD receptor and reverses their depressant or stimulant effects respectively.

Flumazenil abolishes the hypnogenic, psychomotor, cognitive and EEG effects of BZDs.

On i.v. injection action of flumazenil starts in seconds and lasts for 1–2 hr; elimination t½ is 1 hr. It has been used to reverse the effect of BZD employed for i.v. anaesthesia or conscious sedation, and as an antidote for BZD overdose/poisoning.

ETHYL ALCOHOL (Ethanol)

Alcohols are hydroxy derivatives of aliphatic hydrocarbons. When unqualified, 'alcohol' refers to *ethyl alcohol* or *ethanol*. Pharmacology of alcohol is important for its presence in beverages (which have been used since recorded history) and for alcohol intoxication, rather than as a drug.

PHARMACOLOGICAL ACTIONS

Local actions Ethanol is a mild rubefacient and counterirritant when rubbed on skin. By evaporation it produces cooling. Applied to delicate skin (scrotum) or mucous membranes it produces irritation and burning sensation: should not be applied in the mouth. Injected s.c. it causes intense pain, inflammation and necrosis followed by fibrosis. Injected round a nerve it produces permanent damage.

Alcohol is an astringent—precipitates surface proteins and hardens skin. By precipitating bacterial proteins it acts as an antiseptic. The antiseptic action increases with concentration from 20 to 70%, remains constant from 70 to 90% and decreases above that.

CNS Alcohol is a neuronal depressant. Since the highest areas are most easily deranged and these are primarily inhibitory—apparent excitation and euphoria are experienced at lower plasma concentrations (30–100 mg/dl). Hesitation, caution, self-criticism and restraint are lost first. Mood and feelings are altered; anxiety may be allayed. With increasing concentration (100–150 mg/dl) mental clouding, disorganization of thought, impairment of memory and other faculties, alteration of perception and drowsiness supervene. At 150–200 mg/dl the person is sloppy, ataxic and drunk; 200–300 mg/dl result in stupor and above this unconsciousness prevails, medullary centres are paralysed and death may occur. Though alcohol can produce anaesthesia, margin of safety is narrow.

Any measurable concentration of alcohol produces a measurable slowing of reflexes: driving is dangerous. Performance is impaired, fine discrimination and precise movements are obliterated; errors increase.

Alcohol can induce sleep but is not a dependable hypnotic. Some individuals report poor quality of sleep and early morning awakening. Sleep architecture may be disorganized and sleep apnoea aggravated. It raises pain threshold and also alters reaction to it, but is not a dependable analgesic—severe pain can precipitate confusion and convulsions. During the time alcohol is acting on brain, it exerts anticonvulsant action, but this is followed by lowering of seizure threshold: seizures may be precipitated in epileptics. Chronic alcohol abuse damages brain neurones.

Other actions Alcohol affects many body functions in a dose-dependent manner.

1. Vasodilatation, flushing, tachycardia, mild rise in BP at low doses but fall in BP at high levels.
2. Respiratory centre is depressed at high concentrations.
3. Though alcohol is reputed to combat cold because it produces a sense of warmth due to cutaneous vasodilatation, heat loss is actually greater in cold surroundings.
4. Dilute alcohol (10%) stimulates gastric secretion, but high concentrations inhibit it and cause mucosal congestion progressing to gastritis.

Alcohol : conscious → anaesthesia → death.

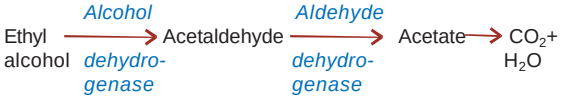
Ether : conscious → anaesthesia → death.

Gastroesophageal reflux is worsened due to decrease in the tone of lower esophageal sphincter. Bowel movement may be altered.

5. Moderate amounts of alcohol do not cause liver damage in well nourished individuals, but chronic alcoholism along with nutritional deficiencies may cause alcoholic cirrhosis of liver.
6. Regular intake of small to moderate amounts of alcohol raises HDL-cholesterol level: risk of coronary artery disease is reduced by 15–35%.
7. Urine flow may increase due to inhibition of ADH secretion.
8. Though reputed as an aphrodisiac, alcohol actually impairs performance of sexual act.
9. Uterine contractions are dampened at moderate blood levels.
10. Hyperglycaemia (due to Adr release) occurs initially, but high levels deplete hepatic glycogen and cause hypoglycaemia.

PHARMACOKINETICS

Though some alcohol is absorbed from stomach, very rapid absorption occurs when it reaches duodenum and small intestine. Limited first pass metabolism takes place in stomach wall and in liver. Alcohol gets distributed widely in the body (vol of distribution 0.7 L/kg), crosses blood-brain barrier efficiently: concentration in brain is very near blood concentration. It also crosses placenta freely. It is oxidized in liver to the extent of 98%. Even with high doses, not more than 10% escapes metabolism.



Metabolism of alcohol follows *zero order* kinetics, i.e. a constant amount (8–12 ml of absolute alcohol/hour) is degraded in unit time, irrespective of blood concentration. Thus, rate of consuming drinks governs whether a person will get drunk.

Excretion occurs though kidney and lungs, but neither is quantitatively significant. Concentration in exhaled air is about 0.05% of blood concentration: this is utilized for medicolegal determination of drunken state. The subject blows in a balloon and alcohol is measured by portable breath analyser.

INTERACTIONS

1. Alcohol synergises with tranquilizers, antidepressants, antihistaminics, hypnotics, opioids → marked CNS depression with motor impairment can occur: Chances of accidents increase.
2. Individuals taking sulfonylureas (especially chlorpropamide), certain cephalosporins (cefoperazone) or metronidazole have experienced bizarre, somewhat disulfiram like reactions when they consume alcohol.
3. Acute alcohol ingestion inhibits, while chronic intake induces tolbutamide, phenytoin (and many other drugs) metabolism.
4. Insulin and sulfonylureas: alcohol enhances hypoglycaemia acutely.
5. Aspirin and other NSAIDs cause more gastric bleeding when taken with alcohol.
6. Alcoholics are more prone to paracetamol toxicity due to enhanced generation of its toxic metabolite.

FOOD VALUE

Alcohol requires no digestion and is metabolized rapidly. It is an energy yielding substrate: 7 Cal/g, but these cannot be stored. It also does not supply body building and other essential constituents of food. Those who consume substantial part of their caloric intake as alcohol, often suffer from nutritional deficiencies. Thus, alcohol is an imperfect and expensive food.

TOXICITY

A. *Side effects of moderate drinking* Nausea, vomiting, flushing, hangover, traffic accidents.

B. *Acute alcoholic intoxication* Hypotension, gastritis, hypoglycaemia, collapse, respiratory depression, coma and death.

Treatment: Institute gastric lavage, maintain patent airway and take steps to prevent aspiration

of vomitus. Positive pressure respiration may be needed if it is markedly depressed. Most patients will recover with supportive treatment, maintenance of fluid and electrolyte balance and correction of hypoglycaemia by glucose infusion till alcohol is metabolized.

C. Chronic alcoholism On chronic intake, tolerance develops to subjective and behavioral effects of alcohol, but is generally of a low degree. It is both pharmacokinetic (reduced rate of absorption due to gastritis and faster metabolism due to enzyme induction) and cellular tolerance. Psychic dependence often occurs even with moderate drinking; depends a lot on individual's likings and attitudes.

Physical dependence occurs only on heavy and round-the-clock drinking (if alcohol is present in the body continuously). Heavy drinking is often associated with nutritional deficiencies, because food is neglected and malabsorption may occur. In addition to impaired mental and physical performance, neurological afflictions are common—polyneuritis, pellagra, tremors, seizures, loss of brain mass, Wernicke's encephalopathy, Korsakoff's psychosis and megaloblastic anaemia. Alcoholic cirrhosis of liver, hypertension, cardiomyopathy, CHF, arrhythmias, stroke, acute pancreatitis, impotence, gynaecomastia, infertility and skeletal myopathy are other complications. Incidence of oropharyngeal, esophageal and hepatic malignancy and respiratory infections is high; immune function is depressed.

Dental implications Alcoholics have higher incidence of heavy dental plaque, calculus deposits, chronic periodontitis and tooth loss due to poor oral hygiene. Dentists, while prescribing metronidazole or certain cephalosporins for periodontal infections should warn patients not to drink. Concurrent ingestion of NSAIDs and alcohol should be prohibited.

Treatment: Psychological and medical supportive measures are needed during withdrawal. Substitution therapy with BZDs like diazepam or chlordiazepoxide is given to suppress withdrawal syndrome, followed by their gradual discontinuation. The long acting opioid antagonist *naltrexone* helps to prevent relapse of alcoholism.

Disulfiram It is an aldehyde dehydrogenase inhibitor which prevents further oxidation of acetaldehyde generated from ingested alcohol. As a result, when the subject drinks a small quantity of alcohol after taking disulfiram, he experiences distressing symptoms like flushing, burning sensation, throbbing headache, sweating, uneasiness, tightness in chest, vomiting, etc. (aldehyde syndrome). This has been used as an aversion technique in chronic alcoholics who have been motivated and have stopped drinking. However, because of risk of severe reaction, it is rarely employed.

CLINICAL USES

Medicinal uses of ethanol are primarily restricted to external application and as a vehicle for liquid preparations used internally.

1. As antiseptic and disinfectant: because of good cleansing property and that it evaporates without leaving any residue, alcohol is used to disinfect working surfaces in dentistry. Being irritant, it is not suitable for application to oral mucosa.
2. Rubefacient and counterirritant for sprains, joint pains, etc.
3. Rubbed into the skin to prevent (but not to treat) bedsores. Astringent action of alcohol is utilized in antiperspirant and aftershave lotions.
4. Alcoholic sponges to reduce body temperature in fever.
5. Intractable neuralgias (trigeminal and others), severe cancer pain—injection of alcohol round the nerve causes permanent loss of transmission.
6. To ward off cold—may benefit by causing vasodilatation of blanched mucosae.
7. As appetite stimulant and carminative.
8. To treat methanol poisoning.

METHYL ALCOHOL (Methanol, Wood alcohol)

Methyl alcohol is added to rectified spirit to render it unfit for drinking. It is only of toxicological importance.

Unscrupulous mixing of methylated spirit with alcoholic beverages or its inadvertent ingestion results in methanol poisoning.

Methanol is metabolized to formaldehyde and formic acid by alcohol and aldehyde dehydrogenases respectively, but the rate is $^1/_7$th that of ethanol. Like ethanol, it follows *zero order* kinetics and t½ of 20–60 hours has been measured.

Methanol also is a CNS depressant, but less potent than ethanol. Toxic effects of methanol are largely due to formic acid, since its further metabolism is slow and folate dependent.

Manifestations of methanol poisoning are vomiting, headache, epigastric pain, uneasiness, dyspnoea, bradycardia and hypotension. Delirium may occur and the patient may suddenly pass into coma. *Acidosis* is prominent and entirely due to production of formic acid. The specific toxicity of formic acid is *retinal damage*. Blurring of vision, congestion of optic disc followed by blindness always precede death which is due to respiratory failure.

Treatment

1. Keep the patient in a quiet, dark room; protect the eyes from light.
2. Gastric lavage with Sod. bicarbonate, supportive measures to maintain ventilation and BP.
3. Combat acidosis by i.v. *Sod. bicarbonate* infusion—the most important measure; prevents retinal damage and other symptoms.
4. Pot. chloride infusion is needed only when hypokalaemia occurs due to alkali therapy.
5. *Ethanol* retards methanol metabolism. This helps by reducing the rate of generation of toxic metabolites.
6. Haemodialysis: clears methanol as well as its toxic metabolite formate and hastens recovery.
7. *Fomepizole* (4-methylpyrazole) is a specific inhibitor of alcohol dehydrogenase—retards methanol metabolism. It has several advantages over ethanol, but is not available commercially.
8. Folate therapy: Calcium leucovorin injected repeatedly has been shown to reduce blood formate levels by enhancing its metabolism.

ANTIEPILEPTIC DRUGS

Epilepsies These are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus, regions into which the discharges spread and postictal depression of these regions. Epilepsies have been classified variously; major types are:

1. Generalised seizures

1. *Generalised tonic-clonic seizures* (GTCS, major epilepsy, grand mal): commonest, lasts 1–2 min.
The usual sequence is aura—cry—unconsciousness—tonic spasm of all body muscles—clonic jerking followed by prolonged sleep and depression of all CNS functions.

2. *Absence seizures* (minor epilepsy, petit mal): prevalent in children, lasts about 1/2 min.
Momentary loss of consciousness, patient apparently freezes and stares in one direction, no muscular component or little bilateral jerking. EEG shows characteristic 3 cycles per second spike and wave pattern.

3. *Atonic seizures* (Akinetic epilepsy): Unconsciousness with relaxation of all muscles due to excessive inhibitory discharges. Patient may fall.

4. *Myoclonic seizures* Shock-like momentary contraction of muscles of a limb or the whole body.

II. Partial seizures

1. *Simple partial seizures* (SPS, cortical focal epilepsy): lasts 1/2–1 min. Often secondary. Convulsions are confined to a group of muscles or localized sensory disturbance depending on the area of cortex involved in the seizure, without loss of consciousness.

2. *Complex partial seizures* (CPS, temporal lobe epilepsy, psychomotor): attacks of bizarre and confused behaviour and purposeless movements, emotional changes lasting 1–2 min along with impairment of consciousness. An aura often precedes. The seizure focus is located in the temporal lobe.

3. *Simple partial or complex partial seizures secondarily generalized* The partial seizure occurs first and evolves into generalized tonic-clonic seizures with loss of consciousness.

Most of the cases are primary (idiopathic), some may be secondary to trauma/surgery on head, intracranial tumour, tuberculoma, cysticercosis, cerebral ischaemia, etc. Treatment is symptomatic and the same whether epilepsy is primary or secondary.

CLASSIFICATION

1. *Barbiturate*	Phenobarbitone
2. *Deoxybarbiturate*	Primidone
3. *Hydantoin*	Phenytoin
4. *Iminostilbene*	Carbamazepine

5. *Succinimide*	Ethosuximide
6. *Aliphatic carboxylic acid*	Valproic acid (sodium valproate)
7. *Benzodiazepines*	Clonazepam, Diazepam, Clobazam
8. *Phenyltriazine*	Lamotrigine
9. *Cyclic GABA analogue*	Gabapentin
10. *Newer drugs*	Vigabatrin, Topiramate

Phenobarbitone

Phenobarbitone is the first efficacious antiepileptic introduced in 1912. $GABA_A$ receptor mediated synaptic inhibition appears to be its most important mechanism of sedative as well as anticonvulsant action. Phenobarbitone has specific anticonvulsant activity which is not entirely dependent on general CNS depression. With continued use of phenobarbitone sedation wanes off but not the anticonvulsant action.

The major drawback of phenobarbitone as an antiepileptic is its sedative action. Long-term administration (as needed in epilepsy) may produce additional side effects like—behavioral abnormalities, diminution of intelligence, impairment of learning and memory, hyperactivity in children, mental confusion in older people.

Uses Phenobarbitone is one of the cheapest and least toxic antiepileptics. It has broad-spectrum efficacy in generalized tonic-clonic (GTC), simple partial (SP) and complex partial (CP) seizures: but is less popular than carbamazepine, phenytoin or valproate.

Status epilepticus: Phenobarbitone may be injected i.m. or i.v. but response is slow to develop.
It is not effective in absence seizures.

Primidone A deoxybarbiturate, converted by liver to phenobarbitone and phenylethyl malonamide (PEMA). Activity is mainly due to these active metabolites. Antiepileptic efficacy and side effects are similar to phenobarbitone. However, it may control seizures in some patients refractory to other drugs.

Phenytoin (Diphenylhydantoin)

Phenytoin is a major antiepileptic drug, but is not a CNS depressant; some sedation occurs at therapeutic doses, that does not increase further with dose; rather toxic doses produce excitement. Tonic-clonic epilepsy is suppressed but paroxysmal focal EEG discharge and 'aura' persist.

Mechanism of action: Phenytoin has a stabilizing influence on neuronal membrane—prevents repetitive detonation of normal brain cells during '*depolarization shift*'. This is achieved by prolonging the inactivated state of voltage sensitive neuronal Na^+ channel (Fig. 9.3) that governs the refractory period of the neurone. As a result, high frequency discharges are inhibited with little effect on normal low frequency discharges. Intracellular accumulation of Na^+ that occurs during repetitive firing is prevented.

Its ability to selectively inhibit high frequency firing confers efficacy in trigeminal neuralgia and cardiac arrhythmias as well.

Pharmacokinetics Absorption of phenytoin by oral route is slow, mainly because of its poor aqueous solubility. It is widely distributed in the body and is 80–90% bound to plasma proteins.

Phenytoin is metabolized in liver by hydroxylation and glucuronide conjugation. The kinetics of metabolism is *capacity limited*; changes from first order to zero order over the therapeutic range—small increments in dose produce disproportionately high plasma concentrations. The t½ (12–24 hr) progressively increases (up to 60 hr) when plasma concentration rises.

Adverse effects These are numerous; some occur at therapeutic plasma concentration after prolonged use, while others are a manifestation of toxicity due to overdose.

At therapeutic levels

(a) Gum hypertrophy: Commonest (20% incidence), more in younger patients and is due to overgrowth of gingival collagen fibres. It can be minimized by maintaining good oral

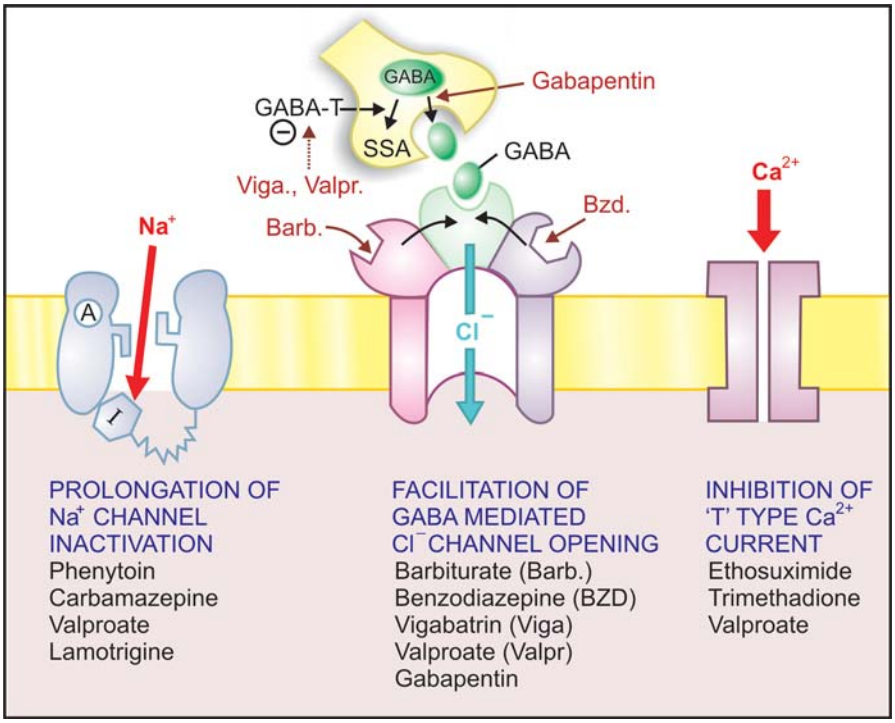


Fig. 9.3: Major mechanisms of anticonvulsant action
A: Activation gate; I: Inactivation gate; GABA-T: GABA transaminase; SSA: Succinic semialdehyde

hygiene. In some patients it may be so massive as to require surgery.

(b) Hirsutism, coarsening of facial features (troublesome in young girls), acne.

(c) Hypersensitivity reactions are—rashes, DLE, lymphadenopathy; neutropenia is rare but requires discontinuation of therapy.

(d) Megaloblastic anaemia: phenytoin decreases folate absorption and increases its excretion.

(e) Osteomalacia

(f) Used during pregnancy—can produce foetal hydantoin syndrome (hypoplastic phalanges, cleft palate, hare lip, microcephaly).

At high plasma levels (dose-related toxicity)

(a) Cerebellar and vestibular manifestations: ataxia, vertigo, diplopia, nystagmus are the most characteristic features.

(b) Drowsiness, behavioral alterations, mental confusion and hallucinations.

(c) Epigastric pain, nausea and vomiting.

(d) Fall in BP and cardiac arrhythmias occur only on i.v. injection. The injected vein may be damaged and thrombosed.

Interactions Phenobarbitone competitively inhibits phenytoin metabolism, while by enzyme induction both enhance each other's degradation—unpredictable overall interaction.

- Carbamazepine and phenytoin increase each other's metabolism.
- Valproate displaces protein bound phenytoin and decreases its metabolism: plasma level of unbound phenytoin increases.
- Chloramphenicol, isoniazid, cimetidine, dicumarol, and warfarin inhibit phenytoin metabolism—can precipitate its toxicity.
- Phenytoin induces microsomal enzymes and increases degradation of steroids (failure of oral contraceptives), digitoxin, doxycycline, theophylline.

Uses Phenytoin is one of the most widely used antiepileptic drugs for—

1. Generalized tonic-clonic, simple and complex partial seizures. It is ineffective in absence seizures.
2. Status epilepticus: occasionally used by slow i.v. injection.
3. Trigeminal neuralgia: second choice drug to carbamazepine.
4. Cardiac arrhythmias: specially digitalis induced.

Carbamazepine

Chemically related to imipramine, it was introduced in the 1960s for trigeminal neuralgia; is now an established antiepileptic drug. Its pharmacological actions resemble phenytoin but many differences have been noted. Though its action on Na^+ channels (prolongation of inactivated state) is similar to phenytoin, the profile of action on neuronal systems in brain is different.

Recently, it has been found to have therapeutic effect in mood disorders. Carbamazepine has an antidiuretic action, probably by enhancing ADH action on renal tubules.

Oral absorption of carbamazepine is slow and variable. It is 75% bound to plasma proteins and metabolized in liver by oxidation to an active metabolite (10-11 epoxy carbamazepine) as well as by hydroxylation and conjugation to inactive ones. Initially, its plasma t½ is 20–40 hours but decreases to 10–20 hr on chronic medication due to autoinduction of metabolism.

Adverse effects Carbamazepine produces dose-related neurotoxicity—sedation, dizziness, vertigo, diplopia and ataxia. Vomiting, diarrhoea, worsening of seizures are also seen with higher doses.

Hypersensitivity reactions are rashes, photosensitivity, hepatitis, lupus like syndrome and rarely agranulocytosis, aplastic anaemia.

Increased incidence of minor foetal malformations has been reported. Its combination with valproate doubles teratogenic frequency.

Interactions Carbamazepine is an enzyme inducer: can reduce efficacy of haloperidol and oral contraceptives. Metabolism of carbamazepine is induced by phenobarbitone, phenytoin, valproate and *vice versa*.

Erythromycin, fluoxetine, isoniazid inhibit metabolism of carbamazepine.

Uses It is the most effective drug for CPS and shares first choice drug status with phenytoin for GTCS and SPS.

Trigeminal and related neuralgias: carbamazepine is the drug of choice. These neuralgias are characterized by attacks of high intensity electric shock-like or stabbing pain set off by even trivial stimulation of certain trigger zones in the mouth or on the face. Drugs benefit by interrupting temporal summation of afferent impulses (by a selective action on high frequency nerve impulses). Carbamazepine is not an analgesic but has a specific action (almost diagnostic) in these neuralgias. About 60% patients respond well. Phenytoin and baclofen are less efficacious alternatives.

Manic depressive illness and acute mania: as an alternative to lithium.

Ethosuximide

It has an entirely different profile of anticonvulsant action than phenytoin and is clinically effective only in absence seizures. The primary action appears to be exerted on thalamocortical system which is involved in the generation of absence seizures. Thalamic neurones exhibit prominent 'T' (transient) current which is low threshold Ca^{2+} current that amplifies repetitive spikes. Ethosuximide selectively suppresses T current without affecting other types of Ca^{2+} or Na^+ currents. It also does not potentiate GABA at therapeutic concentrations. This correlates well with its selective action in absence seizures, which is its only indication.

Valproic acid (Sodium valproate)

It is a broad-spectrum anticonvulsant effective in several experimental models of epilepsy. Remarkably, at anticonvulsant doses, valproate produces little sedation or other central effects. It is effective in partial seizures, GTCS as well as absence seizures.

Valproate appears to act by multiple mechanisms:
(i) A phenytoin like frequency dependent prolongation of Na^+ channel inactivation.
(ii) Attenuation of Ca^{2+} mediated 'T' current (ethosuximide like).
(iii) Augmentation of release of inhibitory transmitter GABA by inhibiting its degradation (by GABA-transaminase).

Adverse effects Toxicity of valproate is low.
Anorexia, vomiting, drowsiness, ataxia and tremor are dose-related side effects. However, cognitive and behavioral effects are not prominent.
Alopecia, curling of hair, and increased bleeding tendency have been observed.
A rare but serious adverse effect is fulminant hepatitis; occurs only in children (especially below 3 yr age).
Used during pregnancy, it has produced neural tube defects (spina bifida) in the offspring.

Uses Valproic acid is the drug of choice for absence seizures.
It is an alternative/adjuvant drug for GTCS, SPS and CPS.
Myoclonic and atonic seizures—control is often incomplete, but valproate is the drug of choice.
Mania and bipolar illness: as alternative to lithium.

Interactions

- Valproate increases plasma levels of phenobarbitone by inhibiting its metabolism.
- It displaces phenytoin from protein binding site and decreases its metabolism → phenytoin toxicity.
- Valproate and carbamazepine induce each other's metabolism.
- Concurrent administration of clonazepam and valproate is contraindicated because absence status may be precipitated.
- Foetal abnormalities are more common if valproate and carbamazepine are given concurrently.

Clonazepam

It is a benzodiazepine with prominent anticonvulsant properties. Though in experimental models of chronic epilepsy it inhibits spread rather than the focus itself, it is singularly ineffective in GTCS.

Benzodiazepines potentiate GABA induced Cl^- influx to produce sedation and the same mechanism has been held responsible for the anticonvulsant property. At large doses, high frequency discharges are inhibited akin to phenytoin.

The most important side effect of clonazepam is sedation and dullness. Motor disturbances and ataxia are dose-related adverse effects.

Clonazepam has been primarily employed in absence seizures. It is also useful as an adjuvant in myoclonic and akinetic epilepsy. However, its value is limited by development of tolerance.

Clobazam This BZD analogue is generally used as adjuvant to other antiepileptic drugs in refractory epilepsy.

Diazepam

It has anticonvulsant activity in a variety of models but is not used for long-term therapy of epilepsy because of prominent sedative action and rapid development of tolerance to the antiepileptic effect. However, it is the drug of choice for emergency control of convulsions, e.g. status epilepticus, tetanus, eclampsia, convulsant drug poisoning, etc.

Rectal instillation of diazepam is the preferred therapy for febrile convulsions in children.

Lamotrigine A new anticonvulsant having carbamazepine-like action profile. Prolongation of Na^+ channel inactivation and suppression of high frequency firing has been demonstrated. In addition, it may directly block voltage sensitive Na^+ channels, thus stabilizing the presynaptic membrane and preventing release of excitatory neurotransmitters, mainly glutamate and aspartate.

Lamotrigine is a broad-spectrum antiepileptic. Initially found useful as add-on therapy in refractory cases of partial seizures and GTCS, it has now been shown effective as monotherapy as well. Absence and myoclonic or akinetic epilepsy cases have also been successfully treated.

Side effects are sleepiness, dizziness, diplopia, ataxia and vomiting.

Gabapentin This lipophilic GABA derivative crosses to the brain and enhances GABA release, but does not act as agonist at $GABA_A$ receptor. Added to a first line drug, it reduces seizure frequency in refractory partial seizures with or without generalization. Beneficial effects in manic depressive illness and migraine have also been reported. Gabapentin is now considered to be the first line drug for pain due to diabetic neuropathy and postherpetic neuralgia.

Vigabatrin (γ vinyl GABA) It is an inhibitor of GABA-transaminase, the enzyme which degrades GABA. Its anticonvulsant action may be due to increase in synaptic GABA concentration. It is effective in many patients with refractory epilepsy, especially partial seizures with or without generalization. It is at present approved only for adjuvant medication.

Topiramate This weak carbonic anhydrase inhibitor has broad-spectrum anticonvulsant activity and appears to act by multiple mechanisms, *viz* phenytoin-like prolongation of Na^+ channel inactivation, GABA potentiation by a postsynaptic effect and antagonism of certain glutamate receptors.

Topiramate is indicated for supplementing primary antiepileptic drug in refractory SPS, CPS and GTCS. Promising results have been obtained in myoclonic epilepsy also.

TREATMENT OF EPILEPSIES

Antiepileptic drugs suppress seizures but do not cure the disorder; the disease may fade out though after years of successful control. The aim of drugs is to control and totally prevent all seizure activity at an acceptable level of side effects. The cause of epilepsy should be searched in the patient; if found and treatable, an attempt to remove it should be made. Some general principles of symptomatic treatment with antiepileptic drugs are:

(i) Choice of drug (Table 9.2) and dose is according to the seizure type(s) and need of the individual patient.

(ii) Initiate treatment early, because each seizure episode increases the propensity to further attacks. Start with a single drug, gradually

Table 9.2: Choice of antiseizure drugs

	Type of seizure	*First choice drugs*	*Second choice drugs*	*Alternative/Add-on drugs*
1.	Generalised tonic-clonic/ simple partial with or without generalization	Carbamazepine, Phenytoin	Valproate, Phenobarbitone, Primidone	Lamotrigine, Gabapentin, Topiramate
2.	Complex partial with or without generalization	Carbamazepine, Valproate, Phenytoin	Gabapentin, Lamotrigine	Clobazam, Vigabatrin, Topiramate
3.	Absence	Valproate, Ethosuximide	Clonazepam, Lamotrigine	Clobazam
4.	Myoclonic	Valproate	Clonazepam, Lamotrigine	Primidone, Clobazam, Topiramate
5.	Atonic	Valproate	Clonazepam, Clobazam	Primidone, Lamotrigine
6.	Febrile seizures	Diazepam (rectal)	—	—
7.	Status epilepticus	Diazepam (i.v.) Clonazepam (i.v.)	Phenytoin (i.v.) Phenobarbitone (i.v., i.m.)	Gen. anaesthetics

increase dose till full control of seizures or side effects appear. Use combinations when all reasonable monotherapy fails.

(iii) Therapy should be as simple as possible. A seizure diary should be maintained.

(iv) All drug withdrawals should be gradual (except in case of toxicity). Prolonged therapy (may be life long, or at least 3 years after the last seizure) is needed. Withdrawal may be attempted in selected cases.

(v) Dose regulation may be facilitated by monitoring of steady-state plasma drug levels.

(vi) When women on antiepileptic therapy conceive, antiepileptic drugs should not be stopped. Though most antiseizure drugs have been shown to increase the incidence of birth defects, discontinuation of therapy carries a high risk of status epilepticus. It may be advisable to substitute valproate.

(vii) In the event of a patient developing an attack of tonic-clonic seizures during dental procedure, the first priority is to prevent injuries due to biting or fall. Any denture or instrument should be immediately removed from the mouth and a gag placed between the teeth. The head should be turned to the side to prevent the tongue from falling back and obstructing the airway. The seizure usually passes off in a few minutes. Continuation or postponement of the procedure after the fit is over depends on the circumstances. The patient must be sent back home with an escort. In case the seizures do not stop, management is as for status epilepticus.

Status epilepticus It is the continuous clinical manifestation of an epileptic discharge without intermission. Recurrent tonic-clonic convulsions without recovery of consciousness is an emergency; fits have to be controlled as quickly as possible to prevent death and permanent brain damage.

(a) Diazepam 10 mg i.v. bolus injection (2 mg/min) followed by fractional doses every 10 min or slow infusion titrated to control the fits is the therapy of choice. Clonazepam (1–2 mg i.v.) is an alternative.

(b) Phenobarbitone (100–200 mg i.m./i.v.) or phenytoin (25 mg/min i.v., maximum 1 g) act more slowly; may be used alternatively to diazepam or substituted for it after the convulsions have been controlled.

(c) A general anaesthetic and curarization with positive pressure respiration may be required in cases not responding to the above drugs.

(d) General measures including maintenance of airway, oxygenation, fluid and electrolyte balance, BP, normal cardiac rhythm, euglycaemia and care of the unconscious must be taken.

ANTIPARKINSONIAN DRUGS

These are drugs that have a therapeutic effect in parkinsonism.

Parkinsonism It is an extrapyramidal motor disorder characterized by *rigidity*, *tremor* and *hypokinesia* with secondary manifestations like defective posture and gait, mask-like face and sialorrhoea; dementia may accompany. If untreated, the symptoms progress over several years to endstage disease in which the patient is rigid, unable to move, unable to breathe properly; succumbs mostly to chest infections/embolism.

Parkinson's disease (PD) is a progressive degenerative disorder, mostly affecting older people, first described by James Parkinson in 1817.

The most consistent lesion in PD is degeneration of neurones in substantia nigra pars compacta and the nigrostriatal (dopaminergic) tract. This results in deficiency of dopamine (DA) in the striatum which controls muscle tone and coordinates movements. An imbalance between dopaminergic (inhibitory) and cholinergic (excitatory) system in the striatum occurs giving rise to the motor defect. Though the cholinergic system is not primarily affected, its suppression (by anticholinergics) tends to restore balance.

Drug-induced temporary parkinsonism due to neuroleptics, metoclopramide (dopaminergic blockers) is now fairly common.

CLASSIFICATION

I. *Drugs affecting brain dopaminergic system*
   (a) *Dopamine precursor* : Levodopa (l-dopa)

(b) *Peripheral decarboxylase inhibitors* : Carbidopa, Benserazide.
(c) *Dopaminergic agonists*: Bromocriptine, Ropinirole, Pramipexole
(d) *MAO-B inhibitor:* Selegiline
(e) *COMT inhibitors:* Entacapone, Tolcapone
(f) *Dopamine facilitator:* Amantadine.

II. *Drugs affecting brain cholinergic system*
(a) *Central anticholinergics :* Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.
(b) *Antihistaminics :* Orphenadrine, Promethazine.

LEVODOPA

Levodopa has a specific salutary effect in PD: efficacy exceeding that of any other drug used alone. It is inactive by itself, but is the immediate precursor of the transmitter DA. More than 95% of an oral dose is decarboxylated in the peripheral tissues (mainly gut and liver). DA thus formed acts on heart, blood vessels, other peripheral organs and on CTZ (though located in the brain, i.e. floor of IV ventricle, it is not bound by blood-brain barrier). About 1–2% of administered levodopa crosses to the brain, is taken up by the surviving dopaminergic neurones, converted to DA which is stored and released as a transmitter.

Actions

1. CNS Levodopa hardly produces any effect in normal individuals. Marked symptomatic improvement occurs in parkinsonian patients. Hypokinesia and rigidity resolve first, later tremor as well. Secondary symptoms of posture, gait, handwriting, speech, facial expression, mood, self-care and interest in life are gradually normalized.

The effect of levodopa on behaviour has been described as a 'general alerting response'. In some patients this progresses to excitement—frank psychosis may occur. Embarrassingly disproportionate increase in sexual activity has also been noted.

2. CVS The peripherally formed DA can cause tachycardia by acting on β adrenergic receptors. Postural hypotension due to central or ganglionic action is quite common.

3. CTZ The peripherally formed DA gains access to the CTZ without hindrance—elicits nausea and vomiting by stimulating dopaminergic D2 receptors. Tolerance occurs gradually to this action.

4. **Endocrine** DA acts on pituitary mammotropes to inhibit prolactin release → blood prolactin level falls.

Pharmacokinetics

Levodopa is rapidly absorbed from the small intestines by utilizing the active transport process meant for aromatic amino acids.

It undergoes high first pass metabolism in g.i. mucosa and liver. The peripheral and central pathway of metabolism of levodopa is depicted in Fig. 9.4.

About 1% of administered dose that enters brain, aided by amino acid carrier mediated active transport across brain capillaries, also undergoes the same transformation. The plasma t½ of levodopa is 1–2 hours. Pyridoxal is a cofactor for the enzyme dopa-decarboxylase. The metabolites are excreted in urine mostly after conjugation.

Adverse effects

Side effects of levodopa therapy are frequent and often troublesome. Some are prominent in the beginning of therapy while others appear late.

1. Nausea and vomiting: Tolerance gradually develops and then the dose can be progressively increased.
2. Postural hypotension: It occurs in about 1/3rd of patients, but is mostly asymptomatic; some patients experience dizziness, few have fainting attacks. Tolerance develops with continued treatment. Care should be taken by the dentist that patients on levodopa therapy do not sit up and leave the dental chair abruptly from a reclining position.

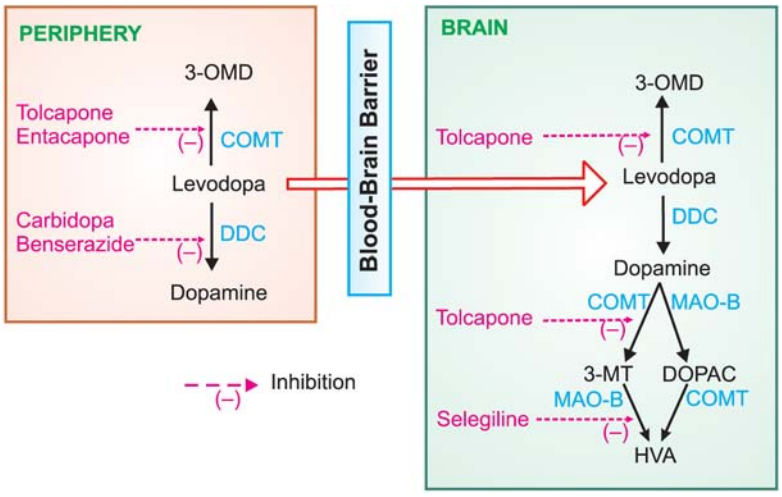


Fig. 9.4: Metabolic pathways of levodopa in the periphery and the brain.
3-OMD—3-O-methyldopa; COMT—catechol-O-methyl transferase; MAO—monoamine oxidase; 3-MT—3-methoxytyramine; DOPAC—3,4 dihydroxy phenylacetic acid; HVA—homovanillic acid (3-methoxy-4-hydroxy phenylacetic acid), DDC—dopa decarboxylase

3. Cardiac arrhythmias
4. Exacerbation of angina
5. Alteration in taste sensation
6. Abnormal movements: Facial tics, grimacing, tongue thrusting, choreoathetoid movements of limbs, etc. start appearing after a few months of use of levodopa. They may become as disabling as the original disease itself—are the most important dose limiting side effects. Orofacial dyskinesias may cause damage to teeth and pose difficulty in wearing dentures.
7. Behavioral effects: Range from mild anxiety, nightmares, etc. to severe depression, mania, hallucinations, mental confusion or frank psychosis.

3. Fluctuation in motor performance: After 2–5 years of therapy, the level of control of parkinsonian symptomatology starts showing fluctuation. 'End of dose' deterioration, develops into rapid 'switches' or 'on-off' effect. With time 'all or none' response develops, i.e. the patient is alternately well and disabled. This is probably a reflection of progression of the disorder: with progressive degeneration of DA neurones the ability to regulate storage and release of DA may be largely lost.

Interactions

1. Pyridoxine: Abolishes therapeutic effect by enhancing peripheral decarboxylation of levodopa.
2. Phenothiazines, butyrophenones, metoclopramide reverse the therapeutic effect of levodopa by blocking DA receptors.
3. Antihypertensives: postural hypotension is accentuated.

PERIPHERAL DECARBOXYLASE INHIBITORS

Carbidopa and *benserazide* are extracerebral dopa decarboxylase inhibitors; they do not penetrate blood-brain barrier and do not inhibit conversion of levodopa to DA in brain. Administered along with levodopa, they increase its t½ in the periphery and make more of it available to cross blood-brain barrier to reach its site of action.

Benefits obtained on combining with levodopa are—
1. The plasma t½ of levodopa is prolonged and its dose is reduced to approximately 1/4th.
2. Systemic concentration of DA is reduced, nausea and vomiting are not prominent.

3. Cardiac complications are minimized.
4. Pyridoxine reversal of levodopa effect does not occur.
5. 'On-off' effect is minimized.
6. Degree of improvement may be higher.

Problems not resolved or accentuated are—

1. Involuntary movements
2. Behavioral abnormalities

} may even be more pronounced and appear earlier.

3. Postural hypotension.

Currently, levodopa is practically always used along with a decarboxylase inhibitor

DOPAMINERGIC AGONISTS

The DA agonists can act on striatal DA receptors even in advanced patients who have largely lost the capacity to synthesize, store and release DA from levodopa. Moreover, they can be longer acting, exert subtype selective activation of DA receptors involved in parkinsonism and not share the concern expressed about levodopa of contributing to dopaminergic neuronal damage by oxidative metabolism.

Bromocriptine It is an ergot derivative which acts as potent agonist on D2, but as partial agonist or antagonist on D1 receptors. Improvement in parkinsonian symptoms occurs within ½–1 hr of an oral dose and lasts 6–10 hours. If used alone, doses needed in parkinsonism are high, expensive and often produce intolerable side effects—vomiting, hallucinations, hypotension, nasal stuffiness, conjunctival injection.

In parkinsonism, bromocriptine is used only in late cases as a supplement to levodopa. It serves to improve control and smoothen 'end of dose' and 'on-off' fluctuations. Dyskinesias are less prominent with bromocriptine compared to levodopa.

Ropinirole and Pramipexole These are two recently developed nonergoline, selective D2/D3 receptor agonists with negligible affinity for D1 and nondopaminergic receptors. Therapeutic effect as supplementary drugs to levodopa in advanced cases of PD, as well as side effect profile is similar to bromocriptine; but they are better tolerated with fewer g.i. symptoms.

Ropinirole and pramipexole are being increasingly used as monotherapy for early PD as well with the possible advantage of lower incidence of dyskinesias and motor fluctuations.

MAO-B INHIBITOR

Selegiline (Deprenyl) It is a selective MAO-B inhibitor. Two isoenzyme forms of MAO, termed MAO-A and MAO-B are recognized; both are present in peripheral adrenergic structures and intestinal mucosa, while the latter predominates in brain and blood platelets. Unlike nonselective MAO inhibitors, selegiline in low doses (10 mg/day) does not interfere with peripheral metabolism of dietary amines; CA accumulation and hypertensive reaction does not develop, while intracerebral degradation of DA is retarded. This is responsible for the therapeutic effect in parkinsonism. Higher doses can produce hypertensive interactions.

Selegiline alone has mild antiparkinsonian action in early cases. Administered with levodopa it prolongs levodopa action, attenuates motor fluctuations and decreases 'wearing off' effect. However, advanced cases with 'on-off' effect are not improved and the peak dose levodopa side effects such as dyskinesias, mental confusion or hallucinations may be worsened.

Selegiline interacts with pethidine causing excitement, rigidity, hyperthermia, respiratory depression. It may interact with tricyclic antidepressants and selective serotonin reuptake inhibitors as well.

COMT INHIBITORS

Two selective, potent and reversible COMT inhibitors *Entacapone* and *Tolcapone* have been introduced recently as adjuvants to levodopa-carbidopa for advanced PD. When peripheral decarboxylation of levodopa is blocked by carbidopa/benserazide, it is mainly metabolized by COMT to 3-O-methyldopa (*see* Fig. 9.4). Blockade of this pathway by entacapone/tolcapone prolongs the t½ of levodopa

and allows a larger fraction of administered dose to cross to brain. Since COMT plays a role in the degradation of DA in brain as well, COMT inhibitors could preserve DA formed in the striatum and supplement the peripheral effect. However, entacapone acts only in the periphery (probably because of short duration of action ~2 hr). For tolcapone also the central action is less important.

Entacapone may be used to smoothen 'wearing off' effect or increase 'on' time with levodopa-carbidopa. Because of reports of acute fatal hepatitis and rhabdomyolysis, use of tolcapone is highly restricted.

DOPAMINE FACILITATOR

Amantadine Developed as an antiviral drug for prophylaxis of influenza A_2, it was found serendipitiously to benefit parkinsonism. It acts rapidly but has lower efficacy than levodopa, though higher than anticholinergics. About 2/3rd patients derive some benefit. However, tolerance develops over months and the efficacy is lost. It appears to act by promoting presynaptic synthesis and release of DA in brain.

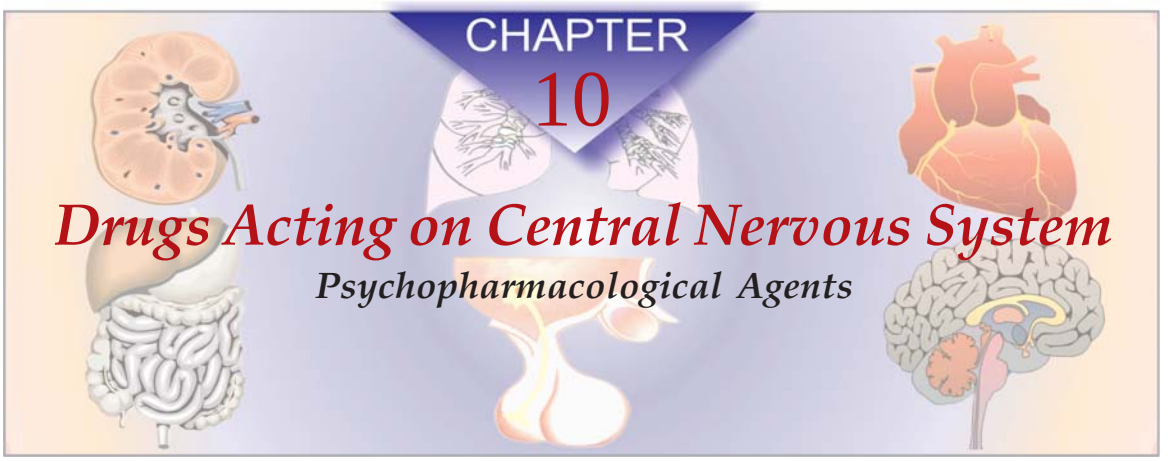
Amantadine can be used in milder cases, or in short courses to supplement submaximal doses of levodopa.

CENTRAL ANTICHOLINERGICS

These are drugs having a higher central : peripheral anticholinergic action ratio than atropine, but the pharmacological profile is similar to it. In addition, certain H_1 antihistaminics have significant central anticholinergic property. There is little to choose clinically among these drugs, though individual preferences vary.

They act by reducing the unbalanced cholinergic activity in striatum of parkinsonian patients. Generally, tremor is benefited more than rigidity; hypokinesia is affected the least. Sialorrhoea is controlled by their peripheral action. The overall efficacy is much lower than levodopa. However, they are cheap and produce less side effects than levodopa. They may be used alone in mild cases. In others, they can be combined with levodopa.

Anticholinergics are the only drugs effective in drug (phenothiazine) induced parkinsonism. The side effect profile is similar to atropine. Xerostomia caused by them may aggravate dental caries.



CHAPTER
10

Drugs Acting on Central Nervous System

Psychopharmacological Agents

The psychopharmacological agents or psychotropic drugs are those having primary effects on *psyche* (mental processes) and are used for treatment of psychiatric disorders.

Psychiatric diagnostic categories are often imprecise. The criteria adopted overlap in individual patients. Nevertheless, broad divisions have to be made, primarily on the basis of predominant manifestations, to guide the use of drugs.

Psychoses These are severe psychiatric illness with serious distortion of thought, behaviour, capacity to recognise reality and of perception (delusions and hallucinations). There is inexplicable misperception and misevaluation; the patient is unable to meet the ordinary demands of life.

(a) *Acute and chronic organic brain syndromes (cognitive disorders)* Such as delirium and dementia; some toxic or pathological basis can often be defined; prominent features are confusion, disorientation, defective memory and disorganized behaviour.

(b) *Functional disorders* No underlying cause can be defined; memory and orientation are mostly retained but emotion, thought and behaviour are seriously altered.

(i) *Schizophrenia* (split mind), i.e. splitting of perception and interpretation from reality—hallucinations, inability to think coherently.

(ii) *Paranoid states* with marked persecutory or other kinds of fixed delusions (false beliefs) and loss of insight into the abnormality.

Affective disorders The primary symptom is change in mood state; may manifest as:

Mania—elation, hyperactivity, uncontrollable thought and speech, may be associated with violent behaviour, or

Depression—sadness, loss of interest and pleasure, worthlessness, guilt, physical and mental slowing, melancholia, self destructive ideation.

It may be bipolar (manic-depressive) with cyclically alternating manic and depressive phases or unipolar (mania or depression) with waxing and waning course.

Neuroses These are less serious; ability to comprehend reality is not lost, though the patient may undergo extreme suffering. Depending on the predominant feature, it may be labelled as:

(a) *Anxiety* An unpleasant emotional state associated with uneasiness and concern for the future.

(b) *Phobic states* Fear of the unknown or of some specific objects, person or situations.

(c) *Obsessive compulsive* Limited abnormality of thought or behaviour (ritual like) which the patient is not able to overcome even on voluntary effort.

(d) *Reactive depression* due to physical illness, loss, blow to self-esteem or bereavement, but is excessive or disproportionate.

(e) *Post-traumatic stress disorder* Varied symptoms following distressing experiences like war, riots, earthquakes, etc.

(f) *Hysterical* Dramatic symptoms resembling serious physical illness, but situational, and always in the presence of others; the patient does not feign but actually undergoes the symptoms, though the basis is only psychic and not physical.

Pathophysiology of mental illness is not clear, though some ideas have been formed, e.g. dopaminergic overactivity in the limbic system may be involved in schizophrenia and mania; monoaminergic (NA, 5-HT) deficit may underlie depression. Treatment is empirical, symptom oriented and not disease specific. However, it is highly effective in many situations. Depending on the primary use, the psychotropic drugs may be grouped into:

1. *Antipsychotic* (neuroleptic, ataractic, major tranquillizer) useful in all types of functional psychosis, especially schizophrenia.
2. *Antianxiety* (anxiolytic-sedative, minor tranquillizer) used for anxiety and phobic states.
3. *Antidepressants* used for minor as well as major depressive illness, phobic states, obsessive-compulsive behaviour, and certain anxiety disorders.
4. *Antimanic* (mood stabiliser) used to control mania and to break into cyclic affective disorders.
5. *Psychotomimetic* (psychedelic, psychodysleptic, hallucinogen). These are seldom used therapeutically but produce psychosis like states, majority are drugs of abuse like LSD, cannabis.

Tranquillizer It is an old term meaning "a drug which reduces mental tension and produces calmness without inducing sleep or depressing mental faculties." It has been interpreted differently by different people; some extend it to cover both chlorpromazine like and antianxiety drugs, others feel that it should be restricted to the antianxiety drugs only. The term 'tranquillizer' is therefore best avoided.

ANTIPSYCHOTIC DRUGS (Neuroleptics)

These are drugs having a salutary therapeutic effect in psychoses.

CLASSIFICATION

1. *Phenothiazines*
   - *Aliphatic side chain*: Chlorpromazine, Triflupromazine
   - *Piperidine side chain*: Thioridazine
   - *Piperazine side chain*: Trifluoperazine, Fluphenazine
2. *Butyrophenones*: Haloperidol, Trifluperidol, Droperidol, Penfluridol
3. *Thioxanthenes*: Thiothixene, Flupenthixol
4. *Other heterocyclics*: Pimozide, Loxapine, Reserpine
5. *Atypical neuroleptics*: Clozapine, Risperidone, Olanzapine

Pharmacology of chlorpromazine (CPZ) is described as prototype. Comparative features of other drugs are presented in Table 10.1.

PHARMACOLOGICAL ACTIONS

1. CNS Effects differ in normal and psychotic individuals.

In normal individuals CPZ produces indifference to surroundings, paucity of thought, psychomotor slowing, emotional quietening, reduction in initiative and tendency to go off to sleep from which the subject is easily arousable. Spontaneous movements are minimized, but slurring of speech, ataxia or motor incoordination does not occur.

In a psychotic CPZ reduces irrational behaviour, agitation and aggressiveness and controls psychotic symptomatology. Disturbed thought and behaviour are gradually normalised, anxiety is relieved. Hyperactivity, hallucinations and delusions are suppressed.

All phenothiazines, thioxanthenes and butyrophenones have the same antipsychotic efficacy, but potency differs in terms of equieffective doses. The aliphatic and piperidine side chain phenothiazines (CPZ, triflupromazine, thioridazine) have low potency, produce more sedation and cause greater potentiation of hypnotics, opioids, etc. The sedative effect is produced immediately while antipsychotic effect takes weeks to develop. Moreover, tolerance develops to the sedative but not to the antipsychotic effect. Thus, the two appear to be independent actions.

Performance and intelligence are relatively unaffected but vigilance is impaired. Extrapyramidal motor disturbances (*see* adverse effects) are intimately linked to the antipsychotic effect but are more prominent in the high potency compounds and least in thioridazine, clozapine, etc. No consistent effect on sleep architecture has been noted.

Table 10.1: Comparative properties of antipsychotic drugs

Drug	Antipsychotic dose (mg/day)	Relative activity				Trade name
		Extrapyramidal	Sedative	Hypotensive	Antiemetic	
1. Chlorpromazine	100–800	++	+++	+++	++	LARGACTIL
2. Triflupromazine	50–200	+++	+++	++	+++	SIQUIL
3. Thioridazine	100–400	+	+++	+++	±	MELLERIL, THIORIL
4. Trifluoperazine	2–20	+++	+	+	+++	TRINICALM
5. Fluphenazine	1–10	+++	+	+	+++	ANATENSOL
6. Haloperidol	2–20	+++	+	+	+++	SERENACE, HALOPIDOL
7. Trifluperidol	1–8	+++	+	+	+++	TRIPERIDOL
8. Flupenthixol	3–15	+++	+	+	+	FLUANXOL
9. Pimozide	2–6	+++	++	+	+	ORAP, NEURAP
10. Loxapine	20–100	++	+	++	+	LOXAPAC
11. Clozapine	50–300	±	++	+++	–	LOZAPIN, SIZOPIN
12. Risperidone	2–12	++	++	+++	–	RESPIDON, SIZODON
13. Olanzapine	2.5–10	+	+	++	–	OLACE, OLZAP

Chlorpromazine lowers seizure threshold and can precipitate fits in untreated epileptics. The piperazine side chain compounds have a lower propensity for this action. Temperature control is knocked off at relatively higher doses rendering the individual poikilothermic—body temperature falls if surroundings are cold. The medullary respiratory and other vital centres are not affected, except at very high doses. It is very difficult to produce coma with these drugs. Neuroleptics, except thioridazine, have potent antiemetic action exerted through the CTZ. However, they are ineffective in motion sickness.

Mechanism of action All antipsychotics (except clozapine like) have potent dopamine D2 receptor blocking action; antipsychotic potency has shown good correlation with their capacity to bind to D2 receptor. Phenothiazines and thioxanthenes also block D1, D3 and D4 receptors. Blockade of dopaminergic projections to the temporal and prefrontal areas constituting the 'limbic system' and in mesocortical areas is probably responsible for the antipsychotic action.

The atypical antipsychotics like clozapine have weak D2 blocking action. However, clozapine has additional 5-HT_2 and α_1 blocking action, and is relatively selective for D4 receptors. Thus, antipsychotic property may depend on a specific profile of action of the drugs on several neurotransmitter receptors.

Dopaminergic blockade in the basal ganglia appears to cause the extrapyramidal symptoms, while that in CTZ is responsible for antiemetic action.

2. ANS Neuroleptics have varying degrees of α adrenergic blocking activity which may be graded as:
CPZ = triflupromazine > thioridazine > fluphenazine > haloperidol > trifluoperazine > clozapine > pimozide, i.e. more potent compounds have lesser α blocking activity.

Anticholinergic property of neuroleptics is weak and may be graded as:

thioridazine > chlorpromazine > triflupromazine > trifluoperazine = haloperidol.

The phenothiazines have weak H_1-antihistaminic and anti-5-HT actions as well.

3. Local anaesthetic Chlorpromazine is as potent a local anaesthetic as procaine. Others have weaker membrane stabilizing action.

4. CVS Neuroleptics produce hypotension (primarily postural) by a central as well as peripheral action on sympathetic tone. The hypotensive action is more marked after parenteral administration and roughly parallels the α adrenergic blocking potency. Partial tolerance develops after chronic use. Reflex tachycardia accompanies hypotension.

High doses of CPZ directly depress the heart and produce ECG changes (Q-T prolongation and suppression of T wave). CPZ exerts some antiarrhythmic action, probably due to membrane stabilization. Arrhythmia may occur in overdose, especially with thioridazine.

5. Endocrine Neuroleptics consistently increase prolactin release by blocking the inhibitory action of DA on pituitary lactotropes. This may result in galactorrhoea and gynaecomastia.

They reduce gonadotropin secretion, but amenorrhoea and infertility occur only occasionally. ACTH release in response to stress is diminished—corticosteroid levels fail to increase under such circumstances. Release of GH is also reduced, but this is not sufficient to cause growth retardation in children or to be beneficial in acromegaly.

Tolerance and dependence Tolerance to the sedative and hypotensive actions develops within days or weeks, but the antipsychotic, extrapyramidal and other actions based on DA antagonism do not display tolerance.

Neuroleptics are hedonically (pleasurably) bland drugs. Physical dependence is probably absent. No drug seeking behaviour is exhibited.

PHARMACOKINETICS

Oral absorption of CPZ is somewhat unpredictable and bioavailability is low. More consistent effects are produced after i.m. or i.v. administration. It is highly bound to plasma as well as tissue proteins. Volume of distribution is large (20 L/kg). It is metabolized in liver into a number of metabolites. The acute effects of a single dose generally last for 6–8 hours. The elimination t½ is variable, but mostly is in the range of 18–30 hours.

Atypical (second generation) neuroleptics Lately some antipsychotic drugs like *clozapine*, *risperidone* and *olanzapine* have been developed which have a pharmacological profile distinct from CPZ, produce few extrapyramidal symptoms, little hyperprolactinaemia; tardive dyskinesia is rare. They tend to suppress both positive and negative symptoms of schizophrenia (the older drugs have little effect on negative symptoms). Many patients refractory to the typical antipsychotics respond to these drugs. Clozapine and olanzapine are weak D2 receptor blockers, while risperidone has medium D2 affinity. However, they have additional 5-HT_2, α adrenergic, muscarinic and H_1 blocking property, and relative selectivity for D4 subtype of dopaminergic receptors. These features may account for the above differences.

The major limitation of clozapine is higher incidence of agranulocytosis and other blood dyscrasias. This is not the case with olanzapine and risperidone. Nevertheless, they are reserve drugs for refractory cases of schizophrenia.

ADVERSE EFFECTS

Neuroleptics are very safe drugs in single or infrequent doses, but side effects are common.

I. Based on pharmacological actions (dose related)

1. CNS Drowsiness, lethargy, mental confusion: more with low potency agents; increased appetite and weight gain; aggravation of seizures in epileptics.

2. α Adrenergic blockade Postural hypotension, palpitation, inhibition of ejaculation (especially with thioridazine) are more common with low potency phenothiazenes. Dentists should instruct patients to get up slowly from a reclining dental chair.

3. Anticholinergic Dry mouth, blurring of vision, constipation, urinary hesitancy in elderly males (thioridazine has the highest propensity); absent in high potency agents.

4. Endocrine Amenorrhoea, infertility, gynaecomastia, galactorrhoea—due to hyperprolactinaemia.

5. Extrapyramidal disturbances These are the major dose limiting side effects; more prominent with high potency drugs like fluphenazine, haloperidol, pimozide, etc., least with thioridazine, clozapine, olanzapine and low doses of risperidone. These are of following types.

(a) *Parkinsonism* with typical manifestations—rigidity, tremor, hypokinesia, mask like facies, shuffling gait. Anticholinergic antiparkinsonian drugs may counteract these symptoms.

A rare form of extrapyramidal side effect is perioral tremors 'rabbit syndrome' that generally occurs after few years of therapy.

(b) *Acute muscular dystonias* Bizarre muscle spasms, mostly involving linguo-facial muscles—grimacing, tongue thrusting, torticollis, locked jaw; occurs within a few hours of a single dose or at the most in the first week of therapy. It is more common in children below 10 years and in girls, particularly after parenteral administration; overall incidence is 2%. It lasts for one to few hours and then resolves spontaneously. One of the central anticholinergics, promethazine or hydroxyzine injected i.m. clears the reaction within 10–15 minutes.

(c) *Akathisia* Restlessness, feeling of discomfort, apparent agitation manifested as a compelling desire to move about but without anxiety is seen in some patients. A central anticholinergic may reduce the intensity in some cases; propranolol is more effective, but most cases require reduction of dose.

(d) *Malignant neuroleptic syndrome* It occurs rarely with high doses of potent agents; the patient develops marked rigidity, immobility, tremor, fever, semiconsciousness, fluctuating BP and heart rate; lasts for 5–10 days after drug withdrawal and may be fatal. Anticholinergics are of no help. Intravenous dantrolene may benefit. Bromocriptine in large doses has been found to be useful.

(e) *Tardive dyskinesia* It occurs late in therapy, sometimes even after withdrawal of the neuroleptic: manifests as purposeless involuntary facial and limb movements like constant chewing, pouting, puffing of cheeks, lip licking, choreoathetoid movements. Dental problems may arise because of involvement of orofacial muscles. It is probably a manifestation of progressive neuronal degeneration along with supersensitivity to DA. There is no satisfactory solution of the problem.

6. Miscellaneous Weight gain, blue pigmentation of exposed skin, corneal and lenticular opacities, retinal degeneration, cardiac arrhythmia are rare complications.

II. Hypersensitivity reactions These are not dose related.

1. Cholestatic jaundice.
2. Skin rashes, urticaria, contact dermatitis, photosensitivity.
3. Agranulocytosis is rare; more common with clozapine.

INTERACTIONS

1. Neuroleptics potentiate all CNS depressants—hypnotics, anxiolytics, alcohol, opioids, antihistaminics and analgesics. Dentists should be careful while prescribing any of these drugs to patients receiving neuroleptics.
2. Neuroleptics block the actions of levodopa and direct DA agonists in parkinsonism.
3. CPZ and few others abolish the antihypertensive action of clonidine and methyldopa, probably due to central α_2 adrenergic blockade.

4. Enzyme inducers (barbiturates, anticonvulsants) can reduce blood levels of neuroleptics.

USES

1. *Schizophrenia* The neuroleptics are used primarily in functional psychoses: have indefinable but definite therapeutic effect: produce a wide range of symptom relief. They control positive symptoms (hallucinations, delusions, disorganized thought, restlessness, insomnia, anxiety, fighting, aggression) better than negative symptoms (apathy, loss of insight and volition, affective flattening, poverty of speech, social withdrawal). Some patients do not respond, and virtually none responds completely. They are only symptomatic treatment, do not remove the cause of illness.

2. *Mania* Antipsychotics are required for rapid control, may be given i.m. Lithium or carbamazepine may be started simultaneously or after the acute phase.

3. *Organic brain syndromes* Neuroleptics are not very effective. May be used on a short-term basis.

4. *Anxiety* Neuroleptics should not be used for simple anxiety. Patients not responding to BZDs, or those having a psychotic basis for anxiety may be treated with a neuroleptic.

5. *As antiemetic* Neuroleptics are potent antiemetics—control a wide range of drug and disease induced vomiting at doses much lower than those needed in psychosis. They are ineffective in motion sickness: probably because dopaminergic pathway through the CTZ is not involved in this condition.

ANTIANXIETY DRUGS

Anxiety Some degree of anxiety is a part of normal life. Treatment is needed when it is disproportionate to the situation and excessive. Some psychotics also exhibit pathological anxiety.

Antianxiety drugs These are an ill-defined group of drugs, mostly mild CNS depressants which are aimed to control the symptoms of anxiety, produce a restful state of mind without interfering with normal mental or physical functions. In dentistry, the most important application of antianxiety drugs is for premedication of apprehensive patients and as adjuncts to local anaesthesia. BZDs also counteract the CNS toxicity of local anaesthetics. The anxiolytic-sedative drugs differ markedly from antipsychotics, and more closely resemble sedative-hypnotics. They:

1. Have no therapeutic effect to control thought disorder of schizophrenia.
2. Do not produce extrapyramidal side effects.
3. Have anticonvulsant property.
4. Produce physical dependence and carry abuse liability.

CLASSIFICATION

1. *Benzodiazepines*	Diazepam
	Chlordiazepoxide
	Oxazepam
	Lorazepam
	Alprazolam
2. *Azapirones*	Buspirone
	Ispapirone
	Gepirone
3. *Sedative antihistaminic*	Hydroxyzine
4. *β blocker*	Propranolol

In addition to the above drugs, antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs) are effective in obsessive-compulsive disorder (OCD), phobias, panic and many types of severe generalized anxiety disorders.

Benzodiazepines

The pharmacology of benzodiazepines (BZDs) as a class is described in Ch. 9. Some members have a slow and prolonged action, relieve anxiety at low doses without producing global CNS depression. In contrast to barbiturates, they are more selective for limbic system and have proven clinically better in both quality and quantity of

improvement in anxiety and stress-related symptoms. At antianxiety doses, cardiovascular and respiratory depression is minor.

Because anxiety is a common complaint, is a part of most physical and mental illness, and because BZDs:

(i) have little effect on other body systems,
(ii) have lower dependence producing liability,
(iii) are relatively safe even in gross overdosage,

they are presently one of the most widely used class of drugs. Potent BZDs like lorazepam and alprazolam injected i.m. have adjuvant role in the management of acutely psychotic and manic patients. Higher doses induce sleep and impair performance.

Adverse effects of BZDs noted in their use as hypnotics are described in Ch. 9. *Side effects* that occur in their use to relieve anxiety are—sedation, light-headedness, psychomotor and cognitive impairment, vertigo, confusional state (especially in elderly), increased appetite and weight gain, alterations in sexual function. Some women fail to ovulate while on regular use of BZDs. The major constraint in their long-term use for anxiety disorders is their potential to produce dependence.

Differences between individual BZDs recommended for anxiety are primarily pharmacokinetic: choice of one over the other is largely empirical.

Buspirone

It is the first azapirone, a new class of antianxiety drugs, distinctly different from BZDs.

- Does not produce significant sedation or cognitive/functional impairment.
- Does not interact with BZD receptor or modify GABAergic transmission.
- Does not produce tolerance or physical dependence.
- Does not suppress BZD or barbiturate withdrawal syndrome.
- Has no muscle relaxant or anticonvulsant activity.

Buspirone relieves mild-to-moderate generalized anxiety, but is ineffective in severe cases, in those showing panic reaction and in OCD. The therapeutic effect develops slowly: maximum benefit may be delayed up to 2 weeks. The mechanism of anxiolytic action is not clearly known, but may be dependent on its selective partial agonistic action on 5-HT_{1A} receptors. By stimulating presynaptic 5-HT_{1A} autoreceptors, it reduces activity of dorsal raphe serotonergic neurones.

Side effects of buspirone are minor: dizziness, nausea, headache, light-headedness, rarely excitement. It does not potentiate CNS depressants. Though most patients on buspirone remain alert, those operating machinery/motor vehicles should be cautioned.

Hydroxyzine A H_1 antihistaminic with sedative, antiemetic, antimuscarinic and spasmolytic properties. It may be used in reactive anxiety or that associated with marked autonomic symptoms.

β Blockers (see Ch. 6)

Many symptoms of anxiety (palpitation, rise in BP, shaking, tremor, gastrointestinal hurrying, etc.) are due to sympathetic overactivity and these symptoms reinforce anxiety. Propranolol and other nonselective β blockers help anxious patients troubled by these symptoms, by cutting the vicious cycle and provide symptomatic relief. They do not affect psychological symptoms such as worry, tension and fear, but are valuable in acutely stressful situations (examination fear, unaccustomed public appearance, etc.). They may be used for performance/situational anxiety or as adjuvant to BZDs.

ANTIDEPRESSANT DRUGS

These are drugs which can elevate mood in depressive illness. Practically all antidepressants affect monoaminergic transmission in the brain in one way or the other and many of them have other associated properties. Particularly over the past two decades, a large number of antidepres-

sants with an assortment of effects on reuptake/metabolism of biogenic amines and on pre/postjunctional aminergic/cholinergic receptors have become available so that a cogent classification is difficult. The following working classification may be adopted.

CLASSIFICATION

I. *Reversible inhibitors of MAO-A (RIMAs)*
Moclobemide, Clorgyline

II. *Tricyclic antidepressants (TCAs)*
A. *NA + 5-HT reuptake inhibitors*
Imipramine, Amitriptyline, Trimipramine, Doxepin, Dothiepin, Clomipramine
B. *Predominantly NA reuptake inhibitors*
Desipramine, Nortriptyline, Amoxapine

III. *Selective serotonin reuptake inhibitors (SSRIs)*
Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram

IV. *Atypical antidepressants*
Trazodone, Mianserin, Mirtazapine, Venlafaxine, Tianeptine, Amineptine, Bupropion.

MAO INHIBITORS

MAO is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines (Adr, NA, DA, 5-HT). Two isoenzyme forms of MAO have been identified.

MAO-A: Preferentially deaminates 5-HT and NA, and is inhibited by clorgyline, moclobemide.

MAO-B: Preferentially deaminates phenylethylamine and is inhibited by selegiline.

Dopamine is degraded equally by both isoenzymes.

Their distribution also differs. Peripheral adrenergic nerve endings, intestinal mucosa and human placenta contain predominantly MAO-A, while MAO-B predominates in certain areas of brain and in platelets. Liver contains both isoenzymes.

Iproniazid, a congener of the antitubercular drug isoniazid, was found to cause mood elevation that was ascribed to its ability to inhibit MAO. Iproniazid and related drugs that were nonselective and irreversible MAO inhibitors were used briefly as antidepressants, but were abandoned because of high toxicity and interaction with several foods and drugs. The most important interaction known as *cheese reaction* occurs when the subject receiving MAO inhibitor ingests tyramine rich foods including certain cheese, beer, wines, etc. The indirectly acting sympathomimetic amine escapes degradation in the intestinal wall and liver → reaches systemic circulation in high concentration and displaces large amounts of NA from transmitter loaded sympathetic nerve endings → hypertensive crisis, cerebrovascular accident and other complications. Similar hypertensive reaction can occur with cold remedies, levodopa, tricyclic antidepressants also. Because these MAO inhibitors in addition inhibit drug metabolizing enzymes, several drugs get potentiated. The opioid pethidine produces excitation, delirium, high fever, convulsions, etc. because its metabolism is diverted to generate excess of norpethidine.

Recently, some MAO-A selective and reversible inhibitors have been developed which have useful antidepressant property coupled with low toxicity and freedom from dangerous interactions in the recommended dose range.

Reversible inhibitors of MAO-A (RIMAs)

Moclobemide It is a reversible and selective MAO-A inhibitor with short duration of action; full MAO activity is restored within 1–2 days of stopping the drug. Because of competitive enzyme inhibition, tyramine is able to displace it—potentiation of pressor response to ingested amines is weak, dietary restrictions are not required. Clinical trials have shown moclobemide to be an efficacious antidepressant, comparable to TCAs, except in severe cases. It lacks the anticholinergic, sedative, cognitive, psychomotor and cardiovascular adverse effects of typical TCAs and is safer in overdose. This makes it a particularly good option in elderly patients and in those with heart disease.

Adverse effects are nausea, dizziness, headache, insomnia, rarely excitement and liver damage. Chances of interaction with other drugs and alcohol are little, but caution is advised while coprescribing pethidine, SSRIs and TCAs.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Imipramine, an analogue of CPZ, was found during clinical trials (1958) to selectively benefit depressed but not agitated psychotics. In contrast to CPZ, it inhibited NA and 5-HT reuptake into

neurones. A large number of congeners were soon added and are collectively called *tricyclic antidepressants (TCAs)*.

PHARMACOLOGICAL ACTIONS

The TCAs inhibit monoamine uptake and interact with a variety of receptors *viz.* muscarinic, α adrenergic, histamine H_1, 5-HT_1, 5-HT_2 and occasionally dopamine D2. However, relative potencies at these sites differ among different compounds. The newer selective serotonin reuptake inhibitors (SSRIs) and atypical antidepressants interact with fewer receptors and have more limited spectrum of action (produce fewer side effects). The actions of imipramine are described as prototype.

1. CNS Effects differ in normal individuals and the depressed.

In normal individuals it induces a peculiar clumsy feeling, tiredness, light-headedness, sleepiness, difficulty in concentrating and thinking, unsteady gait. These effects tend to provoke anxiety. There is no mood elevation or euphoria; effects are rather unpleasant and may become more so on repeated administration.

In depressed patients little acute effects are produced, except sedation. After 2–3 weeks of continuous treatment, the mood is gradually

Table 10.2: Comparative properties and trade names of tricyclic and related antidepressants

Drug	Sedation	Antimuscarinic	Hypotension	Cardiac arrhythmia	Seizure precipitation	Daily dose (mg)	Trade name
Tricyclic antidepressants							
1. Imipramine	+	++	++	+++	++	50–200	DEPSONIL,ANTIDEP
2. Amitriptyline	+++	+++	+++	+++	++	50–200	AMLINE, TRYPTOMER
3. Trimipramine	+++	+++	++	+++	++	50–150	SURMONTIL
4. Doxepin	+++	++	++	++	++	50–150	SPECTRA, DOXIN
5. Clomipramine	++	+++	++	+++	+++	50–150	CLOFRANIL, CLONIL
6. Dothiepin	++	++	++	++	++	50–150	PROTHIADEN
7. Nortriptyline	+	++	+	++	+	50–150	SENSIVAL
8. Amoxapine	+	+	++	++	++	100–300	DEMOLOX
Selective 5-HT reuptake inhibitors							
1. Fluoxetine	±	—	—	—	±	20–60	FLUDAC, FLUNIL
2. Fluvoxamine	±	—	—	—	—	50–200	FLUVOXIN
3. Paroxetine	±	±	—	—	—	20–50	XET
4. Sertraline	±	—	—	—	—	50–200	SERENATA
5. Citalopram	—	—	—	—	—	20–40	CELICA
Atypical antidepressants							
1. Trazodone	+++	—	+	±	—	50–200	TRAZODAC
2. Mianserin	++	+	++	+	++	30–100	TETRADEP
3. Bupropion	–, ↑	—	—	—	+++	150–300	SMOQUIT
4. Mirtazapine	+++	—	±	—	—	15–45	MIRT, MIRTAZ
5. Venlafaxine	—	—	—	±	—	75–150	VENLOR

elevated, patients become more communicative and start taking interest in self and surroundings. Thus, TCAs are not euphorients but only antidepressants. Sedative property varies among different compounds (*see* Table 10.2). The more sedative ones are suitable for depressed patients showing anxiety and agitation. The less sedative or stimulant ones are better for withdrawn and retarded patients.

The TCAs lower seizure threshold and produce convulsions in overdose. Clomipramine, maprotiline and bupropion have the highest seizure precipitating potential. Amitriptyline and imipramine depress respiration in overdose only.

Mechanism of action The TCAs and related drugs inhibit active uptake of biogenic amines NA and 5-HT into their respective neurones and thus potentiate them. They, however, differ markedly in their selectivity and potency for different amines (*see* classification above). Most of the compounds do not inhibit DA uptake, except bupropion.

Uptake inhibition results in increased concentration of the amines in the synaptic cleft in the CNS and periphery. Tentative conclusions drawn are:

- Inhibition of DA uptake correlates with stimulant action; but is not primarily involved in antidepressant action.
- Inhibition of NA and 5-HT uptake is associated with antidepressant action.

Uptake blockade appears to initiate a series of time-dependent changes in the number and sensitivity of aminergic receptors that culminate in antidepressant effect after a few weeks.

None of these compounds, except amoxapine and to some extent maprotiline, block DA receptors or possess antipsychotic activity.

2. ANS Most tricyclic antidepressants are potent anticholinergics—cause dry mouth, blurring of vision, constipation and urinary hesitancy as side effect. The anticholinergic potency is graded in Table 10.2. They potentiate exogenous and endogenous NA by blocking uptake.

3. CVS Effects on cardiovascular function are prominent, and may be dangerous in overdose.

Tachycardia: due to anticholinergic and NA potentiating actions.

Postural hypotension: due to inhibition of cardiovascular reflexes and α_1 blockade.

ECG changes and cardiac arrhythmias: T wave suppression or inversion is the most consistent change. Arrhythmias occur in overdose due to interference with intraventricular conduction, combination of NA potentiating + ACh blocking actions and direct myocardial depression. Older patients are more susceptible. The SSRIs and atypical antidepressants are safer in this regard.

Tolerance and dependence

Tolerance to the anticholinergic and hypotensive effects of imipramine like drugs develops gradually, though antidepressant action is sustained.

Psychological dependence on these drugs is rare because their acute effects are not pleasant.

There is some evidence of physical dependence occurring when high doses are used for long periods, but they do not carry abuse potential.

PHARMACOKINETICS

The oral absorption of TCAs is good, though often slow. They are highly bound to plasma and tissue proteins—have large volumes of distribution (~20 L/kg). They are extensively metabolized in liver; the major route for imipramine and amitriptyline is demethylation whereby active metabolites—desipramine and nortriptyline respectively are formed. Metabolites are excreted in urine over 1–2 weeks. The plasma t½ of amitriptyline, imipramine and doxepin range between 16–24 hours.

ADVERSE EFFECTS

Side effects are common with tricyclic antidepressants.

1. Anticholinergic: dry mouth, bad taste, constipation, epigastric distress, urinary retention (especially in males with enlarged prostate), blurred vision, palpitation. Decreased

salivation increases risk of dental caries, oral thrush, etc.
2. Sedation, mental confusion and weakness, especially with amitriptyline and more sedative congeners.
3. Increased appetite and weight gain is noted with most TCAs and trazodone, but not with SSRIs and bupropion.
4. Some patients may switch to hypomania or mania. Probably, this reflects a basic bipolar illness, the other pole being unmasked by the antidepressant.
5. Sweating and fine tremors are relatively common.
6. Seizure threshold is lowered—fits may be precipitated, especially in children.
7. Postural hypotension, especially in older patients; less severe with desipramine like drugs and insignificant with SSRIs. Patients should not abruptly sit up or stand from a reclining position on the dental chair.
8. Cardiac arrhythmias, especially in patients with ischaemic heart disease—may be responsible for sudden death in these patients.
9. Rashes and jaundice due to hypersensitivity are rare.

Acute poisoning It is frequent; usually self-attempted by the depressed patients, and may endanger life. Manifestations are:
Excitement, delirium and other anticholinergic symptoms followed by muscle spasms, convulsions and coma. Respiration is depressed, body temperature may fall, BP is low, tachycardia is prominent. ECG changes and ventricular arrhythmias are common.
Treatment is primarily supportive with gastric lavage, respiratory support, fluid infusion, maintenance of BP and body temperature. Acidosis must be corrected by bicarbonate infusion.

Diazepam may be injected i.v. to control convulsions and delirium. Most important is treatment of cardiac arrhythmias, for which propranolol / lignocaine may be used.

INTERACTIONS

1. TCAs potentiate directly acting *sympathomimetic amines* (in cold/asthma remedies). Adrenaline containing local anaesthetic should be avoided for dental anaesthesia due to risk of potentiation and precipitation of cardiac arrhythmia.
2. TCAs abolish the antihypertensive action of *clonidine* by preventing its transport into adrenergic neurones.
3. TCAs potentiate *CNS depressants*, including alcohol and antihistaminics.
4. *Phenobarbitone* induces as well as competitively inhibits imipramine metabolism. Carbamazepine and other enzyme inducers enhance metabolism of TCAs.
5. SSRIs inhibit metabolism of TCAs—dangerous toxicity can occur if the two are given concurrently.
6. When used together, the anticholinergic action of neuroleptics and TCAs may add up.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

The major limitations of standard TCAs are:
- Frequent anticholinergic, cardiovascular and neurological side effects.
- Relatively low safety margin, hazardous in overdose; fatalities common.
- Lag time of 2–4 weeks before antidepressant action manifests.
- Significant number of patients respond incompletely and some do not respond.

To overcome these shortcomings, a large number of newer antidepressants have been developed since 1980s. The most significant of these are the SSRIs. Though, none of the newer drugs has surpassed older TCAs in overall efficacy, some patients not responding to one type of drug may respond to the other. More importantly, the newer drugs have improved tolerability, both in therapeutic use as well as in overdose.

The relative safety and better acceptability of SSRIs has made them 1st line drugs in depression

and allowed their extensive use in anxiety, phobias, OCD and related disorders. The SSRIs, produce little or no sedation, do not interfere with cognitive and psychomotor function or produce anticholinergic side effects. They are devoid of α adrenergic blocking action—postural hypotension does not occur—suitable for elderly patients. They have practically no seizure precipitating propensity and do not inhibit cardiac conduction—overdose arrhythmias are not a problem. However, they frequently produce nausea. Weight gain is not a problem with SSRIs, but they more commonly interfere with ejaculation or orgasm. A new constellation of mild side effects, *viz.* nervousness, restlessness, insomnia, anorexia, dyskinesia, headache and diarrhoea is associated with them, but patient acceptability is good. Increased incidence of epistaxis and ecchymosis has been reported, probably due to impairment of platelet function. Gastric blood loss due to NSAIDs may be increased by SSRIs.

The SSRIs inhibit drug metabolizing isoenzymes CYP2D6 and CYP3A4: elevate plasma levels of TCAs, haloperidol, clozapine, terfenadine, astemizole, warfarin, β blockers, some BZDs and carbamazepine.

The overall antidepressant efficacy of SSRIs is similar to that of TCAs, but in severe depression, TCAs appear to be more efficacious.

Other uses of SSRIs The SSRIs are now 1st choice drugs for OCD, panic disorder, social phobia, eating disorders and post-traumatic stress disorder. They are also being increasingly used for many anxiety disorders, body dysmorphic disorder, compulsive buying and kleptomania. Elevation of mood and increased work capacity has been reported in postmyocardial infarction and other chronic somatic illness patients. Thus, SSRIs are being used to improve outlook on life and to feel good, even in apparently nondepressed patients. Wisdom of such use though is questionable.

ATYPICAL ANTIDEPRESSANTS

The distinctive features of some atypical antidepressants are outlined below.

1. Trazodone It is the first atypical antidepressant; selectively but less efficiently blocks 5-HT uptake and has prominent α blocking as well as weak 5-HT_2 antagonistic action. It is sedative but not anticholinergic, causes bradycardia rather than tachycardia, does not interfere with intracardiac conduction—less prone to cause arrhythmia. Inappropriate, prolonged and painful penile erection (priapism) occurs in a few recipients as does postural hypotension.

2. Mianserin It is unique in not inhibiting either NA or 5-HT uptake; but blocks presynaptic α_2 receptors—increases release and turnover of NA in brain which may be responsible for antidepressant effect. Blood dyscrasias and liver dysfunction have restricted its use.

3. Tianeptine This antidepressant is reported to increase rather than inhibit 5-HT uptake, and has shown efficacy in anxiodepressive states particularly with psychosomatic symptoms as well as in endogenous depression.

4. Amineptine Like tianeptine, it enhances 5-HT uptake but has antidepressant property. It produces anticholinergic side effects, postural hypotension, conduction disturbances and arrhythmias.

5. Venlafaxine A novel antidepressant referred to as *'serotonin and noradrenaline reuptake inhibitor'* (SNRI), because it inhibits uptake of both these amines; but, in contrast to older TCAs, does not interact with cholinergic, adrenergic or histaminergic receptors or have sedative property. Venlafaxine does not produce the usual side effects of TCAs; tends to raise rather than depress BP and is safer in overdose.

6. Mirtazapine A recently released antidepressant which acts by a novel mechanism *viz.* blocks α_2 auto- (on NA neurones) and hetero- (on 5-HT neurones) receptors enhancing both NA and 5-HT release. Accordingly, it has been labelled as *"noradrenergic and specific serotonergic antidepressant"* (NaSSA). It is a H_1 blocker and quite sedative, but not anticholinergic or anti-

dopaminergic. Efficacy in depression is reported to be comparable to TCAs and benefit may start earlier.

7. Bupropion This inhibitor of DA and NA uptake has excitant rather than sedative property. It is metabolized into an amphetamine like compound. It has been recently marketed in a sustained release formulation as an aid to smoking cessation. Side effects are insomnia, agitation, dry mouth and nausea. Seizures occur in overdose.

USES

1. *Endogenous (major) depression:* The aim is to relieve symptoms of depression and restore normal social behaviour. The tricyclic and related antidepressants are of proven value. Response takes at least 2–3 weeks to appear, full benefits take still longer. The SSRIs are currently used as first choice for their tolerability and safety. The newer atypical agents also offer some advantages. However, the TCAs are still the most effective in severely depressed patients. After a depressive episode has been controlled, continued treatment at maintenance doses for months is recommended to prevent relapse. Therapy is generally not continued beyond one year.

2. *Obsessive-compulsive and phobic states:* The SSRIs are the drugs of choice due to better patient acceptability. TCAs, especially clomipramine, are highly effective in OCD and panic disorders. SSRIs and TCAs also reduce compulsive eating in *bulimia*, and help patients with *body dysmorphic disorder, compulsive buying* and *kleptomania,* though these habits may not completely die.

3. *Anxiety disorders:* Antidepressants, especially SSRIs, exert a delayed but sustained beneficial effect in many patients of generalized anxiety disorder; may be used along with a short course of BZDs to cover exacerbations. SSRIs have also proven helpful in *post-traumatic stress disorder*.

4. *Neuropathic pain:* Imipramine affords considerable relief in diabetic and some other types of chronic pain.

5. *Attention deficit-hyperactivity disorder in children:* TCAs with less depressant properties like imipramine and nortriptyline are emerging as alternatives to amphetamine like drugs.

6. *Enuresis:* Imipramine 50 mg at bedtime reduces bedwetting in children above 5 years.

7. *Migraine:* Amitriptyline has some prophylactic value.

8. *Pruritus*: Some tricyclics have antipruritic property.

ANTIMANIC (MOOD STABILIZING) DRUGS

LITHIUM CARBONATE

Lithium is a small monovalent cation. In 1949, it was found to exert beneficial effects in manic patients.

Later, the importance of maintaining a narrow range of serum lithium concentration was realized and unequivocal evidence of its efficacy was obtained. At present, lithium is a drug of its own kind to exert a prophylactic effect in bipolar manic depressive illness (MDI). Over the past 2 decades the antiepileptics carbamazepine and valproate have emerged as alternatives to lithium.

Actions and mechanism

1. *CNS* Lithium has practically no acute effects in normal individuals as well as in MDI patients. It is neither sedative nor euphorient; but on prolonged administration, it acts as a mood stabiliser in bipolar disease. Given to patients in acute mania, it gradually suppresses the episode taking 1–2 weeks; continued treatment prevents cyclic mood changes. The markedly reduced sleep time in manic patients is normalized.

The mechanism of antimanic and mood stabilizing action of lithium is not known. It has been proposed that:

(a) Li^+ partly replaces body Na^+ and is nearly equally distributed inside and outside the cells (contrast Na^+ and K^+); this may affect ionic fluxes across brain cells or modify the property of cellular membranes.

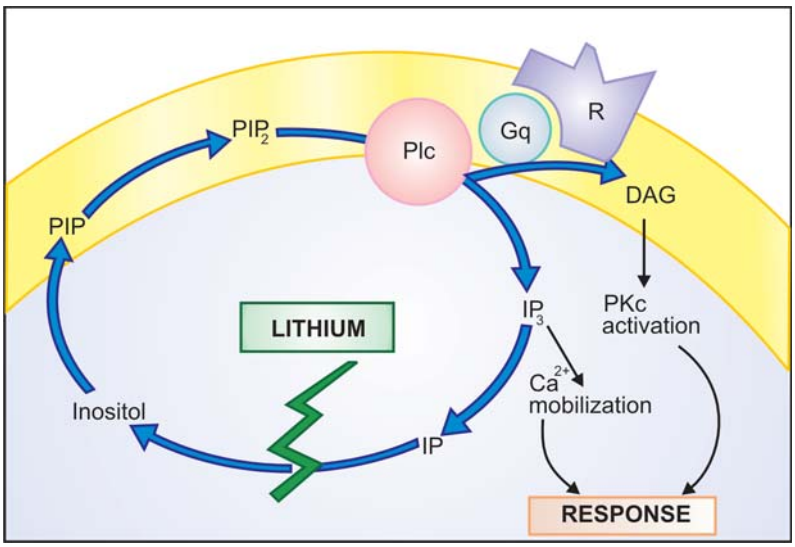


Fig. 10.1: Proposed mechanism of antimanic action of lithium
PIP-Phosphatidyl inositol phosphate; PIP_2-Phosphatidyl inositol bisphosphate; IP_3-Inositol trisphosphate; IP-Inositol-1-phosphate; PLc-Phospholipase C; DAG-Diacyl glycerol; PKc-Protein kinase C; Gq-Coupling Gq protein; R- Neurotransmitter receptor

(b) Li^+ may correct imbalance in the turnover of brain monoamines.
(c) The above hypothesis cannot explain why Li^+ has no effect on people not suffering from mania. An attractive hypothesis has been put forward based on the finding that lithium inhibits hydrolysis of inositol-1-phosphate. As a result, the supply of free inositol for regeneration of membrane phosphatidyl-inositides, which are the source of IP_3 and DAG, is reduced (Fig. 10.1). The hyperactive neurones involved in the manic state may be preferentially affected, because supply of inositol from extracellular sources is meagre. Thus, lithium may ignore normally operating receptors, but 'search out' and selectively, though indirectly, dampen signal transduction in the overactive ones.

2. *Other actions* Lithium inhibits the action of ADH on distal tubules and causes a diabetes insipidus like state.
It has some insulin-like action on glucose metabolism.
Leukocyte count is increased by lithium therapy.
Lithium reduces thyroxine synthesis by interfering with iodination of tyrosine.

Pharmacokinetics and control of therapy

Lithium is well absorbed orally and is neither protein bound nor metabolized. It first distributes in the extracellular water and then gradually enters cells and slowly penetrates into the CNS, ultimately attaining a rather uniform distribution in total body water.

Lithium is handled by the kidney in much the same way as Na^+. Most of the filtered Li^+ is reabsorbed in the proximal convoluted tubule. After a single dose of Li^+, urinary excretion is rapid for 10–12 hours followed by a much slower phase lasting several days. The t½ of the latter phase is 16–30 hours.

There is marked individual variation in the rate of lithium excretion. Since the margin of safety is narrow, monitoring serum lithium concentration is essential for optimal therapy.

Serum lithium level 0.5–0.8 mEq/L is considered optimum for maintenance therapy in bipolar disorder, while 0.8–1.1 mEq/L is required for episodes of mania. Toxicity symptoms occur frequently when serum levels exceed 1.5 mEq/L.

Adverse effects Side effects are common but are mostly tolerable. Toxicity occurs at levels only marginally higher than therapeutic levels.

1. Nausea, vomiting and mild diarrhoea.
2. Thirst and polyuria are experienced by most.
3. Fine tremors and rarely seizures.
4. CNS toxicity manifests as plasma concentration rises—coarse tremors, giddiness, ataxia, motor incoordination, nystagmus, mental confusion, slurred speech, hyper-reflexia. In acute intoxication, these symptoms progress to muscle twitchings, drowsiness, delirium, coma and convulsions. Vomiting, severe diarrhoea, albuminuria, hypotension and cardiac arrhythmias are the other features.
5. On long-term use, some patients develop renal diabetes insipidus and goiter.
6. Lithium is contraindicated during pregnancy; foetal goiter and other congenital abnormalities can occur.

Interactions

1. Diuretics (thiazide, furosemide) raise plasma levels of lithium.
2. NSAIDs also cause Li^+ retention (along with Na^+ retention). Dentists should refer patients for monitoring and adjusting Li^+ therapy when they prescribe NSAIDs. Tetracyclines and ACE inhibitors are other drugs capable of producing Li^+ retention.
3. Lithium tends to enhance insulin/sulfonylurea induced hypoglycaemia.

Use

1. *Acute manic episode* (inappropriate cheerfullness, motor restlessness, nonstop talking, flight of ideas and progressive loss of contact with reality; sometimes violent behaviour): though lithium is effective, response is slow. Most psychiatrists prefer to use a neuroleptic, generally by i.m. route, with or without diazepam, and start lithium after the episode is under control. Maintenance lithium therapy is generally given to prevent recurrences.

2. *Prophylaxis in bipolar disorder* Lithium has proven efficacy in bipolar disorder. It lengthens the interval between cycles of mood swings: episodes of mania as well as depression are attenuated, if not totally prevented.

Recurrent *unipolar depression* also responds to lithium therapy. Combination of antidepressant + lithium is often used initially, and lithium alone is continued in the maintenance phase.

3. Lithium is sporadically used in many other *recurrent neuropsychiatric illness*, cluster headache, etc. and as an adjuvant to TCAs in patients of *major depression* not fully relieved by the latter.

Alternatives to lithium

Approximately 50% patients of mania and bipolar disorder show incomplete or poor response to lithium. Many do not tolerate it or are at special risk of toxicity. Alternatives are:

1. *Carbamazepine* Soon after its introduction as antiepileptic carbamazepine (CBZ) was found to prolong remission in bipolar disorder. Its efficacy in mania and bipolar disorder has now been confirmed and is rated almost equal to lithium. Patients with rapid cycling of mood state do better on combined Li + CBZ treatment.

2. *Sodium valproate* A reduction in manic relapses is noted when valproate is used in bipolar disorder. Trials have also attested to its efficacy in prevention and treatment of acute mania. It can be useful in those not responding to Li or CBZ or not tolerating these drugs. Valproate has a favourable tolerability profile.

The newer anticonvulsants like lamotrigine, gabapentin and topiramate have also been found effective in bipolar disorder, but their relative value is not yet known.

3. *Atypical antipsychotics* Olanzapine has recently been approved for use in acute mania. Olanzapine, risperidone and few other atypical antipsychotics have shown efficacy in bipolar illness as well.

CHAPTER

11

Cardiovascular Drugs

Drugs Affecting Renin-Angiotensin System, Calcium Channel Blockers, Drugs for Hypertension, Angina Pectoris and Myocardial Infarction

Drugs having their major action on heart or blood vessels, or those used primarily for cardiovascular disorders are designated 'Cardiovascular drugs'. They can act directly on the cardiovascular structures or through the autonomic/central nervous system, kidney, autacoids or hormones which regulate cardiovascular function.

ANGIOTENSIN

Angiotensin II (AII) is an octapeptide generated in the plasma from a precursor plasma α_2 globulin, and is involved in electrolyte, blood volume and pressure homeostasis. Drugs that interfere with the generation or action of AII have assumed great importance in the treatment of cardiovascular diseases.

Renin-angiotensin system (RAS) The generation and metabolism of AII in circulation is depicted in Fig. 11.1. The enzyme *renin* secreted by kidney splits off a decapeptide *Angiotensin I* (AI) from angiotensinogen. AI is largely inactive but is rapidly converted to AII by *angiotensin-converting enzyme* (ACE) which removes 2 amino acids from the carboxy terminus of the decapeptide. The ACE is located primarily on the luminal surface of vascular endothelial cells (especially in lungs). Circulating AII has a very short t½ (1 min); due to serial degradation by peptidases termed *angiotensinases*.

Many tissues, especially heart, blood vessels, brain, kidneys, adrenals generate AII inside their cells. Thus, local renin-angiotensin systems appear to operate in several organs in addition to the circulating one.

ACTIONS

1. The most prominent action of AII is vasoconstriction—produced directly as well as by enhancing Adr/NA release from adrenal medulla/adrenergic nerve endings and by increasing central sympathetic outflow. BP rises acutely. As a pressor agent, AII is much more potent than NA.
2. AII increases force of myocardial contraction by promoting Ca^{2+} influx. Reflex bradycardia predominates in the intact animal. Cardiac output is often reduced and cardiac work is increased (due to rise in peripheral resistance).
3. Acting on a chronic basis AII induces hypertrophy, hyperplasia and increased intercellular matrix production in the myocardium and vascular smooth muscle by direct cellular effects. Indirectly, volume overload and increased t.p.r. caused by AII contributes to the hypertrophy and remodeling (abnormal redistribution of muscle mass) in heart and blood vessels. Fibrosis and dilatation of infarcted area with hypertrophy of the noninfarcted ventricular wall is seen after myocardial infarction. Progressive cardiac myocyte death and fibrotic transformation occurs in CHF. These changes are important risk factors for cardiovascular morbidity and mortality. ACE inhibitor therapy retards/reverses many of

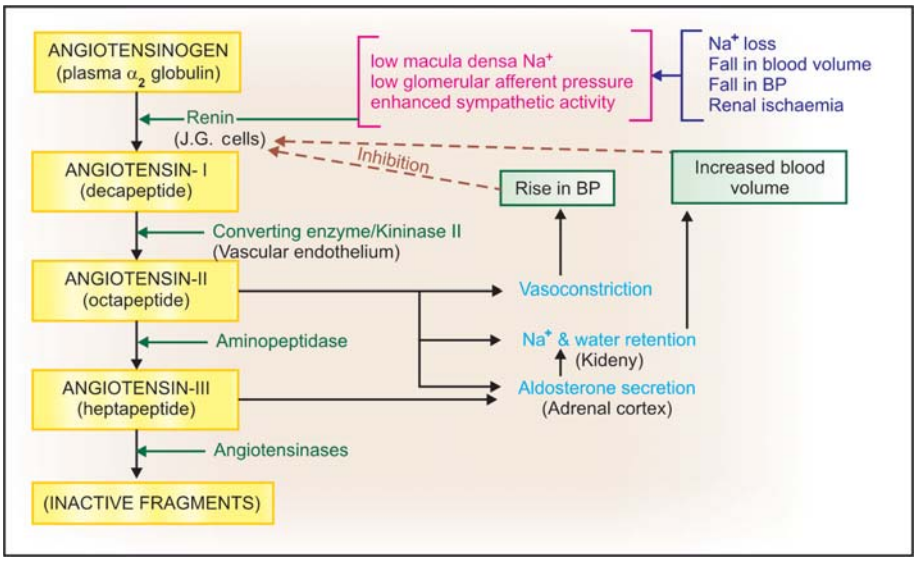


Fig. 11.1: Physiological regulation of electrolyte balance, plasma volume and blood pressure by the renin-angiotensin system

these changes imparting a pivotal role to AII in vascular and ventricular hypertrophy, apoptosis and remodeling.

4. AII contracts many visceral smooth muscles *in vitro*, but *in vivo* effects are insignificant.

5. AII and AIII are trophic to zona glomerulosa of the adrenal cortex—enhance synthesis and release of aldosterone. This acts on distal tubule to promote Na^+ reabsorption and K^+/H^+ excretion. These effects are exerted at concentrations lower than those required to cause vasoconstriction.

6. In addition to exerting indirect effect on kidney through aldosterone, AII promotes Na^+/H^+ exchange in proximal tubule → increased Na^+, Cl^- and HCO_3^- reabsorption.

Angiotensin receptors Specific angiotensin receptors are present on the surface of target cells. Two subtypes (AT_1 and AT_2) have been differentiated pharmacologically: *Losartan* is a selective AT_1 antagonist, while PD 123177 is a selective AT_2 antagonist. Both subtypes are G-protein coupled receptors. However, all known effects of AII appear to be mediated by AT_1 receptor. Though AT_2 receptors have been detected in several tissues, the function subserved by them is not clear.

PATHOPHYSIOLOGICAL ROLES

1. *Mineralocorticoid secretion* AII (also AIII) is the physiological stimulus for aldosterone secretion from adrenal cortex.

2. *Electrolyte, blood volume and pressure homeostasis* The RAS plays an important role in maintaining electrolyte composition and volume of extracellular fluid (*see* Fig. 11.1). Changes that lower blood volume or pressure, or decrease Na^+ content induce renin release by:

(i) Decreasing tension in the afferent glomerular arterioles: *the intrarenal baroreceptor pathway.*

(ii) Low Na^+ concentration in the tubular fluid sensed by macula densa cells: *the macula densa pathway.*

(iii) Baroreceptor and other reflexes which increase sympathetic impulses to JG cells—activated through β_1 receptors: *the* β *adrenoceptor pathway.*

Increased renin is translated into increased plasma AII which produces acute rise in BP by vasoconstriction, and more longlasting effects by directly as well as indirectly increasing Na^+ and water reabsorption in the kidney. Rise in BP in turn inhibits renin release.

3. *Development of hypertension* The RAS is directly involved in renovascular hypertension: plasma renin activity (PRA) is raised in most patients. In essential hypertension and pregnancy-induced hypertension also it appears to have a permissive role.

4. *Secondary hyperaldosteronism* The RAS is instrumental in the development of secondary hyperaldosteronism.

5. *CNS* AII can be formed locally in the brain and may function as transmitter or modulator. Regulation of thirst, hormone release and sympathetic flow may be the responses mediated.

Inhibition of renin-angiotensin system It can be achieved by:

1. Sympathetic blockers (β blockers, adrenergic neurone blockers, central sympatholytics)—decrease renin release.
2. Renin inhibitory peptides and renin specific antibodies block renin action—interfere with generation of AI from angiotensinogen (rate limiting step).
3. Angiotensin converting enzyme inhibitors—prevent generation of the active principle AII.
4. Angiotensin receptor (AT_1) antagonists—block the action of AII on target cells.
5. Aldosterone antagonists—block mineralocorticoid receptors.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Captopril, an orally active dipeptide ACE inhibitor, was introduced in 1977 and quickly gained wide usage. A multitude of ACE inhibitors like *enalapril, lisinopril, benazepril, ramipril, perindopril* and *fosinopril,* etc. are now available. The pharmacology of captopril is described as prototype since most of its effects are class effects common to all ACE inhibitors.

Captopril

It is a sulfhydryl containing dipeptide surrogate of proline which abolishes the pressor action of AI but not that of AII: does not block AII receptors.

It can also increase plasma kinin levels and potentiate the hypotensive action of exogenously administered bradykinin. Elevated kinins (and PGs whose synthesis is enhanced by kinins) may be responsible for cough and angioedema induced by ACE inhibitors in susceptible individuals, but do not appear to be important for their hypotensive action in the long term.

Captopril lowers BP. This effect is more marked in Na^+ depleted subjects and in those with overactive RAS. Captopril-induced hypotension is a result of decrease in total peripheral resistance. Both systolic and diastolic BP fall. It has no effect on cardiac output. Cardiovascular reflexes are not interfered with and there is little dilatation of capacitance vessels. As such, postural hypotension is not a problem.

Reflex (postural) changes in plasma aldosterone are abolished and basal levels are decreased as a consequence of loss of its regulation by AII. However, physiologically sufficient mineralocorticoid is still secreted under the influence of ACTH and plasma K^+.

Pharmacokinetics About 70% of orally administered captopril is absorbed. Presence of food in stomach reduces its bioavailability. Penetration in brain is poor. It is partly metabolized and partly excreted unchanged in urine. The plasma t½ is ~2 hours, but actions last for 6–12 hours.

Adverse effects The adverse effect profile of all ACE inhibitors is similar. Captopril is well tolerated by most patients; adverse effects are:

1. *Hypotension*.
2. *Hyperkalemia* more likely in patients with impaired renal function and in those taking K^+ sparing diuretics, NSAIDs or β blockers.
3. *Cough:* a persistent brassy cough occurs in 4-16% patients within 1–8 weeks. It is not dose

related and appears to be caused by inhibition of bradykinin/substance P breakdown in the lungs of susceptible individuals.
4. *Rashes, urticaria.*
5. *Angioedema*: resulting in swelling of lips, mouth, nose, larynx may develop within hours to a few days.
6. *Dysguesia:* reversible loss or alteration of taste sensation.
7. *Foetopathic:* foetal growth retardation, hypoplasia of organs and foetal death may occur if ACE inhibitors are given during later half of pregnancy.
8. *Headache, dizziness, nausea and bowel upset.*
9. *Granulocytopenia and proteinurea:* are rare.
10. *Acute renal failure:* is precipitated by ACE inhibitors in patients with bilateral renal artery stenosis.

Interactions Indomethacin (and other NSAIDs) attenuate the hypotensive action. Hyperkalemia can occur if K^+ supplements/K^+ sparing diuretics are given with captopril. Antacids reduce bioavailability of captopril, while ACE inhibitors reduce Li^+ clearance and predispose to its toxicity.

Other ACE inhibitors Differences among ACE inhibitors are primarily pharmacokinetic reflected in time course of their action; no single drug is superior to others. Their important features are given in Table 11.1. Enalapril is a prodrug: has to be converted in the body to the active form. Therefore, it acts slowly; is less likely to cause abrupt hypotension and is longer acting. Other ACE inhibitors are also slow acting, longer acting and more potent than captopril. Ramipril is claimed to cause greater inhibition of tissue RAS because of extensive tissue distribution.

USES

1. *Hypertension* ACE inhibitors are now first line drugs in all grades of hypertension. About 50% patients respond to monotherapy with ACE inhibitors, and majority of the rest to their combination with diuretics or β blockers. They offer many advantages:
   (i) Lack of postural hypotension, electrolyte disturbances, feeling of weakness and CNS effects.
   (ii) Safety in asthmatics, diabetics and peripheral vascular disease patients.
   (iii) Reverse left ventricular hypertrophy and increased wall-to-lumen ratio of blood vessels that occurs in hypertensive patients.
   (iv) No hyperuricaemia, no deleterious effect on plasma lipid profile.
   (v) No rebound hypertension on withdrawal.
   (vi) Minimum worsening of quality of life parameters like general wellbeing, work performance, sleep, sexual performance, etc.

2. *CHF* ACE inhibitors cause both arteriolar and venodilatation in CHF patients: reduce afterload as well as preload. Though they have no direct myocardial action, stroke volume and cardiac output are increased while heart rate is

Table 11.1: Comparative features of ACE inhibitors

	Captopril	*Enalapril*	*Lisinopril*	*Perindopril*	*Ramipril*
1. Chemical nature	Sulfhydryl	Carboxyl	Carboxyl	Carboxyl	Carboxyl
2. Activity status	Active	Prodrug	Active	Prodrug	Prodrug
3. Bioavailability (as active form)	70%	50%	25%	20%	60%
4. Time to peak action	1 hr	4–6 hr	6–8 hr	6 hr	3–6 hr
5. Elimination t½	2 hr	11 hr	12 hr	25–30 hr	8–48 hr
6. Mode of excretion	Renal	Renal	Renal	Renal	Renal
7. Duration of action	6–12 hr	24 hr	> 24 hr	> 24 hr	>24 hr
8. Daily dose (mg)	25–150	2.5–40	5–40	2–8	1.25–10

reduced. Considerable symptomatic relief is obtained in nearly all grades of CHF.

ACE inhibitors also retard the progression of left ventricular systolic dysfunction and prolong survival of CHF patients. Long-term benefits of ACE inhibitors may also accrue from withdrawal of AII mediated ventricular hypertrophy, remodeling, accelerated myocyte apoptosis and fibrosis.

3. *Myocardial infarction (MI)* ACE inhibitors administered while MI is evolving (within 24 hr of an attack) and continued for 6 weeks to several years reduce early as well as long-term mortality.

4. *Prophylaxis in high cardiovascular risk subjects* ACE inhibitors are protective in high cardiovascular risk subjects even when there is no associated hypertension or left ventricular dysfunction. Protective effect is exerted both on myocardium as well as vasculature and is independent of hypotensive action.

5. *Diabetic nephropathy* Prolonged ACE inhibitor therapy has been found to prevent or delay end-stage renal disease in type I as well as type II diabetics.

Chronic renal failure due to nondiabetic causes may also be improved by ACE inhibitors.

6. *Scleroderma crisis* ACE inhibitors produce dramatic improvement and are life saving.

ANGIOTENSIN ANTAGONISTS

Over the past decade, several nonpeptide orally active AT_1 receptor antagonists have been developed as alternatives to ACE inhibitors. These include losartan, candesartan, irbesartan and others. Selective antagonists of AT_2 receptors as well as combined AT_1 + AT_2 antagonists have also been produced.

Losartan It is a competitive antagonist of AII, devoid of partial agonistic activity and 10,000 times more selective for AT_1 than AT_2 receptor; does not block any other receptor or ion channel. It blocks all overt actions of AII *viz*. vasoconstriction, central and peripheral sympathetic stimulation, release of aldosterone and Adr from adrenals, renal actions promoting salt and water reabsorption, central actions like thirst, vasopressin release and growth-promoting actions on heart and blood vessels. No inhibition of ACE has been noted.

Pharmacologically, AT_1 antagonists differ from ACE inhibitors in that they do not interfere with degradation of bradykinin and other ACE substrates: no rise in level or potentiation of bradykinin occurs.

Losartan causes fall in BP in hypertensive patients which lasts for 24 hours, while HR remains unchanged and cardiovascular reflexes are not interfered. No significant effect on plasma lipid profile, carbohydrate tolerance, insulin sensitivity has been noted. It is also a mild uricosuric. Data so far suggests that losartan has the same potential for regressing hypertensive left ventricular hypertrophy as ACE inhibitors.

Pharmacokinetics Oral bioavailability of losartan is only 33% due to first pass metabolism. It is partially carboxylated in liver to an active metabolite (E3174) which is a 10-30 times more potent noncompetitive AT_1 antagonist. Both compounds are 98% plasma protein bound, do not enter brain and are excreted by the kidney. The plasma t½ of losartan is 2 hours, but that of E3174 is 6–9 hours.

Adverse effects Losartan is well tolerated; has side effect profile similar to placebo. Like ACE inhibitors, it can cause hypotension and hyperkalemia, but first dose hypotension is uncommon and losartan is largely free of cough and dysguesia inducing potential. Headache, dizziness, weakness and upper g.i. side effects are mild and occasional.

Candesartan is dose to dose more potent, while *Irbesartan* is less potent than losartan, but their pharmacological profile and uses are similar.

Uses of AT_1 antagonists Losartan and other AT_1 antagonists are now first line antihypertensive drugs as alternative to ACE inhibitors, comparable in efficacy and other desirable

features, with the advantage of not inducing cough and a low incidence of angioedema, rash and dysguesia. AT_1 antagonists appear to be as effective as ACE inhibitors in CHF, MI and diabetic nephropathy.

CALCIUM CHANNEL BLOCKERS

These are an important class of cardiovascular drugs which act by inhibiting L-type of voltage sensitive calcium channels in smooth muscles and heart. There are 3 pharmacologically distinct subclasses of calcium channel blockers (CCBs):

(a) *Phenylalkylamines*: Verapamil
(b) *Benzothiazepines*: Diltiazem
(c) *Dihydropyridines*: Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, Nimodipine.

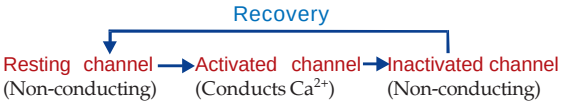
The two most important actions of CCBs are:

(i) Smooth muscle (especially vascular) relaxation.
(ii) Negative chronotropic, inotropic and dromotropic action on heart.

Smooth muscle Smooth muscles depolarise primarily by inward Ca^{2+} movement through voltage sensitive channel. These Ca^{2+} ions trigger release of more Ca^{2+} from intracellular stores and together bring about excitation-contraction coupling. The CCBs cause relaxation by decreasing intracellular availability of Ca^{2+}. They markedly relax arterioles but have mild effect on veins. Extravascular smooth muscle (bronchial, biliary, intestinal, vesical, uterine) is also relaxed.

Heart In the working atrial and ventricular fibres, Ca^{2+} moves in during plateau phase of AP and elicits contraction through binding to troponin. The CCBs would thus have negative inotropic action.

The 0 phase depolarization in SA and A-V nodes is largely Ca^{2+} mediated. Automaticity and conductivity of these cells appear to be dependent on the rate of recovery of the Ca^{2+} channel.



The L-type Ca^{2+} channels activate as well as inactivate at a slow rate. Consequently, Ca^{2+} depolarized cells (SA and A-V nodal) have a considerably less steep 0 phase and longer refractory period. The recovery process which restores the channel to the state from which it can again be activated is delayed by verapamil and to a lesser extent by diltiazem (resulting in depression of pacemaker activity and conduction) but not by DHPs (they have no negative chronotropic/dromotropic action). Moreover, channel blockade by verapamil is enhanced at higher rates of stimulation, that by nifedipine is independent of frequency, while diltiazem is intermediate. Thus, verapamil slows sinus rate

Table 11.2: Comparative properties of representative calcium channel blockers

	Verapamil	*Nifedipine*	*Diltiazem*
1. Channel blocking potency	++	+++	+
2. Frequency dependence of channel blockade	++	–	+
3. Channel recovery rate	Much delayed	No effect	Delayed
4. Cardiac effects (*In vivo* at usual clinical doses)			
Heart rate	↓	↑	↓, –
A-V Conduction velocity	↓↓	–	↓
Contractility	–, ↓	↑	↓,↑
Output	–, ↓	↑	–, ↑
5. Vascular smooth muscle relaxation	++	+++	+

and A-V conduction, but nifedipine does not. Effect of diltiazem on sinus node automaticity and A-V conduction is similar to that of verapamil.

The relative potencies to block slow channels in smooth muscle do not parallel those in heart. The DHPs are more selective for smooth muscle L channels: at concentrations which cause vasodilatation they have negligible negative inotropic action. Diltiazem causes less depression of contractility than verapamil. Important differences between the three representative CCBs are summarized in Table 11.2.

Verapamil causes vasodilatation as well as cardiac depression. Along with lowering of BP, it produces bradycardia, depresses A-V conduction and may worsen heart failure. It should not be used concurrently with β blockers or other cardiac depressants.

Diltiazem has less marked cardiodepressant activity: fall in BP is attended by little change or decrease in the HR. Though it produces milder side effects, drug interactions and contraindications remain the same as for verapamil.

Nifedipine is a rapidly acting dihydropyridine (DHP) with short duration of action. It frequently produces flushing, palpitation, headache and ankle edema. Direct depression of heart is minimal and overshadowed by reflex sympathetic stimulation. Nifedipine has paradoxically worsened angina pectoris in some patients and has been associated with higher mortality among postmyocardial infarct subjects. The slow and long-acting DHPs have replaced nifedipine.

Amlodipine is pharmacokinetically the most distinct DHP. It is absorbed very slowly (peak after 6–9 hours) and acts for > 24 hours. The early vasodilator side effects like flushing, palpitation, headache, postural dizziness are largely avoided. A single daily dose is sufficient.

Felodipine, nitrendipine and *lacidipine* are the other highly vasoselective long-acting DHPs. *Nimodipine* is a short-acting DHP which selectively relaxes cerebral vasculature; has been specifically indicated for prevention of neurological deficit following subarachnoid haemorrhage.

An occasional adverse effect of prolonged CCB therapy having implications in dentistry is gum hyperplasia.

USES

1. *Angina pectoris* All CCBs are effective in reducing frequency and severity of classical as well as variant angina. Benefit in classical angina appears to be primarily due to reduction in cardiac work: mainly as a result of reduced afterload. Though they can increase coronary flow in normal individuals, this is unlikely to be significant in patients with fixed arterial obstruction. Exercise tolerance is increased.

However, myocardial ischaemia may be aggravated by short-acting DHPs. This may be due to decreased coronary flow secondary to fall in mean arterial pressure, reflex tachycardia and coronary steal. Trials using high dose regular short-acting nifedipine formulation have reported increased mortality among MI patients. The sudden rush of sympathetic activity evoked by each dose of these preparations has been held responsible for the deleterious effect.

The capacity of CCBs to prevent arterial spasm is undoubtedly responsible for the beneficial effect in variant angina.

2. *Hypertension* CCBs are one of the first line antihypertensive drugs. Though all 3 subgroups of CCBs are equally efficacious, the long-acting DHPs (e.g. amlodipine) are most commonly used followed by diltiazem. The CCBs lower BP by reducing peripheral resistance without compromising cardiac output. Their advantages are:

1. Do not compromise haemodynamics: no impairment of physical and mental work capacity, no sedation.
2. Can be used in asthma, angina and peripheral vascular disease patients.
3. Do not affect male sexual function.
4. No deleterious effect on plasma lipid profile, uric acid level or electrolyte balance.

5. No impairment of quality of life.
6. No adverse foetal effects when given during pregnancy.

3. *Arrhythmias* Verapamil (diltiazem to a lesser extent) is highly effective in PSVT and for control of ventricular rate in supraventricular arrhythmias.

4. *Hypertrophic cardiomyopathy* The negative inotropic action of verapamil can be salutary in this condition.

ANTIHYPERTENSIVE DRUGS

These are drugs used to lower BP in hypertension.

Hypertension is a very common disorder, particularly past middle age. As such, many patients presenting for dental treatment are likely to be on long-term antihypertensive drug therapy.

Hypertension is not a disease in itself but is an important risk factor for cardiovascular morbidity and mortality. Though the risk appears to increase progressively with BP values over 120 (systolic)/80 (diastolic) mm Hg, hypertension has been defined by WHO-ISH guidelines to be values above 140/90 mm Hg.

Majority of cases are of essential (primary) hypertension, i.e. the cause is not known. Sympathetic and renin-angiotensin systems may or may not be overactive, but they do contribute to tone of blood vessels and c.o. in hypertensives, as they do in normotensives. Many antihypertensive drugs interfere with these regulatory systems at one level or the other.

CLASSIFICATION

1. *ACE Inhibitors*
   Captopril, Enalapril, Lisinopril, Perindopril, Ramipril
2. *Angiotensin (AT_1) Antagonists*
   Losartan, Candesartan, Irbesartan
3. *Calcium Channel Blockers*
   Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine
4. *Diuretics*
   Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide
   High ceiling: Furosemide, etc.
   K^+ Sparing: Spironolactone, Triamterene, Amiloride
5. *β Adrenergic Blockers*
   Propranolol, Metoprolol, Atenolol, etc.
6. *β + α Adrenergic Blockers*
   Labetalol, Carvedilol
7. *α Adrenergic Blockers*
   Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine
8. *Central Sympatholytics*
   Clonidine, Methyldopa
9. *Vasodilators*
   Hydralazine, Sodium nitroprusside

The ACE inhibitors, angiotensin antagonists and CCBs have aldready been described.

DIURETICS

Diuretics have been the standard antihypertensive drugs over the past 4 decades, but they do not lower BP in normotensives. Their pharmacology is described in Ch. 13.

Thiazides and related drugs (chlorthalidone, etc.) are the diuretic of choice in uncomplicated hypertension. The proposed mechanism of antihypertensive action is:

1. Initially, the diuresis reduces plasma and e.c.f. volume by about 10% → decreased c.o.
2. Subsequently, compensatory mechanisms operate to almost regain Na^+ balance and plasma volume; c.o. is restored, but the fall in BP is maintained by a slowly developing reduction in t.p.r.
3. The reduction in t.p.r. is most probably an indirect consequence of a small (~5%) persisting Na^+ and volume deficit. Decrease in intracellular Na^+ concentration in the vascular smooth muscle may decrease stiffness of vessel wall, increase their compliance and dampen responsiveness to constrictor stimuli (NA, AII). Similar effects are produced by salt restriction.

The fall in BP develops gradually over 2–4 weeks. During long-term treatment with thiazides, the heart rate and c.o. are unaffected, while

t.p.r. is reduced despite compensatory increase in plasma renin activity which confirms persisting Na^+ deficit. They have no effect on capacitance vessels, sympathetic reflexes are not impaired: postural hypotension is rare. Thiazides are mild antihypertensives, average fall in mean arterial pressure is 10 mm Hg. They potentiate all other antihypertensives (except DHPs) and prevent development of tolerance to these drugs by not allowing expansion of plasma volume. Maximal antihypertensive efficacy is reached at doses equivalent to 25 mg of hydrochlorothiazide. At 12.5–25 mg/day doses, complications of diuretic therapy like hypokalaemia, fatigue, loss of energy, impotence, carbohydrate intolerance, dyslipidemia, hyperuricaemia are absent or mild.

High ceiling diuretics Furosemide is a strong diuretic, but a weaker antihypertensive than thiazides. The explanation of this paradox may lie in its brief duration of action. The natriuretic action lasting only for 4–6 hours after the conventional morning dose may not maintain Na^+ deficient state in vascular smooth muscle round the clock. They are indicated in hypertension only when it is complicated by:

(a) Chronic renal failure: thiazides are ineffective.
(b) Coexisting refractory CHF.
(c) Resistance to combination regimens containing a thiazide, or marked fluid retention due to use of potent vasodilators.

Potassium sparing diuretics Spironolactone or amiloride themselves lower BP slightly, but they are used only in conjunction with a thiazide diuretic to prevent K^+ loss and to augment the antihypertensive action.

Indapamide It is a mild diuretic, chemically related to chlorthalidone; reduces BP at doses which cause little diuresis or K^+ loss.

β-ADRENERGIC BLOCKERS

The pharmacology and mechanism of antihypertensive action of β blockers is described in Ch. 6. They are mild antihypertensives; do not significantly lower BP in normotensives. Used alone they suffice in 30–40 percent patients—mostly mild-to-moderate cases. In the large majority of the rest, they can be usefully combined with other drugs.

Their hypotensive response develops over 1–3 weeks and is well sustained. Despite short and differing plasma half-lives, the antihypertensive action of most β blockers is maintained over 24 hours with single daily dose.

All β blockers, irrespective of associated properties, exert similar antihypertensive effect.

There are several contraindications to β blockers, including cardiac, pulmonary and peripheral vascular disease and diabetes. The nonselective β blockers have an unfavourable effect on lipid profile (raise triglyceride level and LDL/HDL ratio). They have also fared poorly on quality of life parameters like decreased work capacity, fatigue, loss of libido and subtle cognitive effects (forgetfulness, low drive). However, most of these drawbacks are minimized in the β_1 selective agents and in those which penetrate brain poorly. Thus, there are several reasons to prefer a β_1 selective hydrophilic drug like atenolol over propranolol.

Because of absence of postural hypotension, bowel alteration, salt and water retention; a low incidence of side effects, low cost; once a day regimen and cardioprotective potential, β blockers continue to be one of the first line antihypertensive drugs.

β + α ADRENERGIC BLOCKERS

Labetalol It is a combined α and β blocker; reduces t.p.r. and acts faster than pure β blockers. It has been used i.v. for rapid BP reduction in cheese reaction, clonidine withdrawal, etc. Oral labetalol therapy is restricted to moderately severe hypertension not responding to pure β blocker. Side effects of both α blocker and β blocker occur with it.

Carvedilol This nonselective β + selective α_1 blocker produces vasodilatation and has additional antioxidant/free radical scavenging properties.

α-ADRENERGIC BLOCKERS

Prazosin (*See* Ch. 6)

This prototype of selective α_1 antagonists dilates both resistance and capacitance vessels; effect on the former predominating. The haemodynamic effects—reduction in t.p.r. and mean BP with only slight decrease in venous return and c.o. are similar to that produced by a direct acting vasodilator. However, there is little reflex cardiac stimulation and renin release during long-term therapy. Tachycardia does not compensate for the fall in BP because release inhibitory α_2 (presynaptic) receptors are not blocked: autoregulation of NA release remains intact.

Renal blood flow and g.f.r. are maintained but fluid retention may attend hypotension. Cardiovascular reflexes are not appreciably impaired by chronic therapy, but postural hypotension and fainting may occur in the beginning—called 'first dose effect'

Other advantages of prazosin are:

1. Improves carbohydrate metabolism.
2. Has favourable effect on lipid profile.
3. No impairment of cardiac contractility. Does not alter exercise capacity and uric acid levels.
4. Affords symptomatic improvement in coexisting PVD or benign prostatic hypertrophy.

Prazosin is a moderately potent antihypertensive with many desirable features, but is not used as a first choice drug because fluid retention and tolerance gradually develops.

Terazosin, Doxazosin These are long-acting congeners of prazosin with similar properties and suitable for once daily dosing.

Nonselective α blockers (Phentolamine, Phenoxybenzamine)

The conventional α blockers have been disappointing for routine treatment of hypertension and are reserved for special situations like pheochromocytoma, clonidine withdrawal, cheese reaction, etc., where circulating CAs are responsible for rise in BP.

CENTRAL SYMPATHOLYTICS

Clonidine It is an imidazoline derivative having complex actions. Clonidine is a partial agonist with high affinity and high intrinsic activity at α_2 receptors, especially α_{2A} subtype in brainstem. The major haemodynamic effects result from stimulation of α_{2A} receptors present mainly postjunctionally in medulla (vasomotor centre) → decrease sympathetic outflow → fall in BP and bradycardia (also due to enhanced vagal tone). In addition, clonidine has been shown to activate specific *imidazoline receptors* in the brain that also mediate reduction in central sympathetic tone. Clonidine is a moderately potent antihypertensive.

Pharmacokinetics Clonidine is well absorbed orally; peak occurs in 2–4 hours; 1/2 to 2/3rd of an oral dose is excreted unchanged in urine, the rest as metabolites. Plasma t½ is 8–12 hours. Effect of a single dose lasts for 6–24 hours.

Adverse effects Side effects with clonidine are relatively common and disturbing.

- Sedation, mental depression, disturbed sleep; dryness of mouth, nose and eyes, constipation.
- Impotence, salt and water retention, bradycardia.
- Postural hypotension occurs, but is mild.
- Rebound hypertension with tachycardia, restlessness, headache, sweating occurs on sudden stoppage of clonidine therapy due to:
  (a) Sudden removal of central sympathetic inhibition resulting in release of large quantities of stored CAs.
  (b) Supersensitivity of peripheral adrenergic structures to CAs.

Regular schedule of drug administration must be maintained to prevent withdrawal syndrome.

Interactions Tricyclic antidepressants and chlorpromazine abolish the antihypertensive action of clonidine, probably by blocking α receptors on which clonidine acts.

Use Moderate hypertension: relatively higher incidence of side effects, impotence, impairment of quality of life and risk of withdrawal hypertension limit use of clonidine.

Other uses of clonidine are opioid withdrawal syndrome, postoperative epidural analgesia and menopausal syndrome.

Methyldopa It is the α-methyl analogue of dopa, the precursor of dopamine (DA) and NA. The α methyl-NA (a selective α_2 agonist) formed in brain from methyldopa acts on central α_2 receptors to decrease efferent sympathetic activity. Because methyldopa decreases t.p.r. more than HR or c.o., it may be acting on a different population of neurones in the vasomotor centre than clonidine. In large doses it inhibits the enzyme dopa decarboxylase in brain and periphery → reduces NA synthesis and forms the *false transmitter* methyl-NA in periphery as well.

Methyldopa is a moderate efficacy antihypertensive. Circulating levels of NA and renin tend to fall due to reduction in sympathetic tone.

Less than 1/3 of an oral dose of methyldopa is absorbed. It is partly metabolized and partly excreted unchanged in urine. Antihypertensive effect develops over 4–6 hours and lasts for 12–24 hours.

Adverse effects Sedation, lethargy and reduced mental capacity are common side effects. Cognitive impairment may develop. Dryness of mouth, nasal stuffiness, headache, fluid retention, weight gain, impotence are the other side effects.

Postural hypotension is generally mild but more common than with clonidine.

Positive Coombs' test occurs in 1/6 patients, few develop haemolytic anaemia. Fever, rash, hepatitis, 'flu' like illness, thrombocytopenia and rarely lupus syndrome occur.

Interactions Tricyclic antidepressants reverse its action by blocking its active transport into the adrenergic neurones.

Use Methyldopa has been a widely used antihypertensive for mild-to-moderate cases, especially in combination with a diuretic. However, its use has declined now because of the availability of better tolerated agents. It is safe during pregnancy.

VASODILATORS

Hydralazine/Dihydralazine It is a directly acting arteriolar vasodilator with little action on venous capacitance vessels; reduces t.p.r. It causes greater reduction of diastolic than systolic BP. Reflex compensatory mechanisms are evoked which cause tachycardia, increase in c.o. and renin release → increased aldosterone → Na^+ and water retention. The disproportionate cardiac stimulation appears to involve direct augmentation of NA release and myocardial contractility as well. Angina may be precipitated due to increased cardiac work as well as steal phenomenon. Tolerance to the hypotensive action develops unless diuretics or β blockers or both are given together to block the compensatory mechanisms.

The mechanism of vascular smooth muscle relaxant action is not clearly known. It is partly endothelium dependent: may involve generation of NO (nitric oxide) and stimulation of cGMP. Direct effects on membrane potential and on Ca^{2+} fluxes have also been proposed.

Pharmacokinetics Hydralazine is well absorbed orally. The chief metabolic pathway is acetylation which exhibits a bimodal distribution in the population—there are slow and fast acetylators.

Hydralazine is completely metabolized both in liver and plasma; the metabolites are excreted in urine, t½ 1–2 hours. However, hypotensive effect lasts longer (12 hours), probably because of its persistence in the vessel wall.

Adverse effects are frequent and mainly due to vasodilatation.

1. Facial flushing, conjunctival injection, throbbing headache, dizziness, palpitation, nasal stuffiness, fluid retention, edema, CHF.
2. Angina and MI may be precipitated in patients with coronary artery disease.

3. Paresthesias, tremor, muscle cramps, edema, rarely peripheral neuritis.
4. Lupus erythematosus or rheumatoid arthritis like symptoms develop on prolonged use of doses above 100 mg/day.

Use Hydralazine is used in moderate-to-severe hypertension not controlled by the first line drugs. Usually, low doses are added to diuretics and β blockers already being administered.

It is one of the preferred antihypertensives during pregnancy.

Sodium nitroprusside It is a rapidly (within seconds) and consistently acting vasodilator: has brief duration of action (2–5 min)—vascular tone can be titrated with the rate of i.v. infusion. It relaxes both resistance and capacitance vessels: reduces t.p.r. as well as c.o. (by decreasing venous return). Myocardial work is reduced—ischaemia is not accentuated, as occurs with selective arteriolar dilators (hydralazine). Little reflex tachycardia is produced in supine posture.

Endothelial cells, RBCs (and may be other cells) split nitroprusside to generate NO which relaxes vascular smooth muscle. The enzymes involved are different from those that produce NO from glyceryl trinitrate. Moreover, nitroprusside is spontaneously converted to NO (and CN) by glutathione. This may be responsible for the different pattern of vasodilator action compared to nitrates, as well as for the fact that no nitrate like tolerance develops to nitroprusside action.

Nitroprusside has gained popularity in the management of hypertensive emergencies: 50 mg is added to a 500 ml bottle of saline. The infusion is started at 0.02 mg/min and titrated upward with the response.

Side effects due to the vasodilator action of nitroprusside are—palpitation, nervousness, vomiting, perspiration, pain in abdomen, weakness, disorientation, and lactic acidosis.

Nitroprusside has also been used to produce controlled hypotension and in refractory CHF, pump failure accompanying MI, acute mitral regurgitation. Ventricular performance is improved by reducing both pre- and afterload.

TREATMENT OF HYPERTENSION

The aim of antihypertensive therapy is to prevent morbidity and mortality associated with persistently raised BP by lowering it to an acceptable level, with minimum inconvenience to the patient. Both systolic and diastolic BP predict the likelihood of target organ damage and complications such as:

(a) Cerebrovascular disease, transient ischaemic attacks, stroke.
(b) Hypertensive heart disease—left ventricular hypertrophy, CHF.
(c) Coronary artery disease, angina, myocardial infarction, sudden cardiac death.
(d) Arteriosclerotic peripheral vascular disease, retinopathy.
(e) Dissecting aneurysm.
(f) Glomerulopathy, renal failure.

Nonpharmacological measures (life style modification—diet, exercise, weight reduction, mental relaxation, etc.) should be tried first and concurrently with drugs.

With the establishment of at least four groups (ACE inhibitors/AT_1 antagonists, CCBs, β blockers, diuretics) of first choice drugs and their evaluation in large multicentric trials, an 'individualized care approach' can be adopted for the selection of initial monotherapy, followed if needed, by stepped combination therapy. The principle of this approach is to match the requirements of individual patients with the pharmacological and clinical properties of an appropriate antihypertensive agent. For each class of antihypertensive drugs, certain patients can be identified who are best suited to be treated with that drug as first choice therapy, and those in whom it should be avoided.

Combination therapy Though ~50% hypertensives can be successfully trea ted, at least initially, with a single drug, the addition of a second (and third) drug when monotherapy fails or is not tolerated, is often required. In practice a large majority of hypertensives ultimately require 2 or more drugs.

It is rational in such cases to combine drugs with different mechanisms of action or different patterns of haemodynamic effects:

(a) Drugs which increase plasma renin activity—diuretics, vasodilators, CCBs, ACE inhibitors may be combined with drugs which lower plasma renin activity—β blockers, clonidine, methyldopa.

(b) All sympathetic inhibitors (except β blockers) and vasodilators cause fluid retention: used alone tolerance develops. Addition of a diuretic checks fluid retention and development of tolerance.

(c) Hydralazine and DHPs cause tachycardia which is counteracted by β blockers, while the initial increase in t.p.r. caused by nonselective β blockers is counteracted by the vasodilator.

(d) ACE inhibitors/AT_1 antagonists are particularly synergistic with diuretics; this combination is very good for patients with associated CHF and left ventricular hypertrophy.

(e) Other useful combinations are:
ACE inhibitor + CCB or β blocker or clonidine or methyldopa.
β blocker + prazosin

A three drug combination therapy may be needed in a few patients (of severe or nonresponsive or malignant hypertension).

Combinations to be avoided are:

1. An α or β adrenergic blocker with clonidine: apparent antagonism of clonidine action has been observed.
2. Nifedipine (or other DHPs) with diuretic: synergism between these is unproven.
3. Hydralazine with a DHP or prazosin: similar pattern of haemodynamic action.
4. Verapamil or diltiazem with β blocker: marked bradycardia, A-V block.
5. Methyldopa with clonidine or any two drugs of the same class.

Hypertensive emergencies and urgencies

Controlled reduction of BP over minutes (in emergencies) or hours (in urgencies) is required to counter threat to organ function and life in:

1. Cerebrovascular accident (haemorrhage) or head injury with high BP.
2. Hypertensive encephalopathy.
3. Hypertensive acute LVF and pulmonary edema.
4. Unstable angina or MI with raised BP.
5. Dissecting aortic aneurysm.
6. Eclampsia.
7. Hypertensive episodes in pheochromocytoma, cheese reaction or clonidine withdrawal.

Nifedipine (10 mg soft geletine cap) orally every ½–1 hr was widely employed for rapid BP reduction in urgencies. This practice has now been discarded because of inability to control rate and degree of fall in BP as well as serious adverse consequences/mortality. Other rapidly acting oral drugs like *captopril* (25 mg) or *clonidine* (100 µg) every 1–2 hours have also been found unsatisfactory. Parenteral drugs with controllable action are now used. Mean BP should be lowered by no more than 25% over minutes or a few hours and then gradually to not lower than 160/100 mmHg. Drugs employed are:

1. *Sodium nitroprusside* Because of predictable, instantaneous, titratable and balanced arteriovenous vasodilatory action which persists without tolerance till infused, nitroprusside is the drug of choice for most hypertensive emergencies. However, it needs an infusion pump and constant monitoring.
2. *Glyceryl trinitrate* Given by i.v. infusion GTN also acts within 2–5 min and has brief titratable action. Its predominant venodilator action makes it particularly suitable for lowering BP after cardiac surgery and in acute LVF, MI, unstable angina.
3. *Esmolol* This β blocker given as bolus followed by slow i.v. injection acts in 1–2 min; action lasts for 10–20 min. It is particularly useful when cardiac contractility and work is to be reduced, such as in aortic dissection (nitroprusside may be given concurrently) and during/after anaesthesia.
4. *Phentolamine* This $\alpha_1 + \alpha_2$ blocker is the drug of choice for hyperadrenergic states—hypertensive episodes in pheochromocytoma, cheese reaction, clonidine withdrawal.

ANTIANGINAL DRUGS

Antianginal drugs are those that prevent, abort or terminate attacks of angina pectoris.

Angina pectoris Is a pain syndrome due to induction of an adverse oxygen supply/demand situation in a portion of the myocardium. Two principal forms are recognized:

(a) *Classical angina* (common form) Attacks are predictably (stable angina) provoked by exercise, emotion, eating or coitus and subside when the increased energy demand is withdrawn. The underlying pathology is—severe arteriosclerotic affliction of larger coronary arteries (conducting vessels) which run epicardially and send perforating branches to supply the deeper tissue (Fig. 11.2). The coronary obstruction is 'fixed'; blood flow fails to increase during increased demand despite local factors mediated dilatation of resistance vessels (Fig. 11.3) and ischaemic pain is felt. Due to inadequacy of ischaemic left ventricle, the end diastolic left ventricular pressure rises from 5 to about 25 mm Hg—produces subendocardial 'crunch' during diastole (blood flow to the subendocardial region occurs only during diastole) and aggravates ischaemia in this region.

Drugs that are useful, primarily reduce cardiac work (directly by acting on heart or indirectly by reducing preload hence end diastolic pressure, and afterload). They may also cause favourable redistribution of blood flow to the ischaemic areas.

(b) *Variant/Prinzmetal's angina* (uncommon form) Attacks occur at rest or during sleep and are unpredictable. They are due to recurrent localized (occasionally diffuse) coronary vasospasm (Fig. 11.3) which may be superimposed on arteriosclerotic coronary artery disease. Abnormally reactive and hypertrophied segments in the coronary arteries have been demonstrated. Drugs are aimed at preventing and relieving the coronary vasospasm.

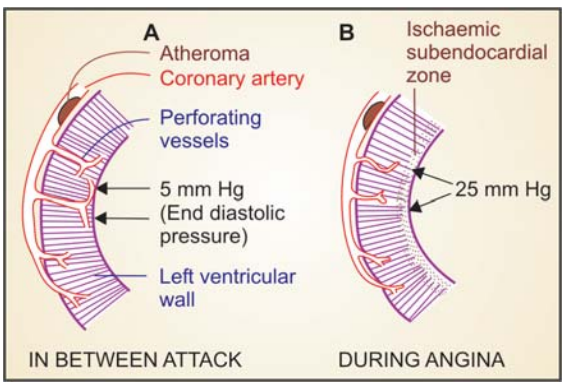


Fig. 11.2: Diagrammatic representation of subendocardial 'crunch' during an attack of angina

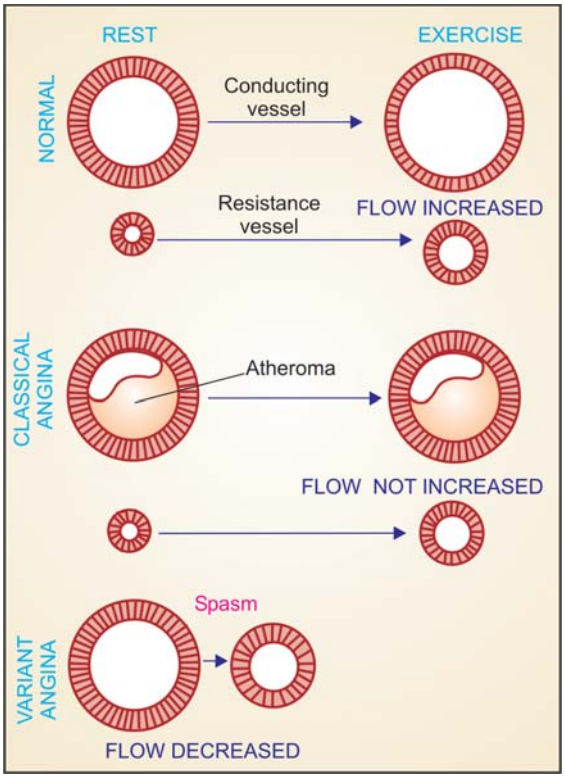


Fig. 11.3: Diagrammatic representation of coronary artery calibre changes in classical and variant angina

Unstable angina with rapid increase in duration and severity of attacks is mostly due to rupture of an atheromatous plaque attracting platelet deposition and progressive occlusion of the coronary artery; occasionally with associated coronary vasospasm.

Antianginal drugs relieve cardiac ischaemia but do not alter the course of coronary artery pathology: no permanent benefit is afforded.

CLASSIFICATION

1. *Nitrates*
(a) *Short acting:* Glyceryl trinitrate (GTN, Nitroglycerine)
(b) *Long acting*: Isosorbide dinitrate (short acting by sublingual route), Isosorbide mononitrate, Erythrityl tetranitrate, Penta erythritol tetranitrate
2. β *Blockers* Propranolol, Metoprolol, Atenolol and others.

3. *Calcium channel blockers*: Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine
4. *Potassium channel opener* Nicorandil
5. *Others* Dipyridamole, Trimetazidine.

Clinical Classification

A. *Used to abort or terminate attack* GTN, Isosorbide dinitrate (sublingually).
B. *Used for chronic prophylaxis* All other drugs.

NITRATES (GTN as prototype)

All organic nitrates share the same action; differ only in time course. The only major action is direct nonspecific smooth muscle relaxation.

Preload reduction The most prominent action is exerted on vascular smooth muscle. Nitrates dilate veins more than arteries → peripheral pooling of blood → decreased venous return, i.e. preload on heart is reduced → end diastolic size and pressure are reduced → decreased cardiac work.

The decrease in end diastolic pressure abolishes the subendocardial crunch by restoring the pressure gradient across ventricular wall due to which subendocardial perfusion occurs during diastole. It is through their action on peripheral veins that nitrates exert major beneficial effects in classical angina.

After load reduction Nitrates also produce some arteriolar dilatation → slightly decrease total peripheral resistance (t.p.r.) or afterload on heart; BP falls somewhat; systolic more than diastolic (reflex sympathetic activity tends to maintain diastolic BP). This action contributes to the reduction of cardiac work which is directly proportional to aortic impedance.

Redistribution of coronary flow In the arterial tree, nitrates preferentially relax bigger conducting (angiographically visible) coronary arteries than arterioles or resistance vessels. This pattern of action may cause favourable redistribution of blood flow to ischaemic areas in angina patients. Dilatation of conducting vessels all over by nitrate along with ischaemia induced dilatation of autoregulatory resistance vessels only in the ischaemic zone increases blood flow to this area; while in the non-ischaemic zones, resistance vessels maintain their tone → flow does not increase, or may decrease to compensate for increased flow to ischaemic zone. In fact, nitrates do not appreciably increase total coronary flow in angina patients.

Mechanism of relief of angina The dilator effect on larger coronary vessels is the principal action of nitrates benefiting variant angina by counteracting coronary spasm. In classical angina, undoubtedly, the primary action is to reduce cardiac work by action on peripheral vasculature, though increased blood supply to ischaemic area may contribute. Exercise tolerance of angina patients is increased because the same amount of exercise causes lesser augmentation of cardiac work.

Heart and peripheral blood flow Nitrates have no direct stimulant or depressant action on heart. They dilate cutaneous (especially over face and neck → flushing) and meningeal vessels → headache. Splanchnic and renal blood flow decreases to compensate for vasodilatation in other areas. They tend to decongest lungs by shifting blood to systemic circulation.

Other smooth muscles Bronchi, biliary tract and esophagus are relaxed; effect on intestine, ureter and uterus is variable and insignificant.

Mechanism of action Organic nitrates are rapidly denitrated enzymatically in the smooth muscle cell to release the reactive free radical *nitric oxide (NO)* which activates cytosolic guanylyl cyclase → increased cGMP → causes dephosphorylation of myosin light chain kinase (MLCK) through a cGMP-dependent protein kinase (Fig. 11.4). Reduced availability of phosphorylated (active) MLCK interferes with activation of myosin → it fails to interact with actin to cause contraction. Consequently, relaxation occurs. Raised intracellular cGMP may also reduce Ca^{2+} entry—contributing to relaxation.

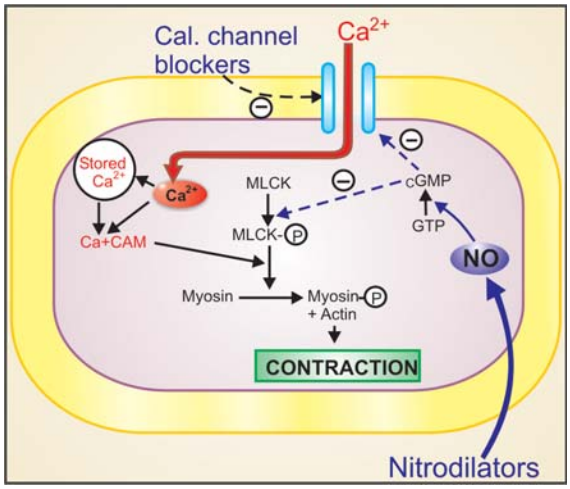


Fig. 11.4: Mechanism of vascular smooth muscle relaxant action of nitrodilators like glyceryl trinitrate and calcium channel blockers; (- - - →) Inhibition
CAM—Calmodulin; NO—Nitric oxide; MLCK—Myosin light chain kinase; MLCK-P—Phosphorylated MLCK; GTP—Guanosine triphosphate; cGMP—Cyclic guanosine monophosphate

Pharmacokinetics Organic nitrates are lipid soluble: well absorbed from buccal mucosa, intestines and skin. All except isosorbide mononitrate undergo extensive but variable first pass metabolism in liver. They are rapidly denitrated by a glutathione reductase.

Adverse effects These are mostly due to vasodilatation.

1. Fullness in head, throbbing headache; some degree of tolerance develops on continued use.
2. Flushing, weakness, sweating, palpitation, dizziness and fainting; these are mitigated by lying down and accentuated by erect posture and alcohol.
3. Methemoglobinemia: is not marked with clinically used doses.
4. Rashes are rare.

Tolerance Attenuation of haemodynamic and antiischaemic effect of nitrates occurs if they are continuously present in the body. This tolerance weans off rapidly (within hours) when the body is free of the drug. Clinically, no significant tolerance develops on intermittent use of sublingual GTN for attacks of angina. However, it may become important when GTN is used orally, transdermally or by continuous i.v. infusion round the clock.

The most practical way to prevent nitrate tolerance is to provide nitrate free intervals every day.

Interactions Sildenafil causes dangerous potentiation of nitrate action: severe hypotension, MI and deaths are on record. Additive hypotension is also possible when nitrate is given to a patient receiving other vasodilators.

1. Glyceryl trinitrate (GTN, Nitroglycerine) It is a volatile liquid which is absorbed on the inert matrix of tablet. The sublingual route is used when terminating an attack or aborting an imminent one is the aim. It acts within 1–2 min (peak blood level in 3–6 min) because of direct absorption into systemic circulation (bypassing liver where almost 90% is metabolized).

Plasma t½ is 2 min, duration of action depends on the period it remains available for absorption from buccal mucosa. The remaining part of the tablet may be spit or swallowed when no longer needed. Sustained release oral capsules containing much larger amounts of GTN can be used for chronic prophylaxis.

Nitroglycerine is readily absorbed from the skin. A transdermal patch in which the drug is incorporated into a polymer bonded to adhesive plaster (*see* p. 8) has been developed which provides steady delivery for 24 hours. However, development of tolerance and dependence may jeopardise its value. It is advised that the patch be taken off for 8 hours daily.

Intravenous infusion of GTN provides rapid, steady, titratable plasma concentration for as long as desired. It has been successfully used for unstable angina, coronary vasospasm, LVF accompanying MI, hypertension during cardiac surgery, etc.

2. Isosorbide dinitrate It can be used sublingually at the time of attack (slightly slower

in action than GTN, peak in 5–8 min) as well as orally for chronic prophylaxis. The t½ is 40 min, but sustained release formulation may afford protection for 6–10 hours.

3. Isosorbide mononitrate This is an active metabolite of isosorbide dinitrate. When administered orally, it undergoes little first pass metabolism: bioavailability is high, interindividual differences are minimal and it is longer acting (t½ 4–6 hr).

4. Erythrityl tetranitrate and pentaerythritol tetranitrate These are longer acting nitrates used only for chronic prophylaxis.

USES

1. *Angina pectoris* Nitrates are effective in classical as well as variant angina. For aborting or terminating an attack, sublingual GTN tablet or isosorbide dinitrate is taken on 'as and when required' basis. Since dental procedures are often an emotional stress, anginal attack may be precipitated. Sublingual GTN tablet should be readily available to abort/terminate such an attack on the dental chair. Nitrates increase exercise tolerance and postpone ECG changes of ischaemia. Longer acting formulations (oral, transdermal) of GTN or other nitrates are used on regular schedule for chronic prophylaxis. Nitrates are effective in unstable angina as well. However, antiplatelet drugs are the primary measure in unstable angina.

2. *CHF and acute LVF* Nitrates afford relief by venous pooling of blood → reduced venous return (preload) → decreased end diastolic volume → improvement in left ventricular function. Intravenous GTN is the preparation of choice for emergency use: rate of infusion must be guided by continuous haemodynamic monitoring.

3. *Myocardial infarction* Carefully titrated i.v. infusion of GTN to avoid tachycardia and started soon after the arterial occlusion can reduce the area of necrosis by favourably altering O_2 balance in the marginal partially ischaemic zone by reducing cardiac work. The ECG signs, arrhythmias and early mortality may also be reduced. Nitrate therapy in the post infarction period does not alter mortality, but it can be used for relief of angina.

4. *Interventional cardiac procedures* Such as percutaneous coronary angioplasty: adjuvant therapy with GTN to dilate coronaries may be employed.

5. *Biliary colic* due to disease or morphine—responds to sublingual GTN or isosorbide dinitrate.

6. *Esophageal spasm* Sublingual GTN promptly relieves pain.

7. *Cyanide poisoning* Nitrates generate methaemoglobin which has high affinity for cyanide radical and forms cyanomethaemoglobin. Cytochrome and other oxidative enzymes are thus protected from cyanide.

β BLOCKERS

These drugs do not dilate coronaries or other blood vessels; total coronary flow is rather reduced due to blockade of dilator β_2 receptors. However, flow to the ischaemic subendocardial area is not reduced because of favourable redistribution and decrease in ventricular wall tension. They act by reducing cardiac work and O_2 consumption (decreased heart rate, inotropic state and mean BP). This is marginal at rest. More importantly, they limit increase in these modalities that occurs during exercise or anxiety (due to antiadrenergic action on heart).

All β blockers are nearly equally effective in decreasing frequency and severity of attacks and increasing exercise tolerance in classical angina, but cardioselective agents (e.g. atenolol, metoprolol) are preferred over nonselective $\beta_1 + \beta_2$ blockers (e.g. propranolol) which may worsen variant angina. Long-term β blocker therapy lowers risk of sudden cardiac death among ischaemic heart disease patients. β blockers are to be taken on a regular schedule; not on 'as and when required' basis.

CALCIUM CHANNEL BLOCKERS

Described earlier (*see* p. 172).

POTASSIUM CHANNEL OPENERS

Minoxidil and diazoxide are K^+ channel openers which have been used since long in severe hypertension and hypertensive emergencies. Novel K^+ channel openers like *nicorandil, pinacidil, cromakalim* and others have been developed recently.

Since intracellular concentration of K^+ is much higher (150 mM) compared to extracellular (4–5 mM), K^+ channel opening results in outflow of K^+ ions and hyperpolarization. There are multiple types of K^+ channels, e.g. voltage dependent, Ca^{2+} activated, receptor operated, ATP sensitive, Na^+ activated and cell volume sensitive which serve diverse functions and exhibit different sensitivities to drugs. As such, K^+ channel openers exhibit considerable diversity in action. The most prominent action of K^+ channel openers is smooth muscle relaxation—vascular as well as visceral.

Nicorandil This novel antianginal drug activates ATP sensitive K^+ channels— hyperpolarizing vascular smooth muscle. Like nitrates it also acts as a NO donor—relaxes blood vessels by increasing cGMP. Thus, arterial dilatation is coupled with venodilatation. Coronary flow is increased; dilatation of both epicardial conducting vessels and deeper resistance vessels has been demonstrated. No significant cardiac effects on contractility and conduction have been noted.

Beneficial effects on angina frequency and exercise tolerance comparable to nitrates, β blockers and CCBs have been obtained in stable as well as vasospastic angina.

Side effects are flushing, palpitation, weakness, headache, dizziness, mouth ulcers, nausea and vomiting.

OTHER ANTIANGINAL DRUGS

1. Dipyridamole It is a powerful coronary dilator, but does not afford symptomatic benefit or avert ECG changes of angina. The pharmacological success but therapeutic failure of dipyridamole has been explained on the basis of 'coronary steal' phenomenon. By dilating resistance vessels in nonischaemic zone as well, it diverts the already reduced blood flow away from ischaemic zone.

Dipyridamole inhibits platelet aggregation. Though not useful as an antianginal drug, it is being employed for prophylaxis of coronary and cerebral thrombosis in post-MI and post-stroke patients, as well as to prevent thrombosis in patients with prosthetic heart valves.

2. Trimetazidine This novel antianginal drug acts by nonhaemodynamic mechanisms. There is no effect on determinants of myocardial O_2 consumption, such as HR and BP, both at rest as well as during exercise, but angina frequency is reduced and exercise capacity is increased. In patients only partially controlled by long-acting nitrate/β blocker/CCB, addition of trimetazidine further reduced anginal attacks and increased exercise duration. The mechanism of action of trimetazidine is not known, but it may improve cellular tolerance to ischaemia.

Trimetazidine is generally well tolerated; side effects are—gastric burning, dizziness, fatigue and muscle cramps.

Status of trimetazidine in ischaemic heart disease and long-term survival benefits are not yet defined. It is mostly used as additional medication to conventional therapy in angina and post-MI patients.

DRUG THERAPY IN MYOCARDIAL INFARCTION

Myocardial infarction (MI) is ischaemic necrosis of a portion of the myocardium due to sudden occlusion of a branch of coronary artery. An acute thrombus at the site of atherosclerotic obstruction is the usual cause. About ¼ patients die before therapy can be instituted. The remaining are best treated in specialized coronary care units with continuous monitoring of the haemodynamic parameters and ECG to guide the selection of drugs and dosage. Those who receive such facility can be greatly benefitted by drug therapy, which according to individual needs is directed to:

1. *Pain, anxiety and apprehension* Opioid analgesics (morphine/pethidine), diazepam.

2. *Oxygenation* By O_2 inhalation and assisted respiration, if needed.

3. *Maintenance of blood volume, tissue perfusion and microcirculation* Slow i.v. infusion of

saline/low molecular weight dextran (avoid volume overload).

4. *Correction of acidosis* Due to lactic acid production—sod. bicarbonate by i.v. infusion.

5. *Prevention and treatment of arrhythmias* Prophylactic infusion of β blocker as soon as the MI patient is seen and its continuation for a few days has been shown to reduce the incidence of arrhythmias and mortality. β blockers used early in evolving MI can reduce the infarct size (myocardial salvage) and subsequent complications.

Tachyarrhythmias may be treated with lignocaine, procainamide or other antiarrhythmics. Routine prophylactic lignocaine infusion is not recommended now. Bradycardia and heart block may be managed with atropine or electrical pacing.

6. *Pump failure* The objective is to increase c.o. and/or decrease filling pressure without unduly increasing cardiac work or reducing BP. Drugs used for this purpose are:
(a) *Furosemide*: indicated if pulmonary wedge pressure is > 20 mm Hg. It decreases cardiac preload.
(b) *Vasodilators*: arteriolar, venous or combined dilator is selected according to the monitored haemodynamic parameters. Drugs like GTN (i.v.), captopril, or nitroprusside have been mainly used. Infused early GTN may in addition limit infarct size and reduce mortality.
(c) *Inotropic agents*: dopamine or dobutamine may be needed to augment the pumping action of heart and tide over crisis.

7. *Prevention of thrombus extension, embolism, venous thrombosis* Heparin followed by oral anticoagulants. However, value is disputed. Any benefit is short term; anticoagulants are not prescribed on long-term basis now.

8. *Thrombolysis* Fibrinolytic agents, i.e. plasminogen activators—streptokinase/urokinase/alteplase to achieve reperfusion of the infarcted area.

9. *Prevention of remodeling and subsequent CHF* ACE inhibitors have proven efficacy and afford long-term survival benefit.

10. *Prevention of future attacks*
(a) Platelet function inhibitors—aspirin given on long-term basis is routinely prescribed.
(b) β blockers—reduce risk of reinfarction, CHF and mortality. All patients not having any contraindication are put on a β blocker for at least 2 years.
(c) Control of hyperlipidaemia—dietary substitution with unsaturated fats, hypolipidemic drugs.

CHAPTER 12

Cardiovascular Drugs

Drugs for Heart Failure and Cardiac Arrhythmia

CARDIAC GLYCOSIDES

These are glycosidic drugs having *cardiac inotropic* property. They increase myocardial contractility and output in a hypodynamic heart without a proportionate increase in O_2 consumption. Thus, efficiency of failing heart is increased. In contrast, 'cardiac stimulants' (Adr, theophylline) increase O_2 consumption rather disproportionately and tend to decrease myocardial efficiency, i.e. increase in O_2 consumption is more than increase in contractility.

The cardiac glycosides are obtained from *Digitalis lanata* (Digoxin), *Digitalis purpurea* (Digitoxin) and many other plants; some have been prepared semisynthetically. They consist of an aglycone moiety made of cyclopentanoperhydrophenanthrene (steroid) ring with attached 5 or 6 membered unsaturated lactone ring and a sugar moiety. Digoxin is the most commonly used glycoside, therefore described as prototype.

PHARMACOLOGICAL ACTIONS

Heart Digitalis has direct effects on myocardial contractility and electrophysiological properties. In addition, it has vagomimetic action, reflex effects due to alteration in haemodynamics and direct CNS effects altering sympathetic activity.

1. Digitalis causes a dose dependent increase in force of contraction of heart—a positive inotropic action. This is specially seen in the failing heart. When a normal heart is subjected to increased impedance to outflow, it generates increased tension so that stroke volume is maintained up to considerably higher values of impedance (Fig. 12.1), while the failing heart is not able to do so and the stroke volume progressively decreases. The digitalized failing heart regains some of its capacity to contract more forcefully when subjected to increased resistance to ejection. There is more complete emptying of failing and dilated ventricles—cardiac output is increased.

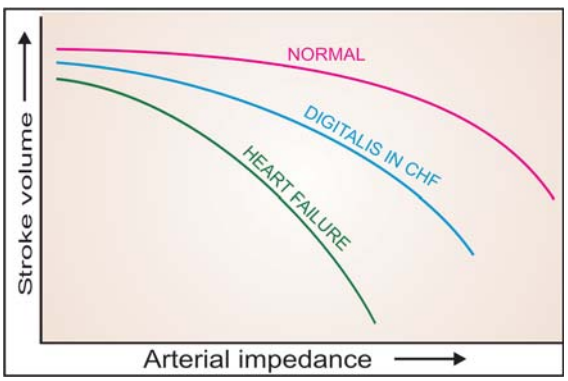


Fig. 12.1: Relationship between peripheral resistance and stroke output in normal and failing heart, and the action of digitalis on failing heart

2. Therapeutic doses of digoxin do not increase myocardial tone or resting tension which is defined by the maximum length of the muscle fibre at a given filling pressure. However, toxic doses do produce myocardial contracture.

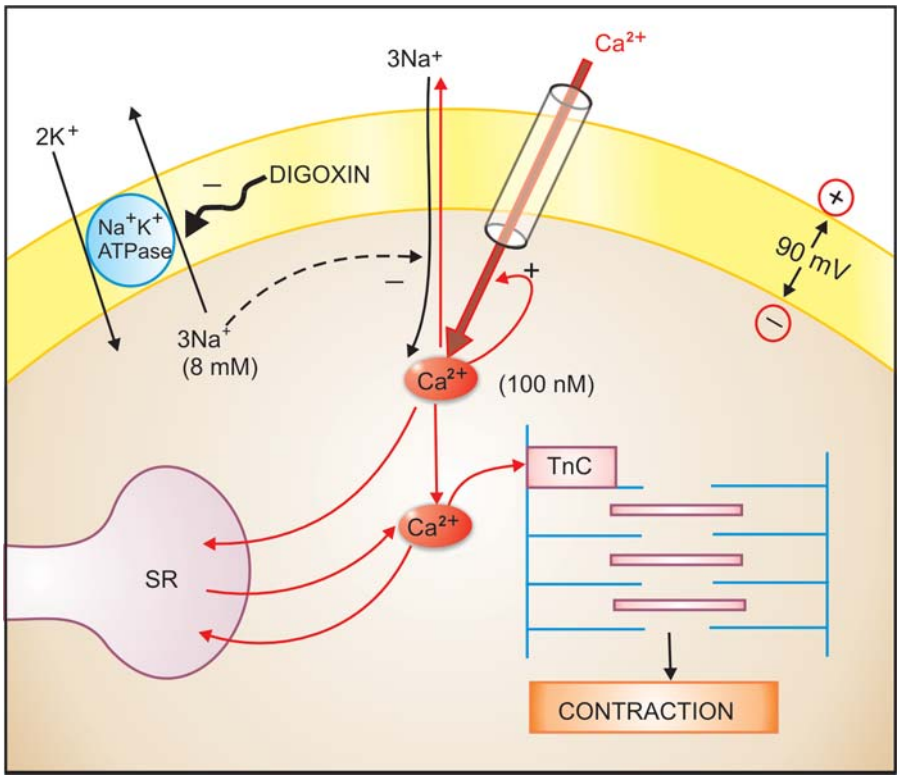


Fig. 12.2: Mechanism of positive inotropic action of cardiac glycosides
SR—Sarcoplasmic reticulum; TnC—Troponin C

3. The heart rate is decreased by digitalis. It produces bradycardia by increasing vagal tone as well as by a direct extravagal action exerted on SA and A-V nodes. In CHF patients improved circulation (due to positive inotropic action) restores the diminished vagal tone and abolishes sympathetic overactivity: bradycardia is more marked.

4. The electrophysiological properties of different types of cardiac fibres are affected differently by digitalis.

- SA and A-V nodal automaticity is depressed while that in Purkinje fibres (PFs) and other pacemakers it is enhanced: arrhythmias may be produced.
- Effective refractory period (ERP) of A-V node and bundle of His is prolonged: the maximal rate at which impulses can be transmitted from atrium to ventricle is reduced.
- A-V conduction is slowed. Partial to complete A-V block can occur.
- Atrial ERP is abbreviated and made more inhomogeneous: atria become more prone to fibrillation. Ventricular ERP is also reduced.
- Myocardial excitability is enhanced, but may be depressed at toxic doses.

Mechanism of action Digitalis increases force of cardiac contraction by inhibiting membrane associated Na^+K^+ ATPase of myocardial fibres (Fig. 12.2). Inhibition of this cation pump results in progressive accumulation of Na^+ intracellularly. This indirectly results in intracellular Ca^{2+} accumulation by Na^+: Ca^{2+} exchange.

The excess Ca^{2+} remaining in cytosol is taken up into sarcoplasmic reticulum (SR) which progressively get loaded with more Ca^{2+} → subsequent calcium transients are augmented →

better excitation-contraction coupling → increased force of contraction.

Binding of glycoside to Na^+K^+ATPase is slow. Moreover, after Na^+K^+ATPase inhibition, Ca^{2+} loading occurs gradually. As such, inotropic effect of digitalis takes hours to develop, even after i.v. administration.

Inhibition of Na^+K^+ ATPase is clearly involved in the toxic actions of digitalis. At high doses, there is depletion of intracellular K^+; toxicity is partially reversed by infusing K^+. Excessive Ca^{2+} loading of SR results in spontaneous cycles of Ca^{2+} release and uptake producing oscillatory after-depolarizations and after-contractions.

Blood vessels Digitalis has mild direct vasoconstrictor action—peripheral resistance is increased in normal individuals. However, in CHF patients this is more than compensated by the indirect effect of improvement in circulation.

Digitalis has no prominent effect on BP. Hypertension is no contraindication to the use of digitalis. Therapeutic doses of digitalis have no significant effect on coronary circulation—coronary insufficiency is no contraindication to its use.

Kidney Diuresis is seen promptly in CHF patients, secondary to improvement in circulation and renal perfusion. The retained salt and water is gradually excreted. No diuresis occurs in normal individuals or in patients with edema due to other causes.

CNS Digitalis has little apparent CNS effect in therapeutic dose. Higher doses cause CTZ activation → nausea and vomiting. Still higher doses produce hyperapnoea, central sympathetic stimulation, mental confusion, disorientation and visual disturbances.

PHARMACOKINETICS

The pharmacokinetic properties of digoxin and digitoxin are presented in Table 12.1.

Digitoxin is the most lipid soluble, digoxin is relatively polar. Bioavailability of digoxin tablets from different manufacturers differs considerably.

Table 12.1: Pharmacokinetic properties of digoxin and digitoxin

	DIGITOXIN	*DIGOXIN*
1. Oral absorption	V. good (90–100%)	Good (60–80%)
2. Plasma protein binding	95%	25%
3. Time course of action*		
–Onset	½–2 hr	15–30 min
–Peak	6–12 hr	2–5 hr
–Duration	2–3 weeks	2–6 days
4. Plasma t½	5–7 days	40 hr
5. Plasma concentration		
–Therapeutic	15–30 ng/ml	0.8–2 ng/ml
–Toxic	> 35 ng/ml	> 2.5 ng/ml
6. Potency**	Least	Intermediate
7. Daily maintenance dose	0.05–0.2 mg	0.125–0.5 mg
8. Daily elimination***	10–15%	35%
9. Route of elimination (predominant)	Hepatic metabolism	Renal excretion
10. Administration	Oral	Oral, i.v.
11. Generally used for	Maintenance	Routine treatment and emergency

* Of full digitalizing dose given i.v.; **judged from i.v. digitalizing dose; *** fraction of total amount present in body.

The volume of distribution of cardiac glycosides is large, e.g. 6–8 L/kg in case of digoxin. All are concentrated in the heart (~20 times than plasma), skeletal muscle, liver and kidney.

Digoxin is primarily excreted unchanged by the kidney: mainly by glomerular filtration; rate of excretion is altered parallel to creatinine clearance.

Cardiac glycosides are cumulative drugs. When maintenance doses are given from the beginning, steady-state levels and full therapeutic effect are attained after 4 × t½, i.e. 6–7 days for digoxin and 4 weeks for digitoxin.

ADVERSE EFFECTS

Toxicity of digitalis is high, margin of safety is low (therapeutic index 1.5–3) and fatalities have occurred occasionally. The manifestations are:

Extracardiac Anorexia, nausea, vomiting and abdominal pain are usually reported first: are due to gastric irritation, mesenteric vasoconstriction and CTZ stimulation. Fatigue, malaise, headache, mental confusion, restlessness, hyperapnoea, disorientation, psychosis and visual disturbances are the other complaints. Skin rashes and gynaecomastia are rare.

Cardiac Almost every type of arrhythmia can be produced by digitalis: pulsus bigeminus, nodal and ventricular extrasystoles, ventricular tachycardia and terminally fibrillation. Partial to complete A-V block may be the sole cardiac toxicity or it may accompany other arrhythmias. Severe bradycardia, atrial extrasystoles, AF or AFl have also been noted.

Treatment Further doses of digitalis must be stopped at the earliest sign of toxicity; nothing more needs to be done in many patients, especially if the manifestations are only extracardiac.

Tachyarrhythmias can be treated with KCl infusion. For ventricular arrhythmias lignocaine is preferred, while propranolol is generally given for atrial arrhythmias. Atropine may be tried in case of severe bradycardia/A-V block. The *Fab* fragment of digoxin antibody is used to bind the glycoside and accelerate its elimination.

PRECAUTIONS AND CONTRAINDICATIONS

(a) *Hypokalemia*: enhances digitalis toxicity.

(b) *Elderly, renal or severe hepatic disease*: patients are more sensitive.

(c) *Myocardial infarction*: arrhythmogenic dose of digitalis may be reduced.

(d) *Thyrotoxicosis*: patients are more prone to develop digitalis arrhythmias.

(e) *Myxoedema*: these patients eliminate digoxin more slowly; cumulative toxicity can occur.

(f) *Ventricular tachycardia*: digitalis is contraindicated.

(g) *Partial A-V block*: may be converted to complete A-V block.

(h) *Acute myocarditis*: Diphtheria, acute rheumatic carditis, toxic carditis—response is poor, more prone to arrhythmias.

(i) *Wolff-Parkinson-White syndrome*: Digitalis is contraindicated.

INTERACTIONS

1. *Diuretics*: cause hypokalemia which can precipitate digitalis arrhythmias.
2. *Calcium*: synergises with digitalis → precipitates toxicity.
3. *Quinidine*: reduces binding of digoxin to tissue proteins as well as its renal and biliary clearance → toxicity can occur.
4. *Adrenergic drugs*: can induce arrhythmias in digitalized patients.
5. Digoxin absorption can be reduced by *metoclopramide* (gastrointestinal hurrying) and *sucralfate* which adsorbs digoxin. *Antacids, neomycin, sulfasalazine*: can also reduce digoxin absorption. Absorption is increased by atropinic drugs, including tricyclic antidepressants (which delay gastric emptying). Erythromycin, omeprazole and tetracycline increase bioavailability of digoxin.
6. *Propranolol, verapamil, diltiazem and disopyramide:* may additively depress A-V conduction and oppose positive inotropic action.

USES

The two main indications of digitalis are CHF and control of ventricular rate in atrial fibrillation/flutter.

1. Congestive heart failure

CHF occurs when cardiac output is insufficient to meet the demands of tissue perfusion. Heart failure may primarily be due to systolic dysfunction or diastolic dysfunction.

Systolic dysfunction The ventricles are dilated and unable to develop sufficient wall tension to eject adequate quantity of blood. This occurs in

ischaemic heart disease, valvular incompetence, dilated cardiomyopathy, myocarditis, tachyarrhythmias.

Diastolic dysfunction The ventricular wall is thickened and unable to relax properly during diastole; ventricular filling is impaired because of which output is low. It occurs in sustained hypertension, aortic stenosis, congenital heart disease, A-V shunts, hypertrophic cardiomyopathy.

However, most patients, especially long-standing CHF, have both systolic and diastolic dysfunction. Cardiac glycosides primarily mitigate systolic dysfunction.

Because of lower inotropic state, the failing heart is able to pump much less blood at the normal filling pressure (Fig. 12.3), more blood remains in the ventricles at the end of systole. The normal venous return is added to it and Frank-Starling compensation is utilized to increase filling pressure: the heart may be able to achieve normal stroke volume, but at a filling pressure which produces congestive symptoms (venous engorgement, edema, enlargement of liver, pulmonary congestion → dyspnoea, renal congestion → oliguria).

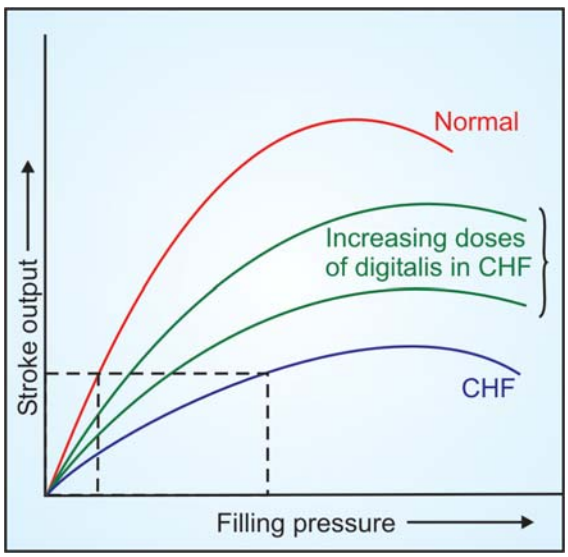


Fig. 12.3: Relationship between filling pressure and cardiac output in normal and failing heart. Digitalis tends to shift the curve towards normal

Digitalis induced enhancement of contractility increases ventricular ejection and shifts the curve relating stroke output to filling pressure towards normal, so that adequate output may be obtained at a filling pressure that does not produce congestive symptoms. Improved tissue perfusion results in withdrawal of sympathetic overactivity → heart rate and central venous pressure (CVP) are reduced. Compensatory mechanisms retaining Na^+ and water are inactivated → diuresis → edema is cleared. Liver regresses, pulmonary congestion is reduced → dyspnoea abates, cyanosis disappears. Low output symptoms like decreased capacity for muscular work are mitigated.

Before the introduction of modern high ceiling diuretics and ACE inhibitors, digitalis was considered an indispensible part of anti-CHF treatment. It is not so now. Many mild-to-moderate cases can be managed without digitalis, i.e. with diuretics and vasodilators, especially an ACE inhibitor. However, digitalis is still the most effective drug capable of restoring cardiac compensation, especially in patients with dilated heart and low ejection fraction; all patients not controlled by diuretic and ACE inhibitor should be additionally treated with digitalis. Continued digitalis therapy is the best course in CHF patients with atrial fibrillation.

The two major limitations in the use of cardiac glycosides are low margin of safety and inability to reverse/retard the processes which cause the heart to fail.

2. Cardiac arrhythmias

A. *Atrial fibrillation (AF)* Digitalis is the drug of choice for controlling ventricular rate in AF, whether associated with CHF or not. However, it is incapable of curing AF, i.e. does not revert it to sinus rhythm, even perpetuates it.

Digitalis reduces ventricular rate in AF by decreasing the number of impulses that are able to pass down the A-V node and bundle of His.

When digitalis is given in AF, average ventricular rate decreases in a dose-dependent manner and pulse deficit is abolished.

B. *Atrial flutter (AFl)* The atrial rate is 200–350/min (less than that in AF), but contractions are regular and synchronous. A variable degree of A-V block, depending on the mean ERP of A-V node, is naturally established. Digitalis enhances this A-V block, reduces ventricular rate and prevents sudden shift of A-V block to a lower degree (as may occur during exercise or sympathetic stimulation). Digitalis may convert AFl to AF by reducing atrial ERP and making it inhomogeneous.

C. *Paroxysmal supraventricular tachycardia (PSVT)* It is a common arrhythmia with a rate 150–200/min and 1 : 1 A-V conduction. It is mostly due to re-entry involving the SA or A-V node. A parenteral glycoside may be injected i.v.—increases vagal tone and depresses the path through the SA/A-V node, or the ectopic focus, and terminates the arrhythmia (success in 1/3 cases). Verapamil/adenosine are more effective, less toxic and act faster. Digitalis is now reserved for preventing recurrences in selected cases.

TREATMENT OF CHF

There are two distinct goals of drug therapy in CHF:

(a) Relief of congestive/low output symptoms and restoration of cardiac performance:
Inotropic drugs—Digoxin, dobutamine/dopamine, amrinone/milrinone
Diuretics—Furosemide, thiazides
Vasodilators—ACE inhibitors/AT_1 antagonists, hydralazine, nitrate
β blocker—Metoprolol, bisoprolol, carvedilol, etc.

(b) Arrest/reversal of disease progression and prolongation of survival:
ACE inhibitors/AT_1 antagonists
β blockers
Aldosterone antagonist—Spironolactone.

Important nonpharmacological measures are rest and salt restriction. The pathophysiological mechnisms which perpetuate heart failure and contribute to disease progression, along with the sites of action of different categories of drugs are depicted in Fig. 12.4.

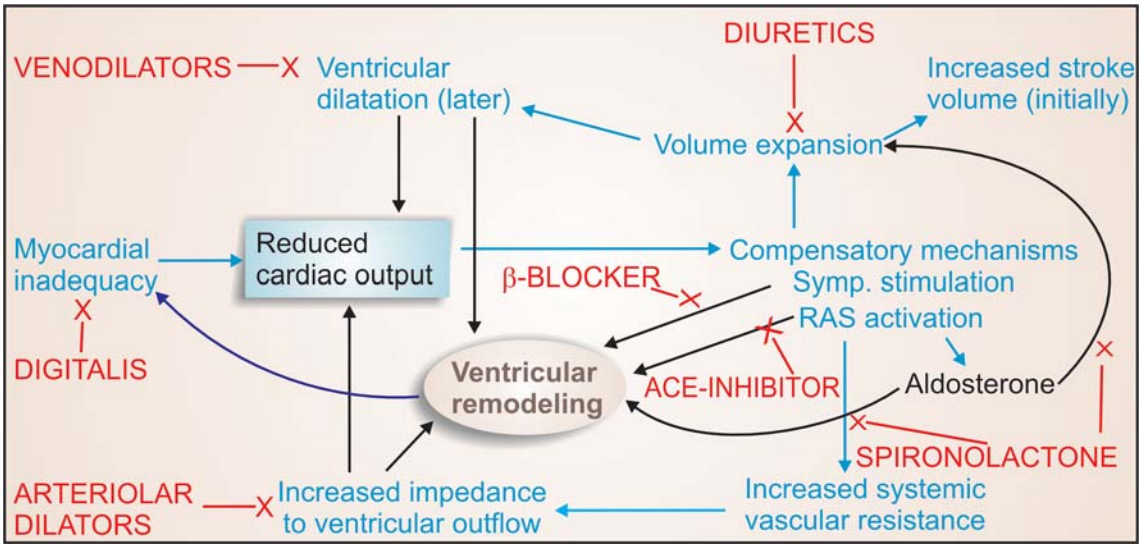


Fig. 12.4: The vicious cycle in CHF: compensatory mechanisms evoked in response to reduced cardiac output themselves perpetuate failure and contribute to remodeling responsible for disease progression. The parameter which is improved by different therapeutic measures is indicated

Diuretics Almost all cases of symptomatic CHF are treated with a diuretic. High ceiling diuretics (furosemide, bumetanide) are the diuretics of choice for mobilizing edema fluid. Diuretics:
(a) Decrease preload and improve ventricular efficiency by reducing circulating volume.
(b) Remove peripheral edema and pulmonary congestion.

However, diuretics do not influence the primary disease process in CHF, though they may dramatically improve symptoms. Despite decades of experience, no prognostic benefit has been demonstrated for diuretics.

Vasodilators They are used i.v. to treat acute heart failure that occurs in advanced cases, in myocardial infarction and cardiogenic shock, as well as orally for long-term therapy of chronic CHF, and have become the mainstay of anti-CHF measures. This class of drugs have been shown to improve life expectancy of CHF patients. Vasodilators with differing profiles of arteriolar and venodilator action are available.

Arteriolar dilators (primarily ↓ afterload)
Hydralazine
Minoxidil
Ca^{2+} channel blockers (Nifedipine)
Pot. channel openers (Nicorandil)

Venodilators (primarily ↓ preload)
Nitrates:
Glyceryl trinitrate
Isosorbide dinitrate

Mixed dilators (↓ pre-and afterload)
ACE Inhibitors
Losartan (AT_1 antagonist)
Prazosin (α_1 blocker)
Phentolamine
Nitroprusside.

(i) *Preload reduction:* Nitrates cause pooling of blood in systemic capacitance vessels and reduce ventricular end-diastolic presure and volume. Controlled i.v. infusion of glyceryl trinitrate affords rapid relief in acute left ventricular failure.

(ii) *Afterload reduction:* Hydralazine like drugs dilate resistance vessels and reduce aortic impedance so that even weaker ventricular contraction is able to pump more blood. They are more effective in forward failure when cardiac index (CI = min output/body surface area) is low (< 2.5 L/min/m^2) without a marked increase in central venous pressure (< 18 mm Hg).
(iii) *Pre-and afterload reduction:* ACE inhibitors (captopril, enalapril and others), losartan, prazosin are orally active medium efficacy nonselective arterio-venous dilators, while Sod. nitroprusside is high efficacy i.v. dilator with equal action on the two types of vessels. These drugs act by both the above mechanisms. Titrated infusion of nitroprusside is employed in conjunction with a loop diuretic + inotropic drug to tideover crisis in severely decompensated patients.

In the long term, survival benefit has been obtained only with a combination of hydralazine + isosorbide dinitrate or with ACE inhibitors; the latter performing better than the former. Only ACE inhibitors (AT_1 antagonist losartan also) alter the course of pathological changes in CHF; afford symptomatic as well as disease modifying benefits by retarding/reversing ventricular hypertrophy and remodeling.

β-Adrenergic blockers Though the immediate haemodynamic action of β blockers is to depress cardiac contractility and ejection fraction, these parameters gradually improve over weeks when β blockers are given to selected CHF patients. After a couple of months, ejection fraction is generally higher than baseline, and slow upward titration of dose further improves cardiac performance. The haemodynamic benefit is maintained over long term and hospitalization/mortality due to worsening cardiac failure, as well as all cause mortality is reduced. The benefits appear to be due to antagonism of ventricular wall stress enhancing, apoptosis promoting and pathological remodeling effects of excess sympathetic activity in CHF, as well as due to prevention of sinister arrhythmias.

However, β blocker therapy in CHF requires caution, proper patient selection and observance of several guidelines.

Aldosterone antagonist (Spironolactone) Over the past decade, it has been realized that rise in plasma aldosterone in CHF, in addition to its well known Na^+ and water retaining action, is an important contributor to disease progression by direct and indirect effects:

(a) Expansion of e.c.f. volume → increased cardiac preload.

(b) Fibrotic change in myocardium → worsening systolic dysfunction and pathological remodeling.

(c) Hypokalemia and hypomagnesemia → increased risk of ventricular arrhythmias and sudden cardiac death.

(d) Enhancement of cardiotoxic effect of sympathetic overactivity.

The aldosterone antagonist spironolactone is a weak diuretic but can benefit CHF by antagonising the above effects of aldosterone. It is indicated as add-on therapy to ACE inhibitors ± other drugs in moderate-to-severe CHF. It can retard disease progression, reduce episodes of decompensation and death due to heart failure as well as sudden cardiac deaths over and above the protection afforded by ACE inhibitors.

Sympathomimetic inotropic drugs

Drugs with β adrenergic and dopaminergic agonistic actions have positive inotropic and vasodilator properties which may be utilized to combat emergency pump failure. Dobutamine, a relatively selective β_1 agonist with prominent inotropic action, has been infused for acute heart failure accompanying myocardial infarction (MI), cardiac surgery as well as to tide over crisis in advanced CHF. Dopamine has been used in cardiogenic shock due to MI and other causes. These drugs afford additional haemodynamic support over and above vasodilators, digitalis and diuretics, but benefits are short lasting. They have no role in the long-term management of CHF.

Phosphodiesterase III inhibitors

Amrinone (Inamrinone), Milrinone These are bipyridine derivatives, and selective phosphodiesterase III (PDE III) inhibitors. This isoenzyme is specific for intracellular degradation of cAMP in heart, blood vessels and bronchial smooth muscles. They increase myocardial cAMP and transmembrane influx of Ca^{2+}.

The two most important actions of amrinone and milrinone are *positive inotropy* and direct *vasodilatation*: have been called inodilators.

They are indicated only for short-term i.v. use in severe and refractory CHF, as additional drug to conventional therapy with digitalis, diuretics and vasodilators.

ANTIARRHYTHMIC DRUGS

These are drugs used to prevent or treat irregularities of cardiac rhythm.

Cardiac arrhythmias arise due to abnormal impulse generation or abnormal impulse conduction or both. Ischaemia, electrolyte and pH imbalance, stretching, injury, neurogenic and drug influences, including antiarrhythmic drugs themselves, can cause arrhythmia by altering electrophysiological properties of cardiac fibres. These result in:

1. Enhanced or ectopic pacemaker activity.
2. 'Early after-depolarizations' (associated with long Q-T interval due to slow repolarization) and 'delayed after-depolarizations' (due to Ca^{2+} overload) which are triggered by a normal or premature action potential (AP) — hence called 'triggered arrhythmias'.
3. Re-entry due to unidirectional conduction block of the impulse and its recirculation around an obstacle (infarcted or refractory myocardium) causing repetitive activation of the adjacent fibres (Fig. 12.5).
4. Fractionation of the impulse due to inhomogeneous refractory periods (RP) of different fibres. The impulse moves rapidly through fibres with short RP, slowly through fibres with longer RP and not at all through those still refractory; different fibres get activated asynchronously.
5. Slowing of impulse conduction through the A-V node producing partial to complete heart block.

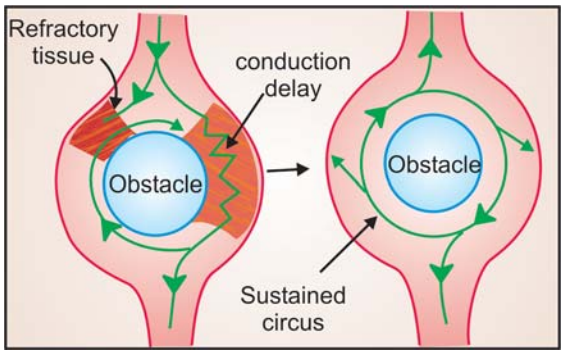


Fig. 12.5: Diagrammatic representation of circus movement re-entry in atrium

The main cardiac arrhythmias and their characteristics are:

1. *Extrasystoles (ES)* are premature beats due to abnormal automaticity or after-depolarization arising from an ectopic focus in the atrium (atrial ES), A-V node (nodal ES) or ventricle (ventricular ES).
2. *Paroxysmal supraventricular tachycardia (PSVT)* is sudden onset episodes of atrial tachycardia (rate 150–200/min) with 1:1 atrioventricular conduction: mostly due to circus movement type of re-entry involving the A-V node or SA node.
3. *Atrial flutter (AFl)* Atria beat at a rate of 220–350/min and there is a physiological 2:1 to 4:1 or higher, A-V block (because A-V node cannot transmit impulses faster than 200/min). This is mostly due to a self-perpetuating re-entrant circuit in the atrium, but some cases may be due to rapid discharge of an atrial focus.
4. *Atrial fibrillation (AF)* Atrial fibres are activated asynchronously at a rate of 350–550/min (due to electrophysiological inhomogeneity of atrial fibres), associated with grossly irregular and often fast (100–160/min) ventricular response. Atria remain dilated and quiver like a bag of worms.
5. *Ventricular tachycardia* is a run of 4 or more consecutive ventricular extrasystoles. It may be a sustained or nonsustained arrhythmia, and is due either to discharges from an ectopic focus, after-depolarizations or circus movement of a re-entrant impulse.
6. *Torsades de pointes* (French: twisting of points) is a life-threatening form of polymorphic ventricular tachycardia with an undulating baseline on ECG. It is generally associated with long Q-T interval.
7. *Ventricular fibrillation (VF)* is grossly irregular, rapid and fractionated activation of ventricles resulting in incoordinated contraction of its fibres with loss of pumping function. It is fatal unless reverted within 2–5 min; is the most common cause of sudden cardiac death.
8. *Atrio-ventricular (A-V) block* is due to depression of impulse conduction through the A-V node and bundle of His.
   First degree A-V block: Slowed conduction resulting in prolonged P-R interval.
   Second degree A-V block : Some supraventricular complexes are not conducted : drop beats.
   Third degree A-V block: No supraventricular complexes are conducted; ventricle generates its own impulse; complete heart block.

CLASSIFICATION

Antiarrhythmic drugs act by blocking myocardial Na^+, K^+ or Ca^{2+} channels. Some have additional or even primary autonomic effects. Classification of antiarrhythmic drugs has been unsatisfactory because many drugs have more than one action. Vaughan Williams and Singh (1969) proposed a 4 class system which takes into account the most important property of a drug which is apparently responsible for its antiarrhythmic action in the clinical setting. This system is arbitrary, but it has been widely accepted.

CLASS I

The primary action of drugs in this class is to limit the conductance of Na^+ (and K^+) across cell membrane—a local anaesthetic action. They interfere with depolarization and decrease responsiveness to excitation. They also reduce rate of phase-4 depolarization responsible for impulse generation in automatic cells.

CLASS	ACTIONS	DRUGS
I.	*Membrane stabilizing agents (Na^+ channel blockers)*	
	A. *Moderate decrease in dv/dt of 0 phase*	Quinidine, Procainamide Disopyramide
	B. *Little decrease in dv/dt of 0 phase*	Lignocaine, Mexiletine Phenytoin
	C. *Marked decrease in dv/dt of 0 phase*	Propafenone, Flecainide
II.	*Antiadrenergic agents* (β *blockers*)	Propranolol, Esmolol Sotalol (also class III)
III.	*Agents widening AP* (*prolong repolarization and ERP*)	Amiodarone, Bretylium (also class II) Dofetilide
IV.	*Calcium channel blockers*	Verapamil, Diltiazem

Note: Class IA agents also have Class III property; Propranolol has Class I action as well; sotalol and bretylium have both Class II and Class III actions.

In addition

1. *For PSVT* : Adenosine, digitalis.
2. *For A-V block* : Sympathomimetics—Isoprenaline etc. Anticholinergics—Atropine.

Subclass IA

The subclass IA containing the oldest antiarrhythmic drugs *quinidine* and *procainamide* are open state Na^+ channel blockers which also moderately delay channel recovery (1–10 s), suppress A–V conduction and prolong refractoriness. The Na^+ channel blockade is greater at higher frequency (premature depolarization is affected more). These actions serve to extinguish ectopic pacemakers that are often responsible for triggered arrhythmias and abolish re-entry by converting unidirectional block into bidirectional block.

Quinidine in addition has antivagal action, which augments prolongation of atrial RP and minimises RP disparity of atrial fibres. It also decreases myocardial contractility: may precipitate failure in damaged hearts. Quinidine can cause fall in BP, decrease contractility of skeletal muscles, augment uterine contractions, induce vomiting and diarrhoea and produce neurological effects like ringing in ears, vertigo, deafness, visual disturbances and mental changes. Like its levoisomer quinine, it has antimalarial action. The drug interactions of quinidine are:

- Rise in blood levels and toxicity of digoxin due to displacement from tissue binding and inhibition of excretion.
- Marked fall in BP in patients receiving vasodilators.
- Risk of *torsades de pointes* is increased by hypokalaemia caused by diuretics.
- Synergistic cardiac depression with β-blockers, verapamil, K^+ salts.

Though quinidine is effective in many atrial and ventricular arrhythmias, it is not used to terminate them because of risk of adverse effects, including that of *torsades de pointes*, sudden cardiac arrest or VF. It is occasionally used to

maintain sinus rhythm after termination of AF or AFl.

Procainamide This orally active amide of the local anaesthetic procaine has cardiac electrophysiological actions similar to quinidine but has minimal antivagal action, causes less depression of contractility and A-V conduction or hypotension. Prolonged use of procainamide can cause systemic lupus erythematosus. Cardiac toxicity is similar to quinidine; clinical use therefore is highly restricted.

Disopyramide is a quinidine-like class IA drug which has prominent cardiac depressant and anticholinergic actions, but no α adrenergic blocking property. However, disopyramide produces less g.i. side effects and is better tolerated. Cardiac decompensation and hypotension can occur in patients with damaged hearts, because it also increases peripheral resistance. The primary indication of disopyramide is prevention of recurrences of ventricular arrhythmia. It may be a better tolerated maintenance drug after cardioversion of AF or AFl.

Subclass IB

The prototype member of this subclass is the most widely used local anaesthetic *lignocaine*. It is a blocker of inactivated Na^+ channels more than that of open state. As such, it is relatively selective for partially depolarized fibres and those with longer action potential duration (APD), whose Na^+ channels remain inactivated for longer period. Unlike quinidine, channel recovery is not delayed. While normal ventricular and conducting tissues are minimally affected, depolarized/damaged fibres are particularly depressed. The most prominent action of lignocaine is suppression of automaticity in ventricular ectopic foci and after-depolarizations. Brevity of atrial AP and lack of prolongation of channel recovery makes lignocaine ineffective in atrial arrhythmias. It does not depress A-V conduction and ventricular contractility or prolong refractoriness.

Lignocaine is inactive orally due to high first pass metabolism. Action of an i.v. bolus dose lasts only for 10–20 minutes because of rapid distribution, while elimination t½ is 1.5–2 hours due to metabolism. Lignocaine is used only in ventricular tachyarrhythmias by repeated i.v. injections or continuous i.v. infusion. Because of rapidly developing and titratable action, it is a good drug in the emergency setting, e.g. arrhythmias following MI or during cardiac surgery. It is also useful in digitalis toxicity.

Mexiletine is an orally active congener of lignocaine with similar cardiac electrophysiological actions. Parenterally, it has been used as an alternative to lignocaine for postinfarction ventricular arrhythmias. Orally, it is used to keep VES and VT suppressed over long term.

Phenytoin is an anticonvulsant that preferentially blocks inactivated Na^+ channels and has been occasionally used to counteract digitalis-induced ventricular arrhythmias.

Subclass IC

The subclass IC drugs like *propafenone* and *flecainide* are the most potent Na^+ channel blockers with more prominent action on open state and the longest channel recovery time (>10 s). They markedly delay conduction in A-V node as well as accessory pathway: have been used in WPW re-entrant tachycardias. Propafenone has additional β adrenergic blocking property — can precipitate CHF and bronchospasm. Though these drugs are effective in many refractory arrhythmias, they also have high proarrhythmic potential. In postinfarct patients they have paradoxically increased the incidence of sudden cardiac death. Therefore, they are used only as reserve drugs for resistant arrhythmias.

CLASS II

The primary action of durgs in this class is to suppress adrenergically mediated ectopic activity and delayed after-depolarizations. Though some β blockers, e.g. propranolol have quinidine like direct membrane stabilizing action at high doses,

antiarrhythmic action is exerted clinically primarily by cardiac adrenergic blockade. The other most important action is to prolong RP of A-V node. This impedes A-V conduction: re-entrant arrhythmias that involve SA or A-V node (many PSVT) may be abolished.

The β blockers are very useful in treating inappropriate sinus tachycardia, atrial and nodal extrasystoles provoked by emotion, exercise or stress (e.g. of dental procedure). They rarely abolish AF or AFl, but can be used to control ventricular rate when digitalis alone is not fully effective. β blockers are highly effective in sympathetically mediated arrhythmias occurring in pheochromocytoma or during anaesthesia with halothane. Digitalis-induced tachyarrhythmias may respond. However, efficacy in chronic ventricular arrhythmias is low. Prophylactic treatment with β blockers reduces mortality in post-MI patients.

Sotalol is a β blocker with prominent class III property of prolonging repolarization by blocking cardiac K^+channels. It delays A-V conduction and prolongs nodal RP. Sotalol is effective in some cases of VT as well as AF and AFl. Risk of *torsades de pointes* is the major limitation

Esmolol is a quick and short-acting β_1 blocker that is used i.v. for emergency control of ventricular rate in AF/AFl. It can also terminate supraventricular tachycardia and arrhythmias associated with anaesthesia.

CLASS III

The characteristic action of class III antiarrhythmics is prolongation of repolarization: AP is widened which increases RP. Myocardial fibres remain refractory even after repolarization: re-entrant arrhythmias are terminated. Prolongation of APD is attributable to blockade of delayed rectifier K^+ channels, which open during repolarization. The most important member of this class a*miodarone* is an unusual iodine containing compound which also blocks Na^+ channels during inactivation and has noncompetitive β adrenergic blocking property. Amiodarone is highly lipophilic, extensively bound in tissues and exceptionally long acting (t½ 3–8 weeks). Given orally, its full action takes weeks to develop, but i.v. loading doses can rapidly terminate life-threatening arrhythmias. Amiodarone is effective in a wide range of ventricular and supraventricular arrhythmias, particularly resistant VT and recurrent VF. However, toxic potential of amiodarone to damage many tissues restricts its use.

Bretylium is an adrenergic neurone blocking drug which prolongs APD by blocking cardiac K^+ channels. Its chief use is in VF refractory to electrical defibrillation. *Dofetilide* is a recently developed pure class III antiarrhythmic which has no other action than blocking delayed rectifier K^+ channels. Its primary indication is to maintain sinus rhythm after conversion of AF and AFl.

CLASS IV

The Ca^{2+} channel blockers verapamil and diltiazem (but not DHPs) exert antiarrhythmic action by depressing Ca^{2+} mediated depolarization. They slow SA node pacemaker, A-V conduction and suppress re-entry through A-V node as well as in partially depolarized (ischaemic) tissue. Verapamil and diltiazem are used i.v. to terminate episodes of PSVT, as well as orally to prevent its recurrences. The other use of verapamil is to control ventricular rate in AF as alternative to or in addition to digitalis. Efficacy of calcium channel blockers in ventricular arrhythmias is poor.

Adenosine Administered by rapid i.v. injection (over 1–3 sec) either as the free base or as ATP adenosine terminates within 30 seconds more than 90% episodes of PSVT involving the A-V node. It activates ACh sensitive K^+ channels and causes membrane hyperpolarization through interaction with A1 type of adenosine receptors on SA node (pacemaker depression → bradycardia), A-V node (prolongation of RP → slowing of conduction) and atrium (shortening of AP, reduced excita-bility). It indirectly reduces Ca^{2+} current in A-V node; depression of the re-entrant circuit through A-V node is responsible for termination of PSVT.

Adenosine has a very short t½ in blood (~10 sec) due to uptake into RBCs and endothelial cells where it is converted to 5-AMP and inosine. Almost complete elimination occurs in a single passage through coronary circulation.

Adverse effects of adenosine are transient dyspnoea, chest pain, fall in BP and flushing in 30–60% patients; ventricular standstill for a few seconds or VF occurs in some patients. Bronchospasm may be precipitated in asthmatics. Adenosine has to be rapidly injected in a large vein and has brief action, not suitable for recurrent cases. Other drugs that can be used i.v. to terminate PSVT are verapamil, diltiazem, esmolol or digoxin.

Drugs for A-V block

Atropine: When A-V block is due to vagal overactivity, e.g. digitalis toxicity, some cases of MI; it can be improved by atropine 0.6–1.2 mg i.m. Atropine abbreviates A-V node RP and increases conduction velocity in bundle of His.

Sympathomimetics (Adr, isoprenaline): These drugs may overcome partial heart block by facilitating A-V conduction and shortening RP of conducting tissues.

They may also be used in complete heart block to maintain a sufficient idioventricular rate (by increasing automaticity of ventricular pacemakers) till external pacemaker can be implanted.

CHAPTER 13

Drugs Acting on Kidney

RELEVANT PHYSIOLOGY OF URINE FORMATION

Urine formation starts from glomerular filtration (g.f.) in a prodigal way. Normally, about 180 L of fluid is filtered every day: all soluble constituents of blood minus the plasma proteins (along with substances bound to them) and lipids, are filtered at the glomerulus. More than 99% of the glomerular filtrate is reabsorbed in the tubules; about 1.5 L urine is produced in 24 hours. The diuretics act primarily by inhibiting tubular reabsorption: just 1% decrease in tubular reabsorption would more than double urine output.

The mechanisms that carry out ion movement across tubular cells are complex and involve a variety of energy dependent transmembrane pumps as well as channels in between the loose fitting cells of the proximal tubule (PT). All Na^+ that enters tubular cells through the luminal membrane is pumped out of it into the renal interstitium at the basolateral membrane by Na^+K^+ ATPase energised Na^+-K^+ antiporter (*see* Figs 13.3 and 13.4). Because there is a large intracellular to extracellular gradient for K^+, it diffuses out through K^+ channels to be recirculated by the Na^+-K^+ antiporter. For simplification, tubular reabsorption can be divided into four sites (Fig. 13.1).

Site I: Proximal tubule Four mechanisms of Na^+ transport have been defined in this segment.

(a) Direct entry of Na^+ along a favourable electrochemical gradient. This is electrogenic.

(b) Transport of Na^+ and K^+ coupled to active reabsorption of glucose, amino acids, other organic anions and PO_4^{3-} through specific symporters.

(c) Exchange with H^+: The PT cells secrete H^+ with the help of carbonic anhydrase (CAse) Fig. 13.2, which exchanges with Na^+ present in tubular fluid through Na^+-H^+ antiporter located in the luminal membrane. There is also net reabsorption of HCO_3^- due to the activity of brush border CAse and Na^+- HCO_3^- symporter at the basolateral membrane.

(d) The disproportionately large HCO_3^-, acetate, PO_4^{3-}, amino acid and other anion reabsorption create passive driving forces for Cl^- which also takes Na^+ and water along.

Major part of filtered K^+ is reabsorbed in the PT.

Site II: Ascending limb of loop of Henle (Asc LH) The thick AscLH is relatively impermeable to water but absorbs salt actively and thus dilutes the tubular fluid.

In the *medullary portion* a distinct luminal membrane carrier transports ions in the stoichiometric ratio of Na^+-K^+-$2Cl^-$ (*see* Fig. 13.3). The Na^+ that enters the cell is pumped to e.c.f. by Na^+ K^+ ATPase at the basolateral membrane. In addition, a Na^+-Cl^- symporter moves Cl^- down

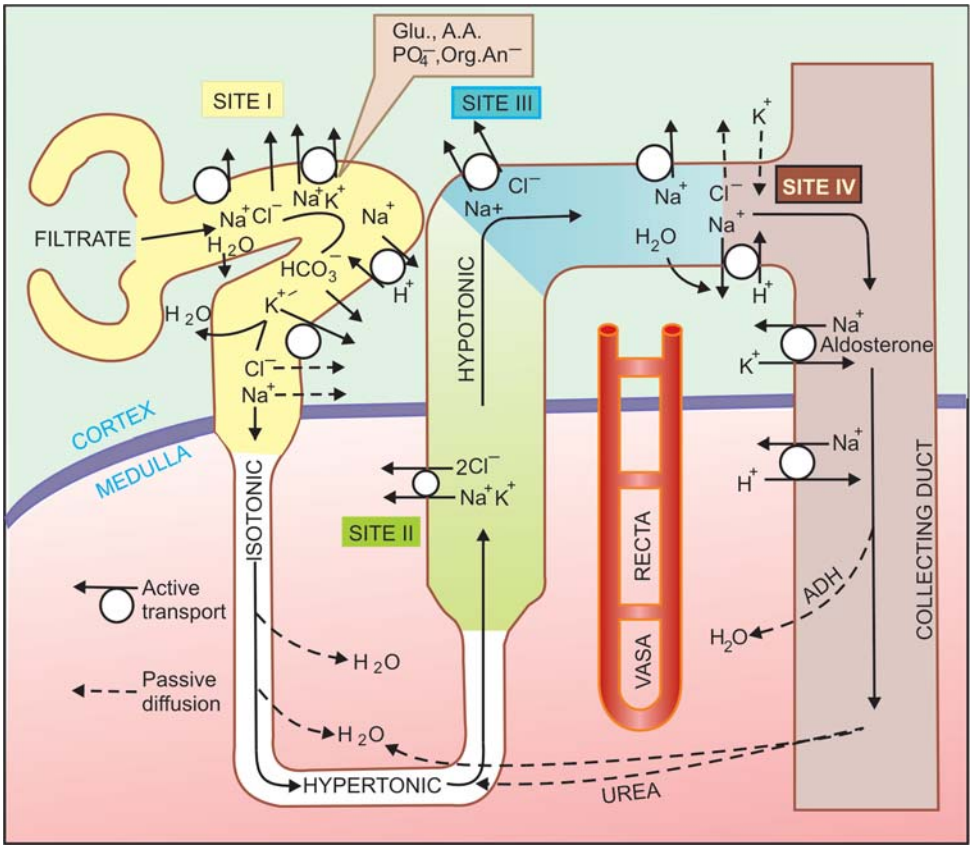


Fig. 13.1: Diagrammatic representation of nephron showing the four sites of solute reabsorption. The thick ascending limb of loop of Henle is impermeable to water; Glu.—Glucose; A.A.—Amino acid; Org. An.—Organic anions.

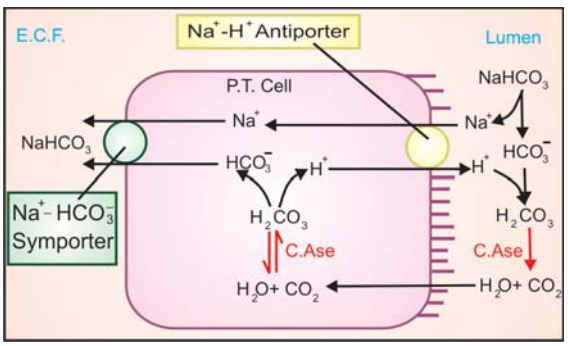


Fig. 13.2: The carbonic anhydrase (C.Ase) mediated bicarbonate absorption in proximal tubule (PT)

its electrochemical gradient into e.c.f. and carries Na^+ along. As the tubular fluid traverses AscLH, it progressively becomes hypotonic. Accumulation of NaCl in the medullary interstitium without accompanying water makes it hypertonic: a corticomedullary osmotic gradient is set up which is essential for production of both concentrated as well as dilute urine.

Site III: Cortical diluting segment of loop of Henle This segment, also impermeable to water, continues to absorb salt, but here it is through a Na^+-Cl^- symporter. Tubular fluid gets further diluted.

Site IV: Distal tubule (DT) and collecting duct (CD) In the late DT and CD, Na^+ is again actively reabsorbed; the cation-anion balance being maintained partly by passive Cl^- diffusion and partly by secretion of K^+ and H^+. Absorption

of Na^+ at this site occurs through a specific amiloride sensitive Na^+ channel and is controlled to a large extent by aldosterone (*see* Fig. 13.5). This provides fine tuning to electrolyte excretion according to body needs.

Any diuretic acting proximal to the aldosterone sensitive ion exchange site causes an increased delivery of Na^+ to the distal nephron—more exchange with K^+ takes place. The net K^+ loss is regulated by variations in the secretory process and depends on:

(i) The Na^+ load delivered to distal segment
(ii) Presence or absence of aldosterone
(iii) Availability of H^+
(iv) Intracellular K^+ stores.

The characteristic feature of cells lining CD is their responsiveness to antidiuretic hormone (ADH). If ADH is absent, the hypotonic fluid entering CD is passed as such → dilute urine is produced during water loading. If ADH levels are high, CD cells become fully permeable to water → equilibrate with hyperosmotic medulla → concentrated urine is passed, as occurs during water deprivation or hypertonic saline infusion.

Relation to diuretic action

The relative magnitudes of Na^+ reabsorption at different tubular sites are:

PT 65–70%;	AscLH 20–25%;
DT 8–9%;	CD 1–2%.

The maximal natriuretic response to a diuretic can give a clue to its site of action. It may appear that diuretics acting on PT should be the most efficacious. However, these agents are either too weak or cause distortion of acid-base balance (CAse inhibitors). Further, their effect may be obscured by compensatory increase in reabsorption further down the nephron, because the reserve reabsorptive capacity of diluting segments is considerable and can overshadow more proximal actions.

A diuretic having primary action on medullary AscLH (furosemide) can produce substantial effect because of limited capacity for salt absorption in DT and CD. This also explains why agents acting on DT and CD (K^+ sparing diuretics) evoke only mild saluretic effect. Diuretics acting on cortical diluting segment (thiazides) are intermediate between these two.

DIURETICS

These are drugs which cause a net loss of Na^+ and water in urine.

CLASSIFICATION

1. *High efficacy diuretics (Inhibitors of Na^+-K^+-$2Cl^-$ cotransport)*
   Furosemide, Bumetanide
2. *Medium efficacy diuretics (Inhibitors of Na^+-Cl^- symport)*
   (a) *Benzothiadiazines (thiazides)*: Hydrochlorothiazide, Benzthiazide, Hydroflumethiazide, Clopamide
   (b) *Thiazide like (related heterocyclics)*: Chlorthalidone, Metolazone, Xipamide, Indapamide.
3. *Weak or adjunctive diuretics*
   (a) *Carbonic anhydrase inhibitors*: Acetazolamide
   (b) *Potassium sparing diuretics*
      (i) *Aldosterone antagonist*: Spironolactone
      (ii) *Directly acting (Inhibitors of renal epithelial Na^+ channel)*: Triamterene, Amiloride.
   (c) *Osmotic diuretics*: Mannitol, Isosorbide, Glycerol.

HIGH CEILING (LOOP) DIURETICS

(Inhibitors of Na^+-K^+-$2Cl^-$ Cotransport)

Furosemide (Frusemide) Prototype drug

The development of this orally and rapidly acting highly efficacious diuretic was a breakthrough. Its maximal natriuretic effect is much greater than that of other classes. The diuretic response goes on increasing with increasing dose: up to 10 L of urine may be produced in a day. It is active even in patients with relatively severe renal failure. The onset of action is prompt (i.v. 2–5 min, i.m. 10–20 min, oral 20–40 min) and duration short (3–6 hours).

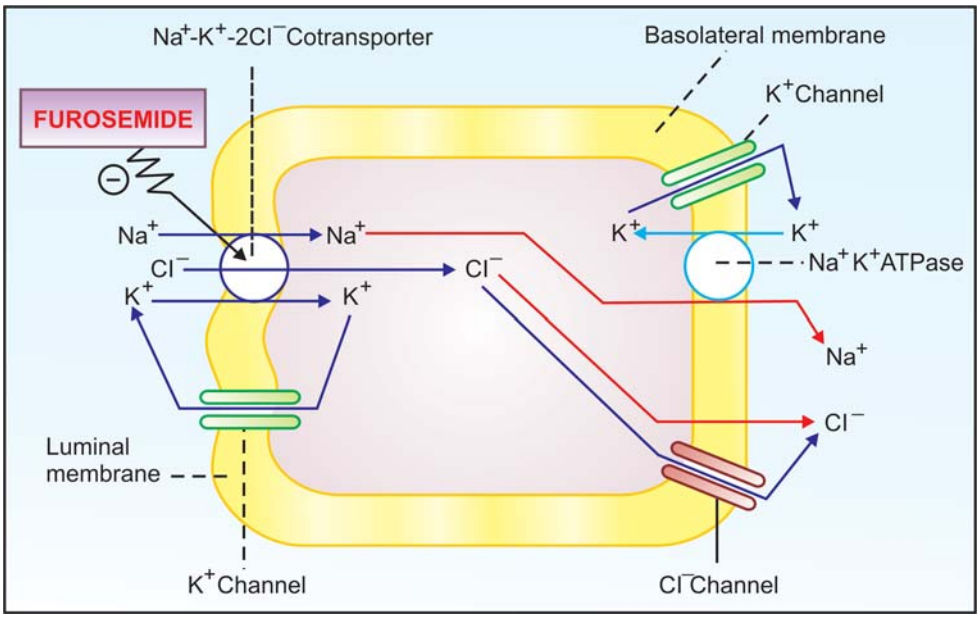


Fig. 13.3: Mechanism of salt reabsorption in the thick ascending limb of loop of Henle (AscLH) cell, and site of action of furosemide on the Na^+-K^+-$2Cl^-$ cotransporter

The major site of action is the thick AscLH (site II) where furosemide inhibits Na^+- K^+-$2Cl^-$ cotransport (Fig. 13.3). It abolishes the cortico-medullary osmotic gradient and blocks positive as well as negative free water clearance. K^+ excretion is increased mainly due to high Na^+ load reaching DT.

Furosemide has weak CAse inhibitory action and increases HCO_3^- excretion as well. Its action is independent of acid-base balance of the body and it causes little distortion of the same.

In addition to its prominent tubular action, furosemide causes acute changes in renal and systemic haemodynamics. After 5 min of i.v. injection, renal blood flow is transiently increased, the result of which is decreased PT reabsorption. The intrarenal haemodynamic changes are brought about by increased local PG synthesis.

Intravenous furosemide causes prompt increase in systemic venous capacitance and decreases left ventricular filling pressure, even before the saluretic response is apparent. This is responsible for the quick relief it affords in LVF and pulmonary edema. This action may be PG mediated.

Furosemide increases Ca^{2+} excretion (contrast thiazides which reduce it) as well as Mg^{2+} excretion. It tends to raise blood uric acid level by decreasing its renal excretion. Hyperglycaemic action of furosemide is less marked than thiazides.

Molecular mechanism of action: A glycoprotein with 12 membrane spanning domains has been found to function as the Na^+-K^+-$2Cl^-$ cotransporter in many epithelia including AscLH. Furosemide attaches to the Cl^- binding site of this protein to inhibit its transport function.

Pharmacokinetics Furosemide is rapidly absorbed orally but bioavailability is about 60%. It is highly bound to plasma proteins. It is partly conjugated with glucuronic acid and mainly excreted unchanged by glomerular filtration as well as tubular secretion.

Bumetanide It is similar to furosemide in all respects, but is 40 times more potent. It induces

very rapid diuresis and is highly effective in pulmonary edema. Hyperuricaemia, K^+ loss, glucose intolerance and ototoxicity are claimed to be less than with furosemide. However, it may rarely cause myopathy.

Use of high ceiling diuretics

1. *Edema* Diuretics are used irrespective of etiology of edema—cardiac, hepatic or renal. The high ceiling diuretics are preferred initially in CHF for rapid mobilization of edema fluid. They are the diuretic of choice for nephrotic and other forms of resistant edema.

2. *Acute pulmonary edema (acute LVF, following MI)* Intravenous administration of furosemide produces prompt relief. This is due to vasodilator action that precedes the saluretic action.

3. *Cerebral edema* Though osmotic diuretics are preferred, furosemide may be employed by i.m. route.

4. *Forced diuresis* In hypnotic or other poisonings; as an alternative to mannitol.

5. *Hypertension* High ceiling diuretics are indicated only in presence of renal insufficiency, CHF, in resistant cases or hypertensive emergencies; otherwise thiazides are preferred

THIAZIDE AND RELATED DIURETICS
(Inhibitors of Na^+-Cl^- symport)

These are medium efficacy diuretics with primary site of action in the cortical diluting segment or the early DT (Site III). Here they inhibit Na^+–Cl^- symport at the luminal membrane. They do not affect the corticomedullary osmotic gradient indicating lack of action at the medullary thick AscLH. Positive free water clearance is reduced (very dilute urine cannot be passed in the absence of ADH), but negative free water clearance (in the presence of ADH) is not affected. Like the Na^+-K^+-$2Cl^-$ cotransporter, the Na^+-Cl^- symporter is also a glycoprotein with 12 membrane spanning domains that binds thiazides but not furosemide or any other class of diuretics. The site of action of thiazide diuretics is shown in Fig. 13.4.

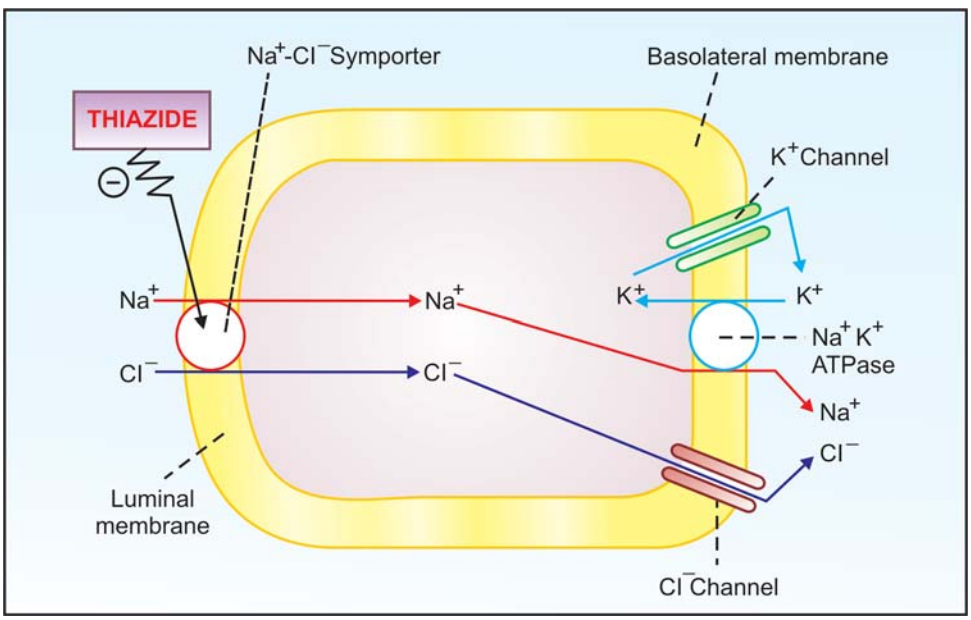


Fig. 13.4: Mechanism of salt reabsorption in early distal tubular cell and site of action of thiazide diuretics on Na^+Cl^- symporter

Some of the thiazides and related drugs have additional CAse inhibitory action which may confer a secondary proximal tubular action to the compounds.

Under their action, increased amount of Na^+ is presented to the distal nephron, more of it exchanges with $K^+ \rightarrow$ urinary K^+ excretion is increased in parallel to the natriuretic response. The different thiazide and related diuretics have nearly the same maximal efficacy as hydrochlorothiazide, though potency (reflected in daily dose) differs markedly. Nevertheless, they are moderately efficacious diuretics because nearly 90% of the glomerular filtrate has already been reabsorbed before it reaches their site of action. They have a flat dose response curve; little additional diuresis occurs when the dose is increased beyond 100 mg of hydrochlorothiazide or equivalent. No significant alteration in acid-base balance of the body is produced.

Renal Ca^{2+} excertion is diminished while Mg^{2+} excertion is enhanced by direct tubular action. They also decrease urate excretion by the same mechanism as furosemide.

The *extrarenal actions* of thiazides consist of a slowly developing fall in BP in hypertensives and elevation of blood sugar in some patients due to decreased insulin release.

All thiazides and related drugs are well absorbed orally, and are administered only by this route. Their action starts within 1 hour, but the duration varies from 8–48 hours. Most of the agents undergo little hepatic metabolism and are excreted as such. They are filtered at the glomerulus as well as secreted in the PT by organic anion transport. Tubular reabsorption depends on lipid solubility: the more soluble ones are highly reabsorbed—prolonging duration of action.

Uses

1. *Edema* Thiazides may be used for mild-to-moderate cases. For mobilization of edema fluid more efficacious diuretics are employed initially, but thiazides are considered better for maintenance therapy. They are powerless in the presence of renal failure. Cirrhotics often develop refractoriness to thiazides due to development of secondary hyperaldosteronism.

2. *Hypertension* They are one of the first line drugs.

3. *Diabetes insipidus* They reduce urine volume.

Complications of high ceiling and thiazide-type diuretic therapy

Most of the adverse effects of these drugs are related to fluid and electrolyte changes caused by them. They are remarkably safe in low doses used over short periods.

1. *Hypokalaemia* This is the most significant problem. It is rare at low doses, but may be of grave consequence when brisk diuresis is induced or on prolonged therapy. The usual manifestations are weakness, fatigue, muscle cramps; cardiac arrhythmias are the serious complications. It can be prevented and treated by:
(a) High dietary K^+ intake or
(b) Supplements of KCl (24–72 mEq/day) or
(c) Concurrent use of K^+ sparing diuretics.

2. *Acute saline depletion* Over enthusiastic use of diuretics, particularly high ceiling ones, may cause dehydration and fall in BP

3. *Dilutional hyponatremia* Occurs in CHF patients in whom vigorous diuresis is induced with high ceiling agents, rarely with thiazides.

4. *GIT and CNS disturbances* Nausea, vomiting, diarrhoea, headache, giddiness, weakness, paresthesias, impotence are the occasional complaints.

5. *Hearing loss* Occurs rarely, only with high ceiling diuretics.

6. *Allergic manifestations* Rashes, photosensitivity occur specially in patients hypersensitive to sulfonamides.

7. Brisk diuresis induced in cirrhotics may precipitate *mental disturbances* and hepatic coma.

8. *Hyperuricaemia* Long-term use of thiazides in hypertension has caused rise in blood urate level; 2% develop clinical gout.

9. *Hyperglycaemia and hyperlipidemia* Have occurred in the use of diuretics as antihypertensive.

10. *Hypercalcaemia* Occurs with thiazides while *hypocalcaemia* occurs with high ceiling diuretics when these are administered chronically.

11. *Magnesium depletion* It may develop after prolonged use of thiazides as well as loop diuretics.

Interactions

1. Thiazides and high ceiling diuretics potentiate all other antihypertensives.

2. Hypokalaemia induced by these diuretics:
(a) Enhances digitalis toxicity.
(b) Increases the incidence of polymorphic ventricular tachycardia due to quinidine and other antiarrhythmics.
(c) Potentiates competitive neuromuscular blockers and reduces sulfonylurea action.

3. High ceiling diuretics and aminoglycoside antibiotics are both ototoxic; produce additive toxicity.

4. High ceiling diuretics enhance nephrotoxicity of aminoglycosides.

5. Indomethacin and most NSAIDs diminish the action of high ceiling diuretics by inhibiting PG synthesis in the kidney. Antihypertensive action of thiazides and furosemide is also diminished by NSAIDs.

6. Probenecid competitively inhibits tubular secretion of furosemide and thiazides: decreases their action.

7. Serum lithium level rises when diuretic therapy is instituted. This is due to enhanced reabsorption of Li^+ in PT.

CARBONIC ANHYDRASE INHIBITORS

Acetazolamide

It is a sulfonamide derivative which noncompetitively but reversibly inhibits CAse in PT cells resulting in slowing of hydration of CO_2 → decreased availability of H^+ to exchange with luminal Na^+. Inhibition of brush border CAse retards dehydration of H_2CO_3 in the tubular fluid so that less CO_2 diffuses back into the cells. The net effect is inhibition of HCO_3^- (and accompanying Na^+) reabsorption in PT → prompt but mild alkaline diuresis ensues.

Secretion of H^+ in DT and CD is also inhibited. The distal Na^+ exchange takes place only with K^+ which is lost in excess. The urine produced under acetazolamide action is alkaline and rich in HCO_3^- which is matched by both Na^+ and K^+. Continued action of acetazolamide depletes body HCO_3^- and causes acidosis; less HCO_3^- (on which its diuretic action depends) is filtered at the glomerulus → self-limiting diuretic action.

The extrarenal actions of acetazolamide are:
(i) Lowering of intraocular tension due to decreased formation of aqueous humour (it is rich in HCO_3^-).
(ii) Raised level of CO_2 in brain and lowering of pH → raising of seizure threshold, sedation.

Uses Because of self-limiting action, production of acidosis and hypokalaemia, acetazolamide is not used as diuretic. Its current clinical uses are:
1. Glaucoma: as adjuvant to other ocular hypotensives.
2. To alkalinise urine.
3. Epilepsy: as adjuvant in absence seizures.
4. Acute mountain sickness: for symptomatic relief as well as prophylaxis.

Adverse effects are frequent.
Acidosis, hypokalaemia, drowsiness, paresthesias, fatigue, abdominal discomfort.
Hypersensitivity reactions—fever, rashes.
Bone marrow depression is rare but serious.

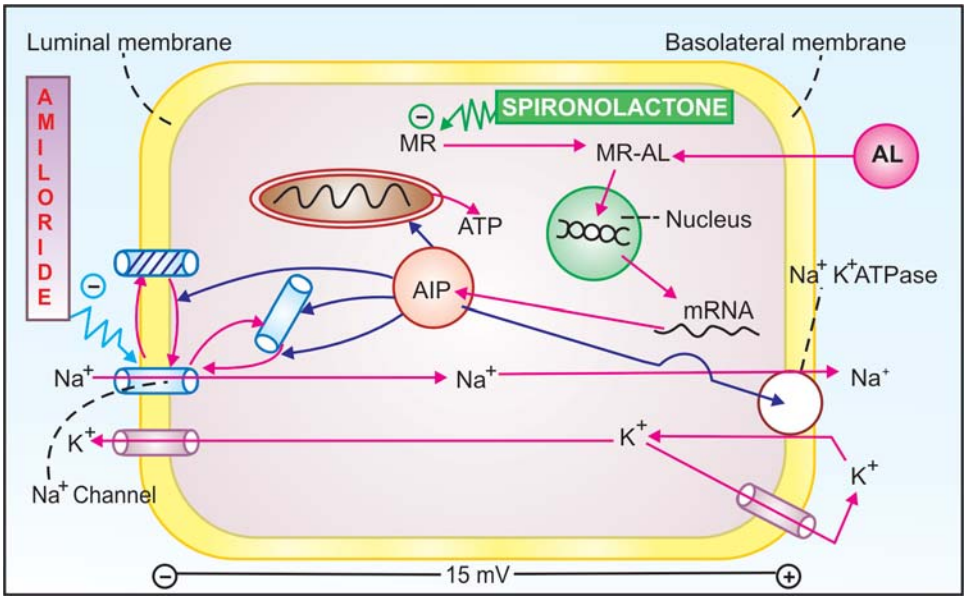


Fig. 13.5: Site and mechanism of action of potassium sparing diuretics on the late distal tubule/collecting duct cell
Aldosterone (AL) penetrates the cell from the interstitial side and combines with the mineralocorticoid receptor (MR). The complex translocates to the nucleus—promotes gene mediated mRNA synthesis. The mRNA then directs synthesis of aldosterone-induced proteins (AIPs). The AIPs include Na^+K^+ ATPase and amiloride sensitive Na^+ channels. The AIPs also activate Na^+ channel, translocate Na^+ channels from cytosolic site to luminal membrane and Na^+K^+ATPase to basolateral membrane, increase ATP production by mitochondria. All these changes promote Na^+ reabsorption—more K^+ and H^+ is secreted indirectly. Spironolactone binds to MR, prevents AL action and produces opposite effects.

Amiloride approaches the Na^+ channel from the luminal side and blocks it—reducing the lumen negative transepithelial potential difference which governs K^+ and H^+ secretion.

POTASSIUM SPARING DIURETICS

These are either aldosterone antagonists or inhibit Na^+ channels in DT and CD cells to indirectly conserve K^+.

Spironolactone (Aldosterone antagonist)

It is a steroid, chemically related to the mineralocorticoid aldosterone. Aldosterone acts on the late DT and CD cells (Fig. 13.5) by combining with an intracellular mineralocorticoid receptor → induces the formation of 'aldosterone-induced proteins' (AIPs) which promote Na^+ reabsorption by a number of mechanisms (*see* legend to Fig. 13.5) and K^+ secretion. Spironolactone combines with the mineralocorticoid receptor and inhibits the formation of AIPs in a competitive manner. It has no effect on Na^+ and K^+ transport in the absence of aldosterone; while under normal circumstances, it increases Na^+ and decreases K^+ excretion.

Spironolactone is a mild saluretic because majority of Na^+ has already been reabsorbed proximal to its site of action. However, it antagonises K^+ loss induced by other diuretics and slightly adds to their natriuretic effect.

Pharmacokinetics The oral bioavailability of spironolactone from microfine powder tablet is 75%. It is highly bound to plasma proteins and completely metabolized in liver; converted to active metabolites, the most important of which is *Canrenone*.

Use Spironolactone is a weak diuretic in its own right and is used only in combination with other more efficacious diuretics.

1. Edema: to break resistance to thiazide diuretics that develops due to secondary hyperaldosteronism.
2. To counteract K^+ loss due to thiazide and loop diuretics.
3. Hypertension: as adjuvant to thiazides.
4. CHF: As additional drug to conventional therapy in moderate-to-severe CHF; can retard disease progression and lower mortality.

Interactions Given together with K^+ supplements—dangerous hyperkalaemia can occur. Aspirin blocks spironolactone action by inhibiting tubular secretion of canrenone.

Adverse effects Drowsiness, confusion, abdominal upset, hirsutism, gynaecomastia, impotence and menstrual irregularities.

Most serious is hyperkalaemia.

Directly acting agents (Inhibitors of renal epithelial Na^+ channel)

Triamterene and amiloride are two nonsteroidal organic bases with identical actions. Their most important effect is to decrease K^+ excretion, particularly when it is high due to large K^+ intake or use of a diuretic that enhances K^+ loss, along with a small increase in Na^+ excretion. The effect on urinary electrolyte pattern is superficially similar to spironolactone, but their action is independent of aldosterone.

Mechanism of action: The luminal membrane of late DT and CD cells expresses a distinct 'amiloride sensitive' or 'renal epithelial' Na^+ channel through which Na^+ enters the cell down its electro-chemical gradient which is generated by Na^+K^+ ATPase operating at the basolateral membrane (Fig. 13.5). This Na^+ entry partially depolarizes the luminal membrane creating a –15 mV transepithelial potential difference which promotes secretion of K^+ into the lumen through K^+ channels. Though there is no direct coupling between Na^+ and K^+ channels, more the delivery of Na^+ to the distal nephron—greater is its entry through the Na^+ channel—luminal membrane is depolarized more —driving force for K^+ secretion is augmented. Amiloride and triamterene block the luminal Na^+ channels—indirectly inhibit K^+ excretion, while the net excess loss of Na^+ is minor (most of it has already been absorbed).

Both triamterene and amiloride are used in conjunction with thiazide type or high ceiling diuretics: prevent hypokalaemia and slightly augment the natriuretic and antihypertensive response. They should not be given with K^+ supplements, dangerous hyperkalaemia may develop. Hyperkalaemia is also more likely in patients receiving ACE inhibitors, and those with renal impairment.

Both drugs elevate plasma digoxin levels.

Amiloride blocks entry of Li^+ through Na^+ channels in the CD cells and mitigates diabetes insipidus induced by lithium.

OSMOTIC DIURETICS

Mannitol

Mannitol is a nonelectrolyte of low molecular weight (182) that is pharmacologically inert—can be given in large quantities sufficient to raise osmolarity of plasma and tubular fluid. It is not metabolized in the body; freely filtered at the glomerulus and undergoes limited reabsorption; therefore, excellently suited to be used as osmotic diuretic. Mannitol appears to limit tubular water and electrolyte reabsorption by:

1. Retaining water isoosmotically in PT—dilutes luminal fluid which opposes NaCl reabsorption.
2. Inhibiting transport processes in the thick AscLH by an unknown mechanism—quantitatively this appears to be the most important cause of diuresis.
3. Expanding extracellular fluid volume—this increases g.f.r. and inhibits renin release.

Administration Mannitol is not absorbed orally; has to be given i.v. as 10–20% solution. It is excreted with a t½ of 0.5–1.5 hours.

Table 13.1: Urinary electrolyte pattern and natriuretic efficacy of some diuretics

Diuretic	Urinary electrolyte excretion				Max. % of filtered	Efficacy
	Na^+	K^+	Cl^-	HCO_3^-	Na^+ excreted	
1. Furosemide	↑↑↑	↑	↑↑	↑	25%	High
2. Thiazide	↑↑	↑	↑	↑	8%	Intermediate
3. Acetazolamide	↑	↑↑	↓↑	↑	5%	Mild
4. Spironolactone	↑	↓	↑	-,↑	3%	Low
5. Triamterene	↑	↓	↑	-,↑	3%	Low
6. Mannitol	↑↑	↑	↑	↑	20%	High

Uses Mannitol is never used for the treatment of chronic edema or as a natriuretic. Its indications are:

1. Increased intracranial or intraocular tension (acute congestive glaucoma, head injury, stroke, etc.): by osmotic action it encourages movement of water from CSF and aqueous humour.

2. To maintain g.f.r. and urine flow in impending acute renal failure.

3. Forced diuresis in hypnotic or other poisonings.

Isosorbide and glycerol These are orally active osmotic diuretics which may be used to reduce intraocular or intracranial tension.

ANTIDIURETICS

These are drugs that reduce urine volume, particularly in *diabetes insipidus* (DI) which is their primary indication. Drugs are:

1. Antidiuretic hormone (ADH, Vasopressin), Desmopressin, Lypressin, Terlipressin
2. Thiazide diuretics, Amiloride.

ANTIDIURETIC HORMONE

It is a nonapeptide secreted by posterior pituitary (neurohypophysis) along with oxytocin. Osmoreceptors present in hypothalamus and volume receptors present in left atrium, ventricles and pulmonary veins primarily regulate the rate of ADH release governed by body hydration. The two main physiological stimuli for ADH release are rise in plasma osmolarity and contraction of e.c.f. volume.

The mammalian ADH is 8-arginine-vasopressin (AVP); 8-*lysine*-vasopressin (lypressin) is found in swine and has been synthetically prepared. Other more potent and longer acting peptide analogues of ADH having agonistic as well as antagonistic action have been prepared.

ADH (Vasopressin) receptors These are G protein coupled cell membrane receptors; two subtypes V_1 and V_2 have been identified, cloned and structurally characterized.

V_1 Receptors All vasopressin receptors except those on renal CD cells and some blood vessels are of the V_1 type.

V_2 Receptors These are located primarily on the collecting duct (CD) cells in the kidney—regulate their water permeability through cAMP production. Vasodilatory V_2 receptors are present in blood vessels.

The V_2 receptors are more sensitive to ADH than are V_1 receptors.

Actions

Kidney ADH acts on the collecting duct (CD) cells to increase their water permeability—water from the lumen diffuses to the interstitium by equilibrating with the hyperosmolar renal medulla. In man, maximal osmolarity of urine that can be attained is 4 times higher than plasma. When ADH is absent, CD cells remain impermeable to water → dilute urine (produced by the diluting segment) is passed as such. Graded effect occurs at lower concentration of ADH: urine volume closely balances fluid intake.

Mechanism of action The V_2 subtype of ADH receptors are present on the basolateral side of CD cell membrane. Activation of these receptors increases cAMP formation intracellularly → phosphorylation of relevant proteins which promote exocytosis of *'aquaporin–2'* water channel containing vesicles (WCVs) through the apical membrane → more aqueous channels get inserted into the apical membrane. The water permeability of CD cells is increased in proportion to the population of aquaporin–2 channels in the apical membrane at any given time.

Blood vessels AVP constricts blood vessels through V_1 receptors and can raise BP (hence the name vasopressin), but much higher concentration is needed than for maximal antidiuresis.

A V_2 receptor mediated vasodilatation can be unmasked when AVP is administered in the presence of a V_1 antagonist. It can also be demonstrated by the use of selective V_2 agonist desmopressin, and appears to be EDRF (NO) mediated.

Other actions Most visceral smooth muscles contract. Increased peristalsis in gut (especially large bowel), evacuation and expulsion of gases may occur.

Uterus is contracted by AVP acting on oxytocin receptors.

AVP is recognized as a peptide neurotransmitter in many areas of brain and spinal cord: may be involved in regulation of temperature, circulation, ACTH release, and in learning of tasks.

AVP induces platelet aggregation and hepatic glycogenolysis. It releases coagulation factor VIII and von Willebrand's factor from vascular endothelium through V_2 receptors.

Pharmacokinetics AVP is inactive orally because it is destroyed by trypsin. It can be administered by any parenteral route or by intranasal application. The peptide chain of AVP is rapidly cleaved enzymatically in many organs, especially in liver and kidney; plasma t½ is short ~25 min.

VASOPRESSIN ANALOGUES

Lypressin It acts on both V_1 and V_2 receptors and has longer duration of action (4–6 hours). It is being used in place of AVP—mostly for V_1 receptor mediated actions.

Terlipressin This synthetic prodrug of vasopressin is specifically used for bleeding esophageal varices.

Desmopressin (dDAVP) This synthetic peptide is a selective V_2 agonist; 12 times more potent antidiuretic than AVP, but has negligible vasoconstrictor activity. It is also longer acting; t½ 1–2 hours; duration of action 8–12 hours. Desmopressin is the preparation of choice for all V_2 receptor related indications. The intranasal route is preferred, though bioavailability is only 10–20%. An oral formulation has been recently marketed with a bioavailability of 1–2%.

Uses

A. Based on V_2 actions (Desmopressin is the drug of choice)

1. *Diabetes insipidus* DI of pituitary origin (neurogenic) is the most important indication for vasopressin. It is ineffective in renal (nephrogenic) DI since kidney is unresponsive to ADH.

2. *Bedwetting in children and nocturia in adults* Intranasal or oral desmopressin at bedtime controls primary nocturia by reducing urine volume.

3. *Renal concentration test* 5–10 U i.m. of aqueous vasopressin or 2 µg of desmopressin causes maximum urinary concentration.

4. *Haemophilia, von Willebrand's disease* Desmopressin may check bleeding by releasing coagulation factor VIII and von Willebrand's factor.

B. Based on V_1 actions

1. *Bleeding esophageal varices* Vasopressin/terlipressin often stops bleeding by constricting mesenteric blood vessels and reducing blood flow through the liver to the varices.

2. *Before abdominal radiography* AVP/lypressin has been occasionally used to drive out gases from bowel.

Adverse effects Because of V_2 selectivity desmopressin produces fewer adverse effects than vasopressin, lypressin or terlipressin.

Nasal irritation, congestion, rhinitis, ulceration and epistaxis can occur on local application. Belching, nausea, abdominal cramps, palor, urge to defecate, backache in females (due to uterine contraction). Fluid retention and hyponatraemia may develop.

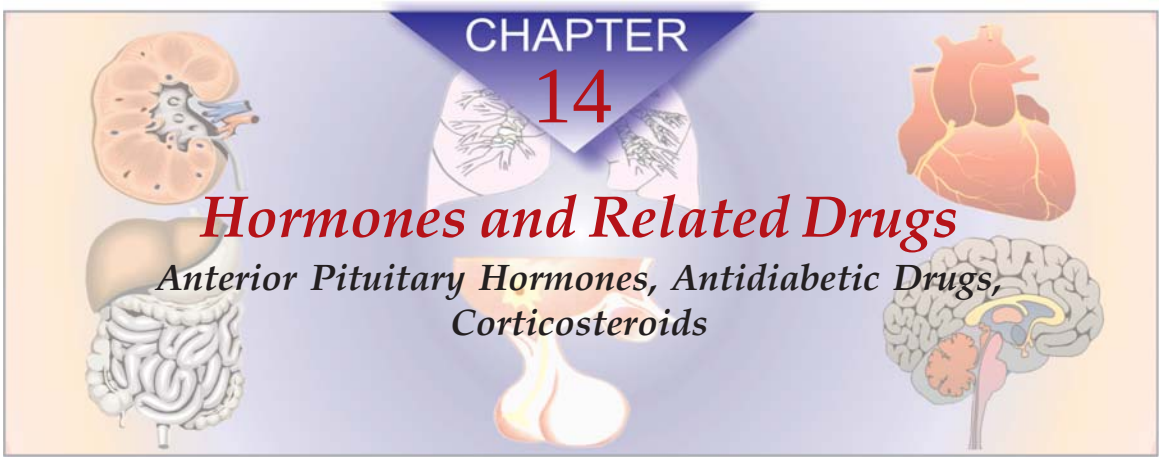
THIAZIDES

Diuretic thiazides paradoxically exert an antidiuretic effect in DI. High ceiling diuretics are also effective but are less desirable because of their short and brisk action. Thiazides reduce urine volume in both pituitary origin as well as renal DI; especially valuable for the latter in which ADH is ineffective. However, their efficacy is low; urine can never become hypertonic as can occur with ADH in neurogenic DI. The mechanism of action is not well understood, possible explanation is:

Thiazides induce a state of sustained electrolyte depletion so that glomerular filtrate is more completely reabsorbed iso-osmotically in PT. Further, because of reduced salt absorption in the cortical diluting segment, a smaller volume of less dilute urine is presented to the CDs and the same is passed out.

Amiloride is the drug of choice for lithium-induced nephrogenic DI.

Indomethacin has also been found to reduce polyuria in renal DI to some extent by reducing renal PG synthesis.



CHAPTER 14

Hormones and Related Drugs

Anterior Pituitary Hormones, Antidiabetic Drugs, Corticosteroids

INTRODUCTION

Hormone (Greek *hormaein*—to stir up) is a substance of intense biological activity that is produced by *specific cells* in the body and is transported *through circulation* to act on its target cells.

Hormones regulate body functions to bring about a programmed pattern of life events and maintain homeostasis in the face of markedly variable external/internal environment.

Body function	Major regulator hormone(s)
1. Availability of fuel	: Insulin, Glucagon, Growth hormone
2. Metabolic rate	: Triiodothyronine, Thyroxine
3. Somatic growth	: Growth hormone, Insulin-like growth factors
4. Sex and reproduction	: Gonadotropins, Androgens, Estrogens, Progestins
5. Circulating volume	: Aldosterone, Antidiuretic hormone
6. Adaptation to stress	: Glucocorticoids, Adrenaline
7. Calcium balance	: Parathormone, Calcitonin, Vitamin D

Hormones are secreted by the *endocrine* or *ductless* glands. These are:

1. **Pituitary**

(a) *Anterior*—Growth hormone (GH), Prolactin (Prl), Adrenocorticotropic hormone (ACTH), Thyroid stimulating hormone (TSH), Gonadotropins—Follicle stimulating hormone (FSH) and Luteinizing hormone (LH).

(b) *Posterior*—Oxytocin, Antidiuretic hormone (ADH, Vasopressin).

2. **Thyroid** Thyroxine (T_4), Triiodothyronine (T_3), Calcitonin.

3. **Parathyroid** Parathormone (PTH).

4. **Pancreas** (*Islets of Langerhans*) Insulin, Glucagon.

5. **Adrenals**

(a) *Cortex* Glucocorticoids (hydrocortisone) Mineralocorticoids (aldosterone) Sex steroids (dehydroepiandrosterone)

(b) *Medulla* Adrenaline, Noradrenaline

6. **Gonads** Androgens (testosterone) Estrogens (estradiol) Progestins (progesterone)

In addition, hypothalamus, which is a part of the CNS and not a gland, produces many releasing and inhibitory hormones which control the secretion of anterior pituitary hormones.

Placenta also secretes many hormones:

Chorionic gonadotropin	Prolactin
Estrogens	Progesterone
Placental lactogen	

The natural hormones and in many cases their synthetic analogues which may be more suitable therapeutically, are used as drugs for substitution therapy as well as for pharmacotherapy. In addition, hormone antagonists and synthesis/release inhibitors are of therapeutic importance.

ANTERIOR PITUITARY HORMONES

Anterior pituitary (adenohypophysis), the master endocrine gland, elaborates a number of important regulatory hormones. All of these are peptide in nature and act at extracellular receptors located on their target cells. Their secretion is controlled by the hypothalamus through *releasing* and *release-inhibitory* hormones that are transported *via* hypothalamohypophyseal portal system, and is subjected to feedback inhibition by hormones of their target glands. Each anterior pituitary hormone is produced by a separate group of cells, which according to their staining characteristic are either acidophilic or basophilic. The acidophils are either somatotropes → GH; or lactotropes → Prl.

The basophils are gonadotropes → FSH and LH; thyrotropes → TSH; and corticotrope-lipotropes → ACTH. The latter in addition to ACTH also produce two melanocyte stimulating hormones (MSHs) and two lipotropins, but these are probably not important in man.

GROWTH HORMONE (GH)

It is a 191 amino acid, single chain peptide of MW 22,000.

Physiological functions GH promotes growth of all organs by inducing hyperplasia. In general, there is a proportionate increase in the size and mass of all parts; but in the absence of gonadotropins, sexual maturation does not take place. The growth of brain and eye is independent of GH. It promotes retention of nitrogen and other tissue constituents: more protoplasm is formed. The positive nitrogen balance results from increased uptake of amino acids by tissues and their synthesis into proteins. GH promotes utilization of fat and spares carbohydrates: uptake of glucose by muscles is reduced while its output from liver is enhanced; fat is broken down.

The growth promoting, nitrogen retaining and certain metabolic actions of GH are exerted *indirectly* through the elaboration of peptides called *Somatomedins* or *Insulin-like growth factors (IGF-1, also IGF-2)* which are extracellular mediators of GH response.

GH acts directly as well to induce lipolysis in adipose tissue, glycogenolysis in liver and decreased glucose utilization by muscles. These effects are opposite to those of IGF-1 and insulin. As such, GH accentuates the metabolic derangement in diabetes.

Pathological involvements Excess production of GH is responsible for *gigantism* in childhood and *acromegaly* in adults. Hyposecretion of GH in children results in *pituitary dwarfism*.

Use The primary indication for GH is pituitary dwarfism. Human GH produced by recombinant DNA technique (*somatrem* and *somatropin*) is used.

GH has also been tried in children with constitutional short stature (only if epiphyses are open) with encouraging results. In adult GH deficient patients it increases lean body mass and decreases body fat and may reudce excess morbidity and mortality but stature is unaffected. Other possible indications are catabolic states like severe burns, bedridden patients, chronic renal failure, osteoporosis, etc. It is now approved for AIDS-related wasting.

PROLACTIN (Prl)

It is a 198 amino acid, single chain peptide of MW 23,000; quite similar chemically to GH. It was originally described as the hormone which causes secretion of milk from crop glands of pigeon and has now been shown to be of considerable importance in human beings as well.

Physiological function Prl is the primary stimulus which, in conjunction with estrogens, progesterone and several other hormones, causes growth and development of breast during pregnancy. It promotes proliferation of ductal as well

as acinar cells in the breast and induces synthesis of milk proteins and lactose. After parturition, Prl induces milk secretion since the inhibitory influence of high estrogen and progesterone levels is withdrawn.

Prl has an inhibitory effect on hypothalamo-pituitary-gonadal axis. Continued high level of Prl during breastfeeding is responsible for lactational amenorrhoea, inhibition of ovulation and infertility for several months postpartum. Prl may affect immune response through action on T-lymphocytes.

Prl is under predominant inhibitory control of hypothalamus through PRIH which is dopamine that acts on pituitary lactotrope D2 receptor. Dopaminergic agonists (DA, bromocriptine, apomorphine) decrease plasma Prl levels, while dopaminergic antagonists (chlorpromazine, haloperidol, metoclopramide) and DA depleters (reserpine, methyldopa) cause hyperprolactinaemia.

Physio-pathological involvement Hyperprolactinaemia has been shown responsible for the galactorrhoea—amenorrhoea—infertility syndrome. In males it causes loss of libido and depressed fertility.

Use There are no clinical indications for Prl.

Bromocriptine

This synthetic ergot derivative, 2-bromo-α-ergocryptine, is a potent dopamine agonist. It has greater action on D2 receptors, while at certain dopamine sites in the brain, it acts as a partial agonist or antagonist of D1 receptor. It is also a weak α adrenergic blocker but not an oxytocic.

Actions

1. Decreases prolactin release from pituitary by activating dopaminergic receptors on lactotrope cells—a strong antigalactopoietic.
2. Increases GH release in normal individuals but decreases the same from pituitary tumours that cause acromegaly.
3. Has levodopa like actions in CNS—antiparkinsonian and behavioral effects.
4. Produces nausea and vomiting by stimulating dopaminergic receptors in CTZ.
5. Hypotension—due to central suppression of postural reflexes and weak peripheral α adrenergic blockade.
6. Decreases gastrointestinal motility.

Uses Bromocriptine is indicated in hyperprolactinaemia causing galactorrhoea, amenorrhoea and infertility in women; gynaecomastia, impotence and sterility in men. It is an alternative drug for acromegaly and an adjuvant drug for parkinsonism.

GONADOTROPINS (Gns)

The anterior pituitary secretes two Gns *viz.* FSH and LH. Both are glycoproteins having a total of 207 amino acid residues. FSH has MW 32,000 while LH has MW 30,000.

Physiological functions FSH and LH act in concert to promote gametogenesis and secretion of gonadal hormones.

FSH In the female it induces follicular growth, development of ovum and secretion of estrogens. In the male it supports spermatogenesis and has a trophic influence on seminiferous tubules. Ovarian and testicular atrophy occurs in the absence of FSH.

LH It induces preovulatory swelling of the ripe graafian follicle and triggers ovulation in female. It then brings about luteinization of the ruptured follicle and maintains corpus luteum till the next menstrual cycle. It is also probably responsible for atresia of the remaining follicles. Progesterone secretion occurs under the influence of LH. In the male LH stimulates testosterone secretion by the interstitial cells and is designated interstitial cell stimulating hormone (ICSH).

Pathological involvement Disturbances of Gn secretion from pituitary may be responsible for delayed puberty or precocious puberty both in girls and boys.

Inadequate Gn secretion results in amenorrhoea and sterility in women; oligozoospermia, impotence and infertility in men. Excess production of Gn in adult women causes polycystic ovaries.

Uses

Gonadotropins are obtained either from urine of postmenopausal women (Menotropins FSH+LH or pure FSH) or urine of pregnant women (Human chorionic gonadotropin—HCG, which is equivalent to LH). They can be used for:

1. Amenorrhoea and infertility in women due to deficient production of Gns by pituitary.
2. Hypogonadotrophic hypogonadism in males manifesting as delayed puberty or male sterility.
3. Cryptorchism: HCG given before 7 years of age can favour descent of testes.
4. To aid *in vitro* fertilization.

Superactive / long acting GnRH agonists Many analogues of GnRH, e.g. Buserelin, Goserelin, Leuprolide, Nafarelin, Histrelin, have been developed: are 15–150 times more potent than natural GnRH and longer acting because of high affinity for GnRH receptor and resistance to enzymatic hydrolysis. They acutely increase Gn secretion, but after 1–2 weeks cause desensitization and down-regulation of GnRH receptors → inhibition of FSH and LH secretion → suppression of gonadal function. Spermatogenesis or ovulation cease and testosterone or estradiol levels fall to castration levels. Recovery occurs within 2 months of stopping treatment.

The superactive GnRH agonists are used as nasal spray or injected s.c. The resulting reversible pharmacological oophorectomy/orchiectomy is being used in precocious puberty, prostatic carcinoma, endometriosis, premenopausal breast cancer, uterine leiomyoma, polycystic ovarian disease and to assist induced ovulation. It also has potential to be used as contraceptive for both males and females.

THYROID STIMULATING HORMONE (TSH, THYROTROPIN)

It is a 210 amino acid, two chain glycoprotein, MW 30,000.

Physiological function TSH stimulates thyroid to synthesize and secrete thyroxine (T_4) and triiodothyronine (T_3).

(i) It induces hyperplasia and hypertrophy of thyroid follicles and increases blood supply to the gland.

(ii) It promotes trapping of iodide by thyroid.

(iii) It promotes organification of trapped iodine and its incorporation into T_3 and T_4 by increasing peroxidase activity.

(iv) It enhances endocytotic uptake of thyroid colloid by the follicular cells and proteolysis of thyroglobulin to release more of T_3 and T_4. This action starts within minutes of TSH administration.

Pathological involvement Only few cases of hypo-or hyperthyroidism are due to inappropriate TSH secretion. In majority of cases of myxoedema TSH levels are markedly elevated because of deficient feedback inhibition. Graves' disease is due to an immunoglobulin of the IgG class which attaches to the thyroid cells and stimulates them in the same way as TSH. Consequently, TSH levels are low.

Use Thyrotropin has no therapeutic use.

ADRENOCORTICOTROPIC HORMONE (ACTH, CORTICOTROPIN)

It is a 39 amino acid single chain peptide, MW 4,500, derived from a larger peptide *pro-opio melanocortin* (MW 30,000) which also gives rise to endorphins, two lipotropins and two MSHs.

Physiological function ACTH promotes steroidogenesis in adrenal cortex by stimulating cAMP formation in cortical cells (through specific cell surface G protein coupled receptors) → rapidly increases the availability of cholesterol for conversion to pregnenolone which is the rate limiting step in the production of gluco, mineralo and weakly androgenic steroids. The stores of adrenal steroids are very limited and rate of synthesis primarily governs rate of release. ACTH also exerts trophic influence on adrenal cortex (again through cAMP): high doses cause hypertrophy and hyperplasia. Absence of ACTH results in adrenal atrophy. However, zona glomerulosa is little affected because angiotensin II also exerts trophic influence on this layer and sustains aldosterone secretion.

Regulation of secretion Hypothalamus regulates ACTH release from pituitary through corticotropin-releasing hormone (CRH). Secretion of ACTH has a circadian rhythm. Peak plasma levels occur in the early morning, decrease during day and are lowest at midnight.

Corticosteroids exert inhibitory feedback influence on ACTH production by acting directly on the pituitary as well as indirectly through hypothalamus.

Pathological involvement Excess production of ACTH from basophil pituitary tumours is responsible for some cases of Cushing's syndrome. Hypocorticism occurs in pituitary insufficiency due to low ACTH production. Iatrogenic suppression of ACTH secretion and pituitary adrenal axis is the most common form of abnormality encountered currently due to the use of pharmacological doses of glucocorticoids in nonendocrine diseases.

ACTH is used primarily for the diagnosis of disorders of pituitary adrenal axis. Injected i.v. 25 IU causes increase in plasma cortisol if the adrenals are functional.

ANTIDIABETIC DRUGS

Diabetes mellitus (DM) It is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipaemia, negative nitrogen balance and sometimes ketonaemia. A widespread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency.

The two major types of diabetes mellitus are:

Type I Insulin-dependent diabetes mellitus (IDDM), juvenile onset diabetes mellitus:

There is β cell destruction in pancreatic islets; majority of cases are autoimmune (type 1A) antibodies that destroy β cells are detectable in blood, but some are idiopathic (type 1B)—no β cell antibody is found. In all type 1 cases circulating insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition.

Type II Noninsulin-dependent diabetes mellitus (NIDDM), maturity onset diabetes mellitus:
There is no loss or moderate reduction in β cell mass; insulin in circulation is low, normal or even high, no anti-β-cell antibody is demonstrable; has a high degree of genetic predisposition; generally has a late onset (past middle age). Over 90% cases are type 2 DM. Causes may be:

- Abnormality in gluco-receptor of β cells so that they respond at higher glucose concentration.
- Reduced sensitivity of peripheral tissues to insulin.
- Excess of hyperglycaemic hormones (glucagon, etc.)/obesity.

INSULIN

The hypoglycaemic hormone insulin is synthesized in the β cells of pancreatic islets. It is a two chain polypeptide having 51 amino acids and MW about 6,000. The A-chain has 21 while B-chain has 30 amino acids. There are minor

Approaches to drug therapy in type 2 DM

Improve insulin availability	Overcome insulin resistance
Exogenous insulin	Biguanides
Sulfonylureas	Thiazolidinediones
Meglitinide analogues	α glucosidase inhibitors
Major limitations	*Major limitations*
Hypoglycaemic episodes	Inability to achieve normoglycaemia by themselves in many patients, especially moderate-to-severe cases
Weight gain	
Concern about premature atherosclerosis due to hyperinsulinaemia	

differences between human, pork and beef insulins:

Species	A-chain		B-chain
	8th AA	*10th AA*	*30th AA*
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

Under basal condition ~1 U insulin is secreted per hour by human pancreas. Much larger quantity is secreted after every meal. Secretion of insulin from β cells is regulated by chemical (primarily glucose, but also amino acids, fatty acids, ketone bodies), hormonal (growth hormone, corticosteroids, thyroxine, glucagon, somatostatin) and neural (adrenergic, cholinergic) mechanisms.

Actions of Insulin

The overall effects of insulin are to favour storage of fuel. The most prominent action of insulin is hypoglycaemia. It facilitates glucose transport across cell membrane and alters the activity of enzymes involved in carbohydrate, fat and protein metabolism in liver, muscle and adipose tissue to lower blood glucose level as well as prevent rise in free fatty acid level, ketone body production and protein breakdown of the diabetic state.

Most of the metabolic actions of insulin are exerted within seconds or minutes and are called the *rapid actions*. Others involving DNA mediated synthesis of glucose transporter and some enzymes of amino acid metabolism have a latency of few hours—the *intermediate* actions. In addition, insulin exerts major *long-term* effects on multiplication and differentiation of cells.

Mechanism of action Insulin acts on specific receptors located on the cell membrane of practically all cells, liver and fat cells are very rich. The insulin receptor is a heterotetrameric glycoprotein consisting of 2 extracellular α and 2 transmembrane β subunits linked together by disulfide bonds. Its orientation across the membrane is depicted in Fig. 14.1. The α subunits carry insulin binding sites, while the β subunits have tyrosine protein kinase activity.

Binding of insulin to α subunits induces aggregation and internalization of the receptor along with the bound insulin molecules. This activates tyrosine kinase activity of the β subunits to phosphorylate tyrosine residues of Insulin Receptor Substrate proteins (IRS1, IRS2). In turn, a cascade of phosphorylation and dephosphorylation reactions is set into motion resulting in stimulation or inhibition of enzymes involved in the rapid metabolic actions of insulin.

Fate of insulin Insulin is distributed only extracellularly. It is a peptide—degraded in the g.i.t. if given orally. Injected insulin or that released from pancreas is metabolized primarily in liver and to a smaller extent in kidney and muscles. The plasma t½ is 5–9 min.

Preparations of insulin

The conventional commercial preparations of insulin are derived from beef and pork pancreas. Regular insulin has to be injected 2 to 3 times daily. It has been modified by adding zinc with or without protamine to yield slowly absorbed and longer acting 'modified' or 'retard'

Actions of insulin producing hypoglycaemia

Liver
- ▲ Increases glucose uptake and glycogen synthesis
- ▲ Inhibits glycogenolysis and glucose output
- ▲ Inhibits gluconeogenesis from protein, pyruvate, FFA and glycerol

Muscle
- ▲ Increases glucose uptake and utilization
- ▲ Inhibits proteolysis and release of amino acids, pyruvate, lactate into blood which form substrate for gluconeogenesis in liver

Adipose tissue
- ▲ Increases glucose uptake and storage as fat and glycogen
- ▲ Inhibits lipolysis and release of FFA + glycerol which form substrate for gluconeogenesis in liver

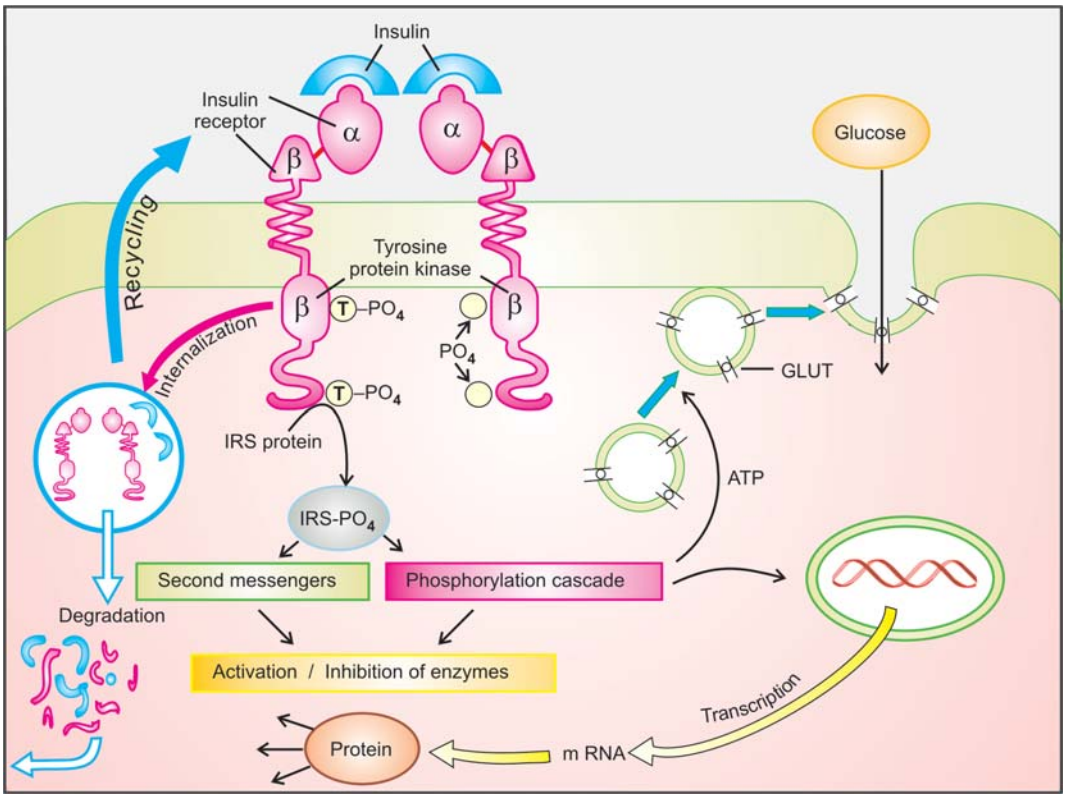


Fig. 14.1: A model of insulin receptor and mediation of its rapid metabolic actions; T—Tyrosine residue, IRS—Insulin receptor substrate, GLUT — Glucose transporter

Table 14.1: Conventional (standard) preparations of insulin

Type	*Onset (hr)*	*Peak (hr)*	*Duration (hr)*
Short Acting			
Regular (soluble) Insulin	0.5–1	2–4	6–8
Prompt Insulin Zinc Suspension (amorphous) or Semilente	1	3–6	12–16
Intermediate Acting			
Insulin Zinc Suspension or Lente (Ultra: Semi: 7:3)	1–2	8–10	20–24
Neutral Protamine Hagedorn (NPH) or Isophane Insulin	1–2	8–10	20–24
Long Acting			
Extended Insulin Zinc Suspension (Crystalline) or Ultralente	4–6	14–18	24–36
Protamine Zinc Insulin (PZI)	4–6	14–20	24–36

preparations. These are tabulated in Table 14.1. Regular, lente and isophane insulins are the most commonly used preparations.

All preparations of insulin are given s.c. Only regular insulin can be injected i.v.or i.m. also.

The conventional or standard preparations of insulin contain 1% (10,000 ppm) or more of other proteins which are potentially antigenic. Highly purified and practically nonantigenic (monocomponent) preparations are now available. Human insulin has been produced by recombinant DNA technology and enzymatic modification of pork insulin. In developed countries the use of human insulins has rapidly overtaken that of conventional and purified animal insulins. In developing countries conventional insulin preparations are still routinely used for economic reasons. Human/highly purified insulins are specially indicated in the following situations:

1. Insulin resistance.
2. Allergy to conventional preparations.
3. Injection site lipodystrophy.
4. Short-term use of insulin in diabetics to tide over surgery, trauma, infections, ketoacidosis, etc.
5. During pregnancy.

Reactions to insulin

1. *Hypoglycaemia* is the most frequent and potentially the most serious reaction to insulin. Hypoglycaemia can occur in any diabetic following inadvertent injection of large doses, by missing a meal (e.g. after a dental procedure) or by performing vigorous exercise. The symptoms can be divided into those due to counter-regulatory sympathetic stimulation—sweating, anxiety, palpitation, tremor; and those due to deprivation of brain of its essential nutrient—glucose (neuroglucopenic symptoms)—dizziness, headache, behavioural changes, visual disturbances, hunger, fatigue, weakness, muscular incoordination and sometimes fall in BP. Generally, the reflex sympathetic symptoms occur before the neuroglucopenic.

Finally, when blood glucose falls further (to < 40 mg/dl) mental confusion, seizures and coma occur.

Treatment Glucose must be given orally or i.v. (for severe cases)—reverses the symptoms rapidly.

2. *Local reactions* Swelling, erythema and stinging sometimes occur, especially in the beginning. *Lipodystrophy* occurs at injection sites after long usage.

3. *Allergy* This is infrequent; is due to contaminating proteins; very rare with human/highly purified insulins. Urticaria, angioedema and anaphylaxis are the manifestations.

Drug interactions

1. β adrenergic blockers prolong hypoglycaemia by inhibiting compensatory mechanisms operating through β_2 receptors (β_1 selective agents are less liable). Warning signs of hypoglycaemia like palpitation, tremor and anxiety are masked.
2. Thiazides, furosemide, corticosteroids, oral contraceptives, salbutamol tend to raise blood sugar and reduce effectiveness of insulin.
3. Acute ingestion of alcohol can precipitate hypoglycaemia by depleting hepatic glycogen.
4. Salicylates, lithium and theophylline may also accentuate hypoglycaemia by enhancing insulin secretion and peripheral glucose utilization.

Use of insulin in diabetes mellitus The purpose of therapy in diabetes mellitus is to restore metabolism to normal, avoid symptoms due to hyperglycaemia and glucosuria, prevent short-term complications (infection, ketoacidosis, etc.) and long-term sequelae (cardiovascular, retinal, neurological, renal, etc.)

Insulin is effective in all forms of diabetes mellitus and is a must for type 1 cases. Many type 2 cases can be controlled by diet, reduction in body weight and appropriate exercise. Insulin is needed by such cases when:

(i) Not controlled by diet and exercise.
(ii) Primary or secondary failure of oral hypoglycaemics.

(iii) Underweight patients.
(iv) Temporarily to tide over infections, trauma, surgery, pregnancy. In the perioperative period and during labour, monitored i.v. insulin infusion is preferable.
(v) Any complication of diabetes, e.g. ketoacidosis, diabetic and non-ketotic hyperosmolar coma, gangrene of extremities.

ORAL HYPOGLYCAEMIC DRUGS

These drugs lower blood glucose levels and are effective orally.

SULFONYLUREAS

First generation	*Second generation*
Tolbutamide	Gilbenclamide
Chlorpropamide	(Glyburide)
	Glipizide
	Gliclazide
	Glimepiride

BIGUANIDES

Phenformin, Metformin

MEGLITINIDE ANALOGUES

Repaglinide, Nateglinide

THIAZOLIDINEDIONES

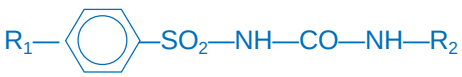
Rosiglitazone, Pioglitazone

α GLUCOSIDASE INHIBITORS

Acarbose, Miglitol

SULFONYLUREAS

The generic formula of sulfonylureas is:



All have similar pharmacological profile—sole significant action being lowering of blood glucose level in normal subjects and in type 2 diabetics, but not in type 1 diabetics.

Sulfonylureas provoke a brisk release of insulin from pancreas. They act on the so-called 'sulfonylurea receptors' on the pancreatic β cell membrane—cause depolarization by reducing conductance of ATP sensitive K^+ channels. This enhances Ca^{2+} influx → degranulation and insulin release. That they do not cause hypoglycaemia in pancreatectomised animals and in type 1 diabetics (presence of at least 30% functional β cells is essential for their action) confirms their indirect action through pancreas.

After chronic administration, the insulinaemic action of sulfonylureas declines probably due to downregulation of sulfonylurea receptors on β cells, but improvement in glucose tolerance is maintained. In this phase, they sensitize the target tissues (especially liver) to the action of insulin. This is due to increase in number of insulin receptors and/or a postreceptor action—improving translation of receptor activation.

Pharmacokinetics All sulfonylureas are well absorbed orally. Their pharmacokinetic and distinctive features are given in Table 14.2.

Interactions

Drugs that enhance sulfonylurea action (may precipitate hypoglycaemia) are:

(a) *Inhibit metabolism/excretion:* Cimetidine, sulfonamides, warfarin, chloramphenicol, acute alcohol intake (also synergises by causing hypoglycaemia).

(b) *Synergise with or prolong pharmacodynamic action:* Salicylates, propranolol, sympatholytic antihypertensives, lithium, theophylline.

Drugs that decrease sulfonylurea action (vitiate diabetes control) are:

(a) *Induce metabolism:* Phenobarbitone, phenytoin, rifampicin, chronic alcoholism.

(b) *Opposite action/suppress insulin release:* Corticosteroids, thiazides, furosemide, oral contraceptives.

Adverse effects

1. *Hypoglycaemia* It is the commonest problem, may occasionally be severe and rarely fatal.

Treatment is to give glucose, may be for a few days because hypoglycaemia may recur.

2. *Nonspecific side effects* Nausea, vomiting, flatulence, diarrhoea or constipation, headache, paresthesias and weight gain.

Table 14.2: Important features of oral hypoglycaemics

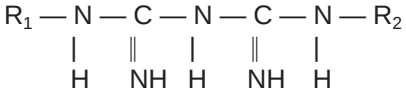
Drug	Plasma t½ (hr)	Duration of action (hr)	Clearance route*	Daily dose	Remarks
SULFONYLUREAS					
1. Tolbutamide	6–8	6–8	L	0.5–3g	Weaker, shorter acting, flexible dosage, safer in those prone to hypoglycaemia
2. Chlorpropamide	30–36	36–48	K,L	0.1–0.5g	Longest acting, can cause prolonged hypoglycaemia, potentiates ADH action, more cholestatic jaundice, alcohol flush
3. Glibenclamide (Glyburide)	4–6	18–24	L	5–15mg	Potent but slow acting, marked initial insulinaemic action, may work when others fail, metabolite excreted in urine as well as bile, single daily dose possible despite short t½
4. Glipizide	3–5	12–18	L	5–20mg	Fast acting, insulinaemic action persists even after prolonged use, can be given once daily despite short t½, weight gain less likely
5. Gliclazide	8–20	12–24	L	40–240mg	Has antiplatelet action, reduces free radicals, may delay diabetic retinopathy, less weight gain
6. Glimepiride	5–7	24	L	1–6mg	Stronger extrapancreatic action; less hyper-insulinaemia. Divide in two if daily dose > 4 mg
BIGUANIDES					
1. Phenformin	3–10	8–12	L,K	25–150 mg	Lactic acidosis more common, withdrawn in many countries
2. Metformin	1.5–3	6–8	K	0.5–2g	Not metabolized at all, lactic acidosis less common
MEGLITINIDE ANALOGUES					
1. Repaglinide	< 1	2–3	L	1.5–8mg	Given ½ hr before each meal for limiting p.p. hyperglycaemia
2. Nateglinide	1.5	2–3	L	180–480 mg	Stimulates 1st phase insulin secretion, less likely to cause delayed hypoglycaemia
THIAZOLIDINEDIONES					
1. Rosiglitazone	4	12–24	L	4–8mg	Reverses insulin resistance. No hypoglycaemia, C/I in liver and heart disease
2. Pioglitazone	3–5	24	L	15–45mg	-do-; May improve lipid profile

*L—Metabolized in liver, K—Excreted unchanged by kidney, p.p.—postprandial

3. *Hypersensitivity* Rashes, photosensitivity, purpura, transient leukopenia, rarely agranulocytosis.

BIGUANIDES

The generic formula of biguanides is:



They differ markedly from sulfonylureas: cause little or no hypoglycaemia in nondiabetic subjects.

Mechanism of action of biguanides is not clearly understood. They do not cause insulin release, but presence of some insulin is essential for their action. Explanations offered for their hypoglycaemic action are:

(i) Suppress hepatic gluconeogenesis and glucose output from liver: the major action.

(ii) Enhance insulin-mediated glucose disposal in muscle and fat.
(iii) Promote peripheral glucose utilization by enhancing anaerobic glycolysis.
(iv) Inhibit intestinal absorption of glucose, other hexoses, amino acids and vit B_{12}.

Adverse effects Abdominal pain, anorexia, nausea, metallic taste, mild diarrhoea and tiredness are the frequent side effects. Metformin does not cause hypoglycaemia except in overdose.

Lactic acidosis is the most serious complication. It is more common with phenformin.

Vit B_{12} deficiency due to interference with its absorption can occur—especially with high dose of metformin.

MEGLITINIDE ANALOGUES

These are recently developed quick and short-acting insulin releases.

Repaglinide Though not a sulfonylurea, it acts in an analogous manner by binding to sulfonylurea receptor as well as to other distinct receptors → closure of ATP dependent K^+ channels → depolarisation → insulin release.

Repaglinide induces rapid onset short-lasting insulin release. It is administered before each major meal to control postprandial hyperglycaemia; the dose may be omitted if a meal is missed. Because of short-lasting action, it may have a lower risk of serious hypoglycaemia. Side effects are mild headache, dyspepsia, arthralgia and weight gain.

Repaglinide is indicated only in type 2 DM as an alternative to sulfonylureas, or to supplement metformin/long-acting insulin.

Nateglinide has more rapid onset and shorter duration of hypoglycaemic action than repaglinide. There is little effect on fasting blood glucose level. Episodes of hypoglycaemia are less frequent than with sulfonylureas.

THIAZOLIDINEDIONES

Two thiazolidinediones *Rosiglitazone* and *Pioglitazone* have recently become available.

This novel class of oral antidiabetic drugs are selective agonists for the nuclear *peroxisome proliferator-activated receptor* γ (PPARγ) which enhances the transcription of several insulin responsive genes. They tend to reverse insulin resistance by stimulating GLUT4 expression and translocation: entry of glucose into muscle and fat is improved. Hepatic gluconeogenesis is also suppressed. Improved glycaemic control results in lowering of circulating insulin levels in type 2 DM patients.

Both pioglitazone and rosiglitazone are well tolerated; adverse effects are plasma volume expansion, edema, weight gain, headache, myalgia and mild anaemia. Monotherapy with glitazones is not associated with hypoglycaemic episodes.

Failure of oral contraception may occur during pioglitazone therapy. Ketoconazole inhibits metabolism of pioglitazone.

The thiazolidinediones are indicated in type 2 DM, but not in type 1 DM. They are primarily used to supplement sulfonylureas/metformin and in case of insulin resistance.

α GLUCOSIDASE INHIBITORS

Acarbose It is a complex oligosaccharide which reversibly inhibits α-glucosidases, the final enzymes for the digestion of carbohydrates in the brush border of small intestine mucosa. It slows down and decreases digestion and absorption of polysaccharides and sucrose: postprandial glycaemia is reduced without increasing insulin levels.

Acarbose is a mild antihyperglycaemic and not a hypoglycaemic: may be used as an adjuvant to diet (with or without a sulfonylurea) in obese diabetics.

Oral hypoglycaemics in diabetes mellitus

Oral hypoglycaemics are indicated only in type 2 diabetes, when not controlled by diet and exercise. They are best used in patients with—

1. Age above 40 years at onset of disease.
2. Obesity at the time of presentation.
3. Duration of disease < 5 years when starting treatment.
4. Fasting blood sugar < 200 mg/dl.
5. Insulin requirement < 40 U/day.
6. No ketoacidosis or a history of it, or any other complication.

Implications in dentistry Diabetes mellitus is associated with increased incidence of many dental problems like caries tooth, periodontal disease, oral infections, etc. Dental extractions and other simple procedures under local anaesthesia do not usually pose any special problems in diabetics, provided blood sugar levels are well controlled. If the diabetic who is being treated with insulin/oral hypoglycaemics is to miss the meals after a dental procedure, care should be taken that he/she does not develop hypoglycaemia. For more extensive dental procedures or those to be done under general anaesthesia, it is advisable to monitor urine and blood sugar levels and cover the perioperative period with regular insulin injected s.c. Severe/uncontrolled diabetics may be given an i.v. infusion of regular insulin along with 5% glucose solution.

Prophylactic antibiotics should be given to cover dental procedures in diabetics, particularly if they are poorly controlled.

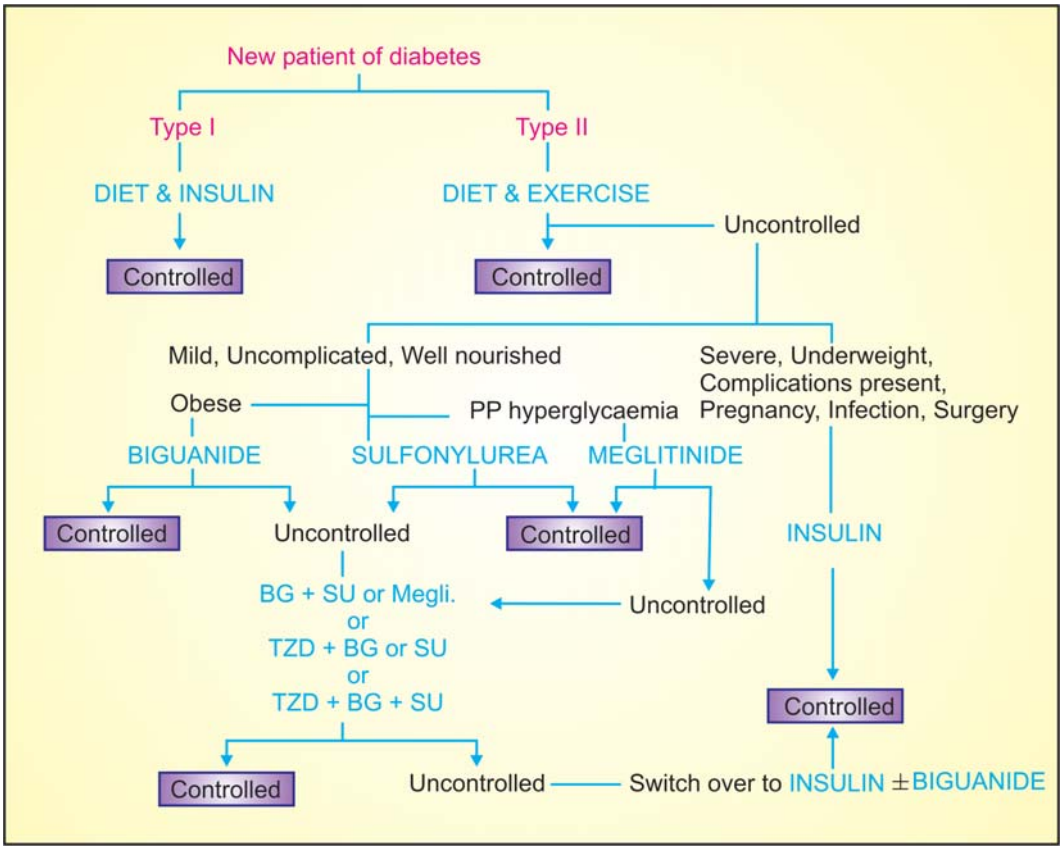


Fig. 14.2: Flow chart of management approach in diabetes mellitus.
BG: Biguanide; SU: Sulfonylureas; TZD: Thiazolidinedione; PP: Postprandial

GLUCAGON

The hyperglycaemic hormone glucagon is a single chain polypeptide containing 29 amino acids, MW 3,500. It is secreted by the α cells of the islets of Langerhans in pancreas.

Glucose has opposite effects on insulin and glucagon release, i.e. high glucose level inhibits glucagon secretion.

Glucagon is hyperglycaemic; most of its actions are opposite to that of insulin. Glucagon causes hyperglycaemia primarily by enhancing glycogenolysis and gluconeogenesis in liver; suppression of glucose utilization in muscle and fat contributes modestly.

Glucagon increases the force and rate of cardiac contraction and this is not antagonized by β blockers.

Mechanism of action Glucagon, through its own receptor and coupling Gs protein activates adenylyl cyclase and increases cAMP in liver, fat cells, heart and other tissues; most of its actions are mediated through this cyclic nucleotide.

Uses Glucagon can be used to counteract insulin hypoglycaemia as an expedient measure, and occasionally to stimulate the heart in cardiogenic shock.

CORTICOSTEROIDS

The adrenal cortex secretes steroidal hormones which have glucocorticoid, mineralocorticoid and weakly androgenic activities. Conventionally, the term 'corticosteroid' or 'corticoid' includes natural gluco- and mineralocorticoids and their synthetic analogues.

The corticoids (both gluco and mineralo) are 21 carbon compounds having a cyclopentanoperhydro-phenanthrene (steroid) nucleus. They are synthesized in the adrenal cortical cells from cholesterol. Adrenal steroidogenesis takes place under the influence of ACTH which makes more cholesterol available for conversion to pregnenolone and induces steroidogenic enzymes. Since adrenal cortical cells store only minute quantities of the hormones, rate of release is governed by the rate of biosynthesis.

The normal rate of secretion of the two principal corticoids in man is—

Hydrocortisone—10 mg daily (nearly half of this in the few morning hours).
Aldosterone— 0.125 mg daily.

ACTIONS

The corticoids have widespread actions. They maintain fluid-electrolyte, cardiovascular and energy substrate homeostasis and functional status of skeletal muscles and nervous system. They prepare the body to withstand effects of all kinds of noxious stimuli and stress. The involvement of hypothalamo-pituitary-adrenal axis in stress response is depicted in Fig. 14.3.

Actions of corticoids are divided into:

Glucocorticoid Effects on carbohydrate, protein and fat metabolism, and other activities that are inseparably linked to these.

Mineralocorticoid Effects on Na^+, K^+ and fluid balance.

Marked dissociation between these two types of actions is seen among natural as well as synthetic corticoids. Accordingly, compounds are labelled as 'glucocorticoid' or 'mineralocorticoid'.

Mineralocorticoid actions

Enhancement of Na^+ reabsorption in distal convoluted tubule of kidney associated with increased K^+ and H^+ excretion is the principal action. Excessive action leads to Na^+ and water retention, edema, progressive rise in BP, hypokalaemia and alkalosis. Mineralocorticoid deficiency results in progressive Na^+ loss → dilutional hyponatraemia → cellular hydration → decreased blood volume. Hyperkalaemia and acidosis accompany. These distortions of fluid and electrolyte balance progress and contribute to circulatory collapse.

The action of aldosterone is expressed by gene mediated increased transcription of m-RNA in renal tubular cells which directs synthesis of proteins (aldosterone-induced proteins—AIP). The Na^+K^+ ATPase of tubular basolateral membrane responsible for generating gradients for movement of cations in these cells is the major AIP (*See* Ch. 13).

Glucocorticoid actions

1. Carbohydrate and protein metabolism Glucocorticoids promote glycogen deposition in liver

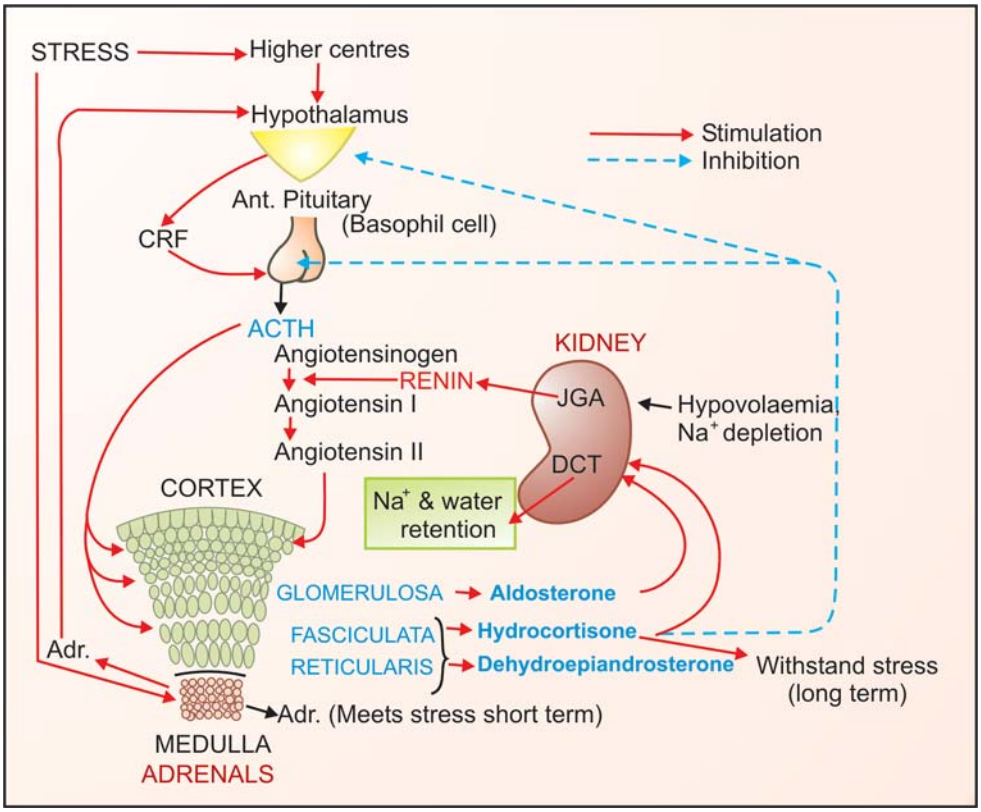


Fig. 14.3: Hypothalamo-pituitary-adrenal axis; regulation of corticosteroid production and response to stress

by inducing hepatic glycogen synthetase and promoting gluconeogenesis. They inhibit glucose utilization by peripheral tissues. This along with increased glucose release from liver results in hyperglycaemia, resistance to insulin and a diabetes-like state. They also cause protein breakdown and amino acid mobilization from peripheral tissues—responsible for side effects like muscle wasting, lympholysis, loss of osteoid from bone and thinning of skin. The amino acids so mobilized funnel into liver → used up in gluconeogenesis, excess urea is produced → negative nitrogen balance. Glucocorticoids are thus catabolic. Their function appears to be oriented to maintaining blood glucose levels during starvation—so that brain continues to get its nutrient.

They also increase uric acid excretion.

2. **Fat metabolism** Corticoids promote lipolysis. Fat depots in different areas respond differently—redistribution of body fat occurs. Subcutaneous tissue over extremities loses fat which is deposited over face, neck and shoulder —'moon face', 'fish mouth', 'buffalo hump'.

3. **Calcium metabolism** They inhibit intestinal absorption and enhance renal excretion of Ca^{2+}. There is also loss of calcium from bone indirectly due to loss of osteoid. Spongy bones (vertebrae, ribs, etc.) are more sensitive.

4. **Water excretion** Glucocorticoids, but not aldosterone, maintain normal g.f.r.

5. **CVS** Glucocorticoids restrict capillary permeability, maintain tone of arterioles and myocardial contractility.

Adrenal insufficiency is attended by low cardiac output, arteriolar dilatation, poor response to Adr and increased permeability of capillaries.

6. Skeletal muscles Optimum level of corticosteroids is needed for normal muscular activity. Weakness occurs in both hypo-and hypercorticism, but the causes are different.
Hypocorticism: diminished work capacity and weakness are primarily due to hypodynamic circulation.
Hypercorticism: excess mineralocorticoid action → hypokalaemia → weakness;
Excess glucocorticoid action → muscle wasting and myopathy → weakness.

7. CNS Mild euphoria is quite common with pharmacological doses of glucocorticoids. This sometimes progresses to cause insomnia, anxiety or depression.

8. Stomach Secretion of gastric acid and pepsin is increased—may aggravate peptic ulcer.

9. Lymphoid tissue Glucocorticoids enhance the rate of destruction of lymphoid cells (T cells are more sensitive than B cells). A marked lytic response is shown by malignant lymphatic cells—used in lymphomas.

10. Inflammatory responses Irrespective of the type of injury or insult, the attending inflammatory response is suppressed by glucocorticoids. This is the basis of most of their clinical uses. The action is nonspecific and includes reduction of—increased capillary permeability, local exudation, cellular infiltration, phagocytic activity and late responses like capillary proliferation, collagen deposition, fibroblastic activity and ultimately scar formation. The action is direct and local—topical use is possible. The cardinal signs of inflammation—redness, heat, swelling and pain are suppressed.

Glucocorticoids interfere at several steps in the inflammatory response, but the most important overall mechanism appears to be limitation of recruitment of inflammatory cells at the local site.

Production of PGs and several other mediators of inflammation like LTs, PAF, TNF_{α} and cytokines is interfered by negative regulation of relevant enzymes. They also induce formation of anti-inflammatory protein lipocortin, which inhibits phospholipase A that is responsible for release of arachidonic acid from membrane phospholipids for PG and LT synthesis.

Corticoids are only palliative, do not remove the cause of inflammation; the underlying disease continues to progress while manifestations are dampened. They favour spread of infections as capacity of defensive cells to kill microorganisms is impaired. They also interfere with healing and scar formation: peptic ulcer may perforate asymptomatically.

11. Immunological and allergic responses Glucocorticoids impair immunological competence. They suppress all types of hypersensitization and allergic phenomena. The clinical effect appears to be due to suppression of recruitment of leukocytes at the site of contact with antigen and of inflammatory response to immunological injury.

They cause greater suppression of CMI in which T cells are primarily involved, e.g. delayed hypersensitivity and graft rejection—basis of use in autoimmune diseases and organ transplantation. Factors involved may be inhibition of IL-1 release from macrophages; inhibition of IL-2 formation and action → T cell proliferation is not stimulated; suppression of natural killer cells, etc.

Mechanism of action at cellular level

Corticosteroids penetrate cells and bind to a high affinity cytoplasmic receptor protein → migration into the nucleus and binding to specific sites on the chromatin → transcription of specific m-RNA → regulation of protein synthesis (*see* Fig. 3.7). This process takes at least 30–60 min : effects of corticosteroid are not immediate, and once the appropriate proteins are synthesized—effects persist much longer than the steroid itself.

Table 14.3: Relative activity of systemic corticosteroids

		Compound	*Gluco*	*Mineralo*	*Equiv. dose (antiinflammatory)*
GLUCOCORTICOIDS	Short acting, (Biological t½ < 12 hr)	1. Hydrocortisone (cortisol)	1	1	20 mg
		2. Cortisone	0.8	0.8	25 mg
	Intermediate acting, (Biological t½ 12–36 hr)	3. Prednisolone	4	0.8	5 mg
		4. Methyl-prednisolone	5	0.5	4 mg
		5. Triamcinolone	5	0	4 mg
	Long acting, (Biological t½ > 36 hr)	6. Dexamethasone	25	0	0.75 mg
		7. Betamethasone	25	0	0.75 mg
MINERALO-CORTICOIDS					*Equiv. salt retaining dose*
		8. Desoxycortico-sterone acetate (DOCA)	0	100	2.5 mg (sublingual)
		9. Fludrocortisone	10	150	0.2 mg
		10. Aldosterone	0.3	3,000	not used clinically

PHARMACOKINETICS

All natural and synthetic corticoids are absorbed by the oral route.

Hydrocortisone undergoes high first pass metabolism, has low oral: parenteral activity ratio. Oral bioavailability of synthetic corticoids is high.

Hydrocortisone is 90% bound to plasma protein, mostly to a specific corticosteroid binding globulin (transcortin) as well as to albumin.

The steroids are metabolized primarily by hepatic microsomal enzymes. The metabolites are excreted in urine.

The plasma t½ of hydrocortisone is 1.5 hours. However, biological effect t½ is longer because of action through intracellular receptors and regulation of protein synthesis—effects that persist long after the steroid is removed from plasma.

The synthetic derivatives are more resistant to metabolism and are longer acting.

Phenobarbitone and phenytoin induce metabolism of hydrocortisone, prednisolone and dexamethasone, etc. to decrease their therapeutic effect.

DISTINCTIVE FEATURES

The relative potency and activity of different natural and synthetic corticosteroids employed systemically is compared in Table 14.3.

1. Hydrocortisone (cortisol) In addition to primary glucocorticoid, it has significant mineralocorticoid activity and is short acting.

2. Prednisolone It is 4 times more potent than hydrocortisone, also more selective glucocorticoid, but fluid retention does occur with high doses. Has intermediate duration of action: causes less pituitary-adrenal suppression when a single morning dose or alternate day treatment is given. It is used for allergic, inflammatory, autoimmune diseases and in malignancies.

3. Methylprednisolone Slightly more potent and more selective than prednisolone.

Pulse therapy with high dose methylprednisolone (1 g infused i.v. every 6–8 weeks) has been tried in nonresponsive active rheumatoid arthritis, renal transplant, pemphigus, etc.

4. Triamcinolone Slightly more potent than prednisolone but highly selective glucocorticoid.

5. Dexamethasone Very potent and highly selective glucocorticoid. Long acting, causes

marked pituitary-adrenal suppression, but fluid retention and hypertension are not a problem.

It is used for inflammatory and allergic conditions, shock, cerebral edema, etc.

6. Betamethasone Similar to dexamethasone. Dexamethasone or betamethasone are preferred in cerebral edema and other states in which fluid retention must be avoided.

ADVERSE EFFECTS

These are extension of the pharmacological action occurring with prolonged therapy, and are a great limitation to use of corticoids in chronic diseases.

A. Mineralocorticoid Sodium and water retention, edema, hypokalaemic alkalosis and a progressive rise in BP.

Gradual rise in BP occurs due to excess glucocorticoid action as well.

B. Glucocorticoid

1. Cushing's habitus: characteristic appearance with rounded face, narrow mouth, supraclavicular hump, obesity of trunk with relatively thin limbs.
2. Fragile skin, purple striae—easy bruising, telengiectasis, hirsutism. Cutaneous atrophy occurs with topical use also.
3. Hyperglycaemia, precipitation of diabetes.
4. Muscular weakness; myopathy occurs occasionally.
5. Susceptibility to infection; opportunistic infections with low-grade pathogens (*Candida*, etc.).
6. Delayed healing of wounds.
7. Peptic ulceration.
8. Osteoporosis: Specially involving vertebrae and other flat spongy bones.
9. Growth retardation: in children occurs even with small doses if given for long periods.
10. Foetal abnormalities: cleft palate and other defects are produced in animals, but have not been encountered in pregnant women.
11. Psychiatric disturbances.
12. Suppression of hypothalamo-pituitary-adrenal (HPA) axis: occurs depending both on dose and duration of therapy. In time, adrenal cortex atrophies and stoppage of exogenous steroid precipitates a withdrawal syndrome and reactivation of the disease. Subjected to stress, these patients may go into acute adrenal insufficiency.

Any patient who has received > 20–25 mg/day hydrocortisone or equivalent for longer than 2–3 weeks should be put on a scheme of gradual withdrawal. Such patients may need protection with steroids if a stressful situation develops up to one year after withdrawal.

If a patient on steroid therapy develops an infection—the *steroid should not be discontinued* despite its propensity to weaken host defence. Rather, the dose may have to be increased to meet the stress of infection.

Measures that minimise HPA axis suppression are:

(a) Use shorter acting steroids (hydrocortisone, prednisolone) at the lowest possible dose.
(b) Use steroids for the shortest period of time possible.
(c) Give the entire daily dose at one time in the morning.
(d) Switch to alternate-day therapy if possible.
(e) If appropriate, use local (dermal, inhaled, ocular, nasal, buccal, rectal, intrasynovial) preparations.

USES

Systemic as well as topical corticosteroids have one of the widest spectrum of medical uses for their antiinflammatory and immunosuppressive properties. They are powerful drugs: have the potential to cause dramatic improvement in many severe diseases, but can produce equally serious adverse effects. Important conditions in which they are used are:

1. Collagen and autoimmune diseases: systemic lupus erythematosus, polyarteritis

nodosa, nephrotic syndrome, glomerulonephritis, rheumatoid arthritis, rheumatic fever, acute gouty arthritis, haemolytic anaemia, thrombocytopenia, myasthenia gravis, etc.
2. Severe allergic reactions: anaphylaxis, angioneurotic edema, urticaria, serum sickness.
3. Bronchial asthma, aspiration pneumonia, allergic rhinitis.
4. Eye diseases: allergic conjunctivitis, iridocyclitis, keratitis, uveitis, retinitis, optic neuritis, etc.
5. Skin diseases: mostly topical use in dermatitis; systemic steroids are needed in pemphigus vulgaris, exfoliative dermatitis, Stevens-Johnson syndrome and other serious disorders.
6. Inflammatory bowel disease: ulcerative colitis, Crohn's disease.
7. Infective diseases: only in serious/life-threatening infective diseases under effective antimicrobial cover, e.g. in bacterial/tubercular meningitis, miliary tuberculosis, severe lepra reaction, etc.
8. Malignancies: acute lymphatic leukaemia, Hodgkin's disease, lymphomas, etc.
9. Renal and other organ transplantation, skin allograft.
10. Substitution therapy in acute and chronic adrenal insufficiency and congenital adrenal hyperplasia.

CONTRAINDICATIONS

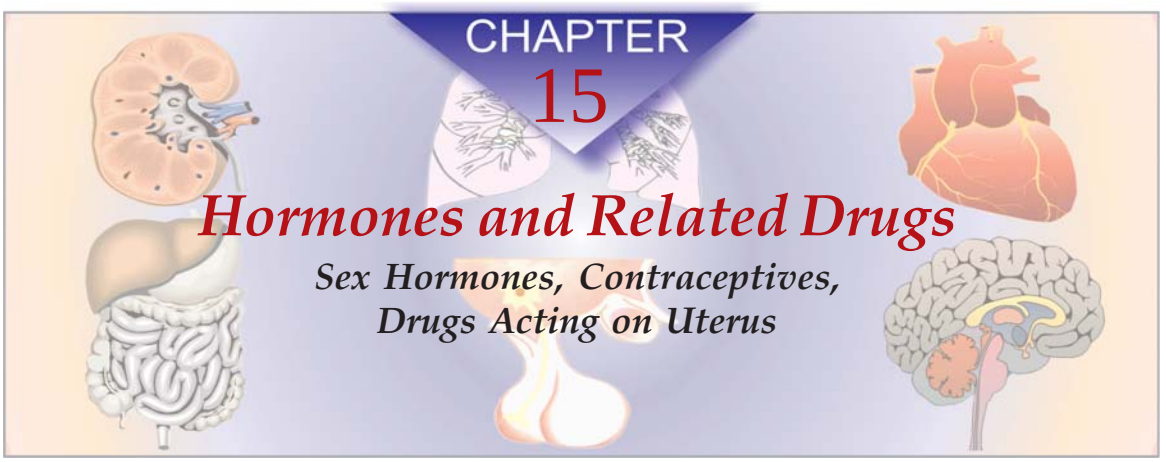
The following diseases are aggravated by corticosteroids. Since steroids may have to be used as a life-saving measure, all of these are relative contraindications:

1. Peptic ulcer
2. Diabetes mellitus
3. Hypertension
4. Viral and fungal infections
5. Tuberculosis and other infections
6. Osteoporosis
7. Herpes simplex keratitis
8. Psychosis
9. Epilepsy
10. CHF
11. Renal failure.

Implications in dentistry

Application of corticosteroids in dental conditions is rather limited. Recurrent oral ulceration may be treated with topical steroids, but maintaining long enough contact between the steroid and the oral lesion is often difficult. Severe oral lesions like pemphigus, erosive lichen planus, etc. need to be treated with systemic corticosteroids. Pain from exposed dental pulp is occasionally treated with locally applied steroids. Intra-articular hydrocortisone is sometimes injected in the temporomandibular joint to relieve refractory pain and stiffness. Only rarely a corticosteroid is needed to suppress pain and swelling due to dental surgery, (e.g. impacted third molar extraction), for which NSAIDs are the first line drugs.

In the case of patients who are/have been in recent past on long-term corticosteroid therapy, consideration has to be given to the need for supplementary prophylactic corticoid to cover a dental procedure. In general, simple extractions and other mildly traumatic surgeries do not warrant additional steroid dose. For traumatic procedures and those to be performed under general anaesthesia, supplementary steroids may be needed, particularly if the dose and duration of steroid therapy are such as to have caused significant adrenal suppression, or the patient is excessively anxious. Monitoring of BP of such patients during surgery is required. In case BP falls, hydrocortisone should be injected i.v. immediately.



CHAPTER 15

Hormones and Related Drugs

Sex Hormones, Contraceptives, Drugs Acting on Uterus

The gonads produce steroidal hormones which have androgenic, estrogenic and progestational activities. Their synthetic analogues have similar or antagonistic actions and form an important class of drugs.

ANDROGENS (Male sex hormones)

These are substances which cause development of secondary sex characters in the castrated male. *Testosterone* produced by the testes is the principal androgen, a part of which is converted in extraglandular tissues by the enzyme steroid 5α reductase to the more active compound *dihydrotestosterone*. Whereas in most target tissues dihydrotestosterone is the active androgen, testosterone itself is active at the spermatogenic (in testes) and erythropoietic (in bone marrow) cells, and for feedback inhibition of LH at the hypothalamic/pituitary site.

Actions

1. *Sex organs and secondary sex characters (Androgenic)* Testosterone is responsible for all the changes that occur in a boy at puberty:
Growth of genitals—penis, scrotum, seminal vesicles, prostate.
Growth of hair—pubic, axillary, beard, moustache, body hair and male pattern of its distribution.
Thickening of skin, proliferation and increased activity of sebaceous glands—especially on the face, acne vulgaris.
Larynx grows and voice deepens.
Behavioral effects are—increased physical vigour, aggressiveness, penile erections.
Testosterone is also important for the intrauterine development of the male phenotype.

2. *Testes* Testosterone is needed for normal spermatogenesis and maturation of spermatozoa. However, larger doses administered exogenously cause testicular atrophy by inhibiting Gn secretion from pituitary.

3. *Skeleton and skeletal muscles (Anabolic)* Testosterone is responsible for the pubertal spurt of growth in boys and to a smaller extent in girls. There is rapid bone growth. After puberty, the epiphyses fuse and linear growth comes to a halt. Testosterone also promotes muscle building, especially if aided by exercise. There is accretion of nitrogen, minerals (Na, K, Ca, P, S) and water—body weight increases rapidly, more protoplasm is built.

4. *Erythropoiesis* Testosterone accelerates erythropoiesis by increasing erythropoietin production and probably direct action on haeme synthesis.

Pharmacokinetics

Testosterone is inactive orally due to high first pass metabolism in liver. Slowly absorbed esters of testosterone are used by the i.m. route.

The major metabolic products of testosterone are androsterone and etiocholanolone which are excreted in urine. Small quantities of estradiol are also produced from testosterone by aromatization of A ring in extraglandular tissues. Plasma t½ of testosterone is 10–20 min.

Side effects

1. Virilization and menstrual irregularities in women.
2. Acne: in males and females.
3. Frequent, sustained and often painful erections.
4. Oligozoospermia with moderate doses given for a few weeks.
5. Precocious puberty and shortening of stature.
6. Cholestatic jaundice: occurs with 17-alkyl substituted derivatives but not with parenterally used esters of testosterone.

Uses

Testosterone is used for replacement therapy in case of primary or secondary testicular failure resulting in delayed puberty, loss of libido and impotence. However, impotence due to psychological and other factors, and not testosterone deficiency, does not respond.

The anabolic effect of testosterone can be used to improve weakness and muscle wasting in AIDS patients.

Attacks of hereditary angioneurotic edema can be prevented by 17α-alkylated androgens (methyltestosterone, stanozolol, danazol) but not by testosterone. They act by increasing synthesis of complement (C1) esterase inhibitor.

ANABOLIC STEROIDS

These are synthetic androgens with supposedly higher anabolic and lower androgenic activity. Drugs are *Nandrolone*, *Oxymetholone*, *Stanozolol*, *Methandienone* and others.

The anabolic steroids have been used for osteoporosis in elderly males, in catabolic states like severe trauma, major surgery, during convalescence and in hypoplastic/malignancy associated anaemia. They may reduce nitrogen load in renal insufficiency. Use for promoting suboptimal growth in children is controversial, and misuse by athletes to enhance physical ability is illegal.

IMPEDED ANDROGENS / ANTIANDROGENS

Danazol It is an orally active ethisterone derivative having weak androgenic, anabolic and progestational activity. Though labelled as an impeded/attenuated androgen, the most prominent action is suppression of Gn secretion from pituitary in both men and women → inhibition of testicular/ovarian function. It suppresses gonadal function directly as well by inhibiting steroidogenic enzymes. Endometrial atrophy occurs over a few weeks and amenorrhoea may supervene.

Danazol is used in endometriosis wherein it relieves dysmenorrhoea, dyspareunia and excessive bleeding. It reduces blood loss in menorrhagia and affords symptomatic relief in fibrocystic breast disease. Other indications are hereditary angioneurotic edema and precocious puberty in boys.

Flutamide A nonsteroidal drug having specific antiandrogenic, but no other hormonal activity. Its active metabolite 2-hydroxyflutamide competitively blocks androgen action on accessory sex organs as well as on pituitary—increases LH secretion by blocking feedback inhibition. Plasma testosterone levels increase in males which partially overcome the direct antiandrogenic action of flutamide. Palliative effect may occur in advanced prostatic carcinoma, but it is better used in conjunction with a GnRH agonist or after castration. Reports of liver damage have restricted its use.

5 α-REDUCTASE INHIBITOR

Finasteride A competitive inhibitor of the enzyme 5 α-reductase which converts testosterone into more active dihydrotestosterone responsible for androgen action in many tissues including

prostate gland and hair follicles. Plasma LH and testosterone levels are unchanged because testosterone itself mediates feedback pituitary LH inhibition: libido and potency are largely preserved.

Treatment with finasteride has resulted in decreased prostate size and increased peak urinary flow rate in ~50% patients with symptomatic benign hypertrophy of prostate (BHP).

The relief of obstructive symptoms, however, is less marked compared to surgery and α_1-blockers. Concurrent treatment with α_1 blocker + finasteride produces greater symptomatic relief.

Finasteride has also been found effective in male pattern baldness.

ESTROGENS

These are substances which can induce estrus in spayed animals.

Estradiol is the major estrogen secreted by the ovary. It is synthesized in the graafian follicle, corpus luteum and placenta from cholesterol. Estradiol is rapidly oxidized in liver to *estrone* which is hydroxylated to form *estriol*. All three are found in blood, but estradiol is the most potent.

Natural estrogens are inactive orally and have a short duration of action due to rapid metabolism in liver. Synthetic estrogens are:

Steroidal	Ethinylestradiol, Mestranol, Tibolone.
Nonsteroidal	Diethylstilbestrol (stilbestrol): Hexestrol, Dienestrol.

Actions

1. *Sex organs* The estrogens bring about pubertal changes in the female—growth of uterus, fallopian tubes and vagina. Vaginal epithelium gets thickened, stratified and cornified. They are responsible for the proliferation of endometrium in the preovulatory phase and it is only in concert with estrogens that progesterone brings about secretory changes.

Estrogens increase rhythmic contractions of the fallopian tubes and uterus, and induce a watery alkaline secretion from the cervix—favourable to sperm penetration. They also sensitize the uterus to oxytocin. Deficiency of estrogens is responsible for atrophic changes in the female reproductive tract that occur after menopause.

2. *Secondary sex characters* Estrogens produced at puberty cause growth of breasts. The pubic and axillary hair appear, feminine body contours and behaviour are influenced.

3. *Metabolic effects* Estrogens are anabolic, similar to but weaker than testosterone. Continued action of estrogen promotes fusion of epiphyses. They are important in maintaining bone mass primarily by retarding bone resorption and promoting positive calcium balance.

Combination contraceptives containing higher doses of estrogens and progestins impair glucose tolerance. However, amounts used for HRT and low dose contraception do not affect carbohydrate metabolism.

Estrogens decrease plasma LDL cholesterol while HDL and triglyceride levels are raised. The raised HDL : LDL ratio is probably responsible for rarity of atherosclerosis in premenopausal women. However, blood coagulability is increased due to induction of synthesis of clotting factors. They increase lithogenicity of bile.

Pharmacokinetics Estrogens are well absorbed orally and transdermally, but natural estrogens are inactive orally due to rapid metabolism in liver. Estradiol esters injected i.m. are slowly absorbed and exert prolonged action.

Estradiol is converted to estrone and vice versa in liver. Estriol is derived from estrone. All three are conjugated with glucuronic acid and sulfate—excreted in urine and bile. Considerable enterohepatic circulation occurs due to deconjugation in intestines and reabsorption—ultimate disposal occurs mostly in urine.

Ethinylestradiol is metabolized very slowly, orally active and more potent.

Adverse effects

Most of the adverse effects of estrogens are described with oral contraceptives (*see* p. 236). In addition, adverse effects noted when use is made for other indications are:

1. Suppression of libido, gynaecomastia and feminization when given to males.
2. Fusion of epiphyses and reduction of adult stature when given to children.
3. In postmenopausal women, estrogens can increase the risk of endometrial carcinoma. A progestin given concurrently blocks the risk.
4. Increased incidence of breast cancer is possible.
5. Long-term estrogen therapy doubles the incidence of gallstones.
6. Estrogens increase the incidence of thromboembolic diseases.
7. Migraine and endometriosis may be worsened by estrogens.

Uses

Currently, the two most common uses of estrogens are as contraceptives and for hormone replacement therapy (HRT) in postmenopausal women. Estrogen HRT is highly efficacious in suppressing the menopausal syndrome.

Hot flushes, palpitation, mood changes and other symptoms are mitigated. HRT improves general physical, mental and sexual well being. Atrophic changes are arrested. The vulval and urinary symptoms are effectively relieved.

HRT restores calcium balance, further bone loss is prevented.

However, the benefits of HRT must be weighed against the risks (predisposition to breast cancer, gallstones, venous thromboembolism, worsening of migraine, etc.) in individual women.

Other indications of estrogens are senile vaginitis, dysfunctional uterine bleeding (as adjuvant to progestin), advanced carcinoma prostate and as substitution therapy for delayed puberty in girls.

Antiestrogen

1. Clomiphene citrate It acts as a pure estrogen antagonist in all human tissues and induces Gn secretion in women by blocking estrogenic feedback inhibition of pituitary. In response, the ovaries enlarge and ovulation occurs if the ovaries are responsive to Gn. Antagonism of peripheral actions of estrogen results in hot flushes. Endometrium and cervical mucus may be modified.

The chief use of clomiphene is in sterility due to failure of ovulation. Conception occurs in many women who previously were amenorrhoeic or had anovular cycles.

Polycystic ovaries, multiple pregnancy, hot flushes are the adverse effects.

Oligozoospermia: Clomiphene increases Gn secretion in men as well → promotes spermatogenesis and testosterone secretion. It may be used for male infertility.

Selective estrogen receptor modulators (SERMs)

Tamoxifen citrate It acts as potent estrogen antagonist in breast carcinoma cells, blood vessels and at some peripheral sites, but as partial agonist in uterus, bone, liver and pituitary. Inhibition of human breast cancer cells and hot flushes reflect antiestrogenic action, while the weak estrogen agonistic action manifests as stimulation of endometrial proliferation, lowering of Gn and prolactin levels in postmenopausal women as well as improvement in their bone density. Similar to estrogen HRT, it increases the risk of deep vein thrombosis by 2–3 times.

Tamoxifen is the first choice hormonal treatment of breast cancer in both pre- and postmenopausal women. It is also approved for primary prophylaxis of breast cancer in high-risk women.

Improvement in bone mass due to antiresorptive effect, and in lipid profile (lowering coronary artery disease risk) are the other benefits of tamoxifen therapy. However, endometrial

thickening occurs and risk of endometrial carcinoma is increased 2 to 3-fold.

Side effects are hot flushes, vomiting, vaginal bleeding and menstrual irregularities.

Raloxifene This recently introduced SERM is an estrogen partial agonist in bone and cardiovascular system, but an antagonist in endometrium and breast.

Raloxifene prevents bone loss in postmenopausal women; bone mineral density (BMD) may even increase. It also reduces the risk of breast cancer.

Raloxifene does not stimulate endometrial proliferation and there is no increase in risk of endometrial carcinoma.

Hot flushes, leg cramps are mild side effects. The only serious concern is 3-fold increase in risk of deep vein thrombosis and pulmonary embolism.

Raloxifene is an effective alternative to HRT for prevention and treatment of osteoporosis in postmenopausal women.

PROGESTINS

These are substances which convert the estrogen primed endometrium to secretory and maintain pregnancy in animals spayed after conception (*Progestin* = favouring pregnancy).

Progesterone, a 21 carbon steroid, is the natural progestin. It is secreted by the corpus luteum in the later half of menstrual cycle under the influence of LH. Its production declines a few days before the next menstrual flow. If the ovum gets fertilized and implants—the blastocyst immediately starts producing chorionic gonadotropin which is absorbed and sustains the corpus luteum in early pregnancy. Placenta starts secreting lots of estrogens and progesterone from 2nd trimester till term.

A number of synthetic progestins having high oral activity have been produced. These are either progesterone derivatives (21 C) or 19-nortestosterone derivatives (18 C). Whereas the progesterone derivatives are almost pure progestins, have weaker antiovulatory action and are used primarily as adjuvants to estrogens for HRT, threatened abortion, endometriosis, etc. some of the 19-nortestosterone derivatives have additional weak estrogenic, weak androgenic, anabolic and potent antiovulatory action: are used primarily in combined contraceptive pills.

Progesterone derivatives
Medroxyprogesterone acetate
Dydrogesterone
Hydroxyprogesterone caproate
19-Nortestosterone derivatives
Norethindrone (Norethisterone)
Lynestrenol (Ethinylestrenol)
Allylestrenol
Levonorgestrel
Desogestrel

Actions

The main function of progesterone is preparation of uterus for nidation and maintenance of pregnancy. The latter is due to prevention of endometrial shedding, decreased uterine motility and inhibition of immunological rejection of the foetus: progesterone depresses T-cell function and cell-mediated immunity (CMI).

1. Progesterone brings about secretory changes in the estrogen primed endometrium while epithelial proliferation is suppressed. It is lack of progestational support which causes mucosal shedding during menstruation.
2. It converts the watery cervical secretion induced by estrogens to viscid, scanty and cellular secretion which is hostile to sperm penetration.
3. Progesterone induces pregnancy like changes in the vaginal mucosa. The pregnancy associated increased incidence of gingival inflammation has been ascribed to high levels of progesterone.
4. Progesterone causes proliferation of acini in the mammary glands. Acting in concert with estrogens, it prepares breast for lactation.

Withdrawal of these hormones after delivery causes release of prolactin from pituitary and milk secretion starts.

5. It causes a slight (0.5ºC) rise in body temperature by resetting hypothalamic thermostat and increasing heat production. This is responsible for the higher body temperature seen during the luteal phase.
6. Prolonged use of oral contraceptives impairs glucose tolerance in some women. This has been ascribed to the progestational component. Progestins tend to raise LDL and lower HDL levels.
7. Progesterone is a weak inhibitor of Gn secretion from pituitary. Administration of progestin during follicular phase suppresses the preovulatory LH surge and prevents ovulation; synergises with estrogen for this action.

Pharmacokinetics

Progesterone, unless specially formulated, is inactive orally because of high first pass metabolism in liver. It is primarily injected i.m. in oily solution. Even after an i.m. dose, it is rapidly cleared from plasma, has a short t½ (5–7 min). It is nearly completely degraded in the liver.

A micronized formulation of progesterone has been developed recently for oral administration.

Most of the synthetic progestins are orally active and are metabolized slowly; have plasma t½ ranging from 8–24 hours.

Adverse effects

- Breast engorgement, headache, rise in body temperature, esophageal reflux, and mood swings may occur with higher doses.
- Irregular bleeding or amenorrhoea can occur if a progestin is given continuously.
- Blood sugar may rise and diabetes may be precipitated.

Uses

1. *As contraceptive*: Most common use.
2. *Hormone replacement therapy (HRT):* To counteract the risk of inducing endometrial carcinoma by the estrogen given alone.
3. *Dysfunctional uterine bleeding:* A progestin in relatively large doses promptly stops bleeding and keeps it in abeyance as long as given.
4. *Endometriosis:* It is due to the presence of ectopic endometrium; manifestations are dysmenorrhoea, painful pelvic swellings and infertility. Continued administration of progestins affords symptomatic relief.
5. *Threatened/habitual abortion:* Progestins are almost routinely prescribed, but benefit only when there is progestin deficiency.
6. *Endometrial carcinoma:* Progestins are palliative.
7. Progesterone treatment may improve oral aphthous ulcers that are related to menstruation in women.

ANTIPROGESTIN

Mifepristone It is a 19-norsteroid with potent competitive antiprogestational and significant antiglucocorticoid as well as antiandrogenic activity.

Given during the follicular phase, its antiprogestin action results in attenuation of midcycle Gn surge from pituitary → slowing of follicular development and delay/failure of ovulation. During the luteal phase, it prevents secretory changes normally brought about by progesterone. Later in the cycle, it blocks progesterone support to the endometrium, unrestrains PG release from it—this stimulates uterine contractions. Mifepristone also sensitizes myometrium to PGs and induces menstruation. If implantation has occurred, it blocks decidualization, conceptus is dislodged.

Uses of mifepristone are:

1. Termination of pregnancy of up to 7 weeks.
2. To induce cervical ripening before attempting abortion/ induction of labour.

3. As postcoital contraceptive. It has also been tried as once-a-month contraceptive.
4. Cushing's syndrome: for its antiglucocorticoid property.

HORMONAL CONTRACEPTIVES

These are hormonal preparations used for reversible suppression of fertility.

Over 100 million women worldwide are currently using hormonal contraceptives. With these drugs, fertility can be suppressed at will, for as long as desired, with almost 100% confidence and complete return of fertility on discontinuation. The efficacy, convenience, low cost and overall safety of oral contraceptives (OCs) has allowed women to decide if and when they will become pregnant and to plan their activities. A variety of oral and parenteral preparations are now available offering individual choices.

TYPES OF METHODS

1. Combined pill It contains an estrogen and a progestin. With accumulated experience, it has been possible to reduce the amount of estrogen and progestin in the 'second generation' OC pills without compromising efficacy, but reducing side effects and complications. Ethinylestradiol 30 µg daily is considered threshold but can be reduced to 20 µg/day if a progestin with potent antiovulatory action is included. While both estrogens and progestins synergise to inhibit ovulation, the progestin ensures prompt bleeding at the end of a cycle and blocks the risk of developing endometrial carcinoma due to the estrogen. One tablet is taken daily for 21 days, starting on the 5th day of menstruation. The next course is started after a gap of 7 days in which bleeding occurs. Thus, a cycle of 28 days is maintained. Calendar packs of pills are available. This is the most popular and most efficacious method.

2. Phased regimens These have been introduced to permit reduction in total steroid dose. The estrogen dose is kept constant (or varied slightly between 30–40 µg), while the amount of progestin is low in the first phase and progressively higher in the second and third phases.

3. Minipill (luteal supplement) A low-dose progestin only pill is taken daily continuously without any gap. The menstrual cycle tends to become irregular and ovulation occurs in 20–30% women, but other mechanisms contribute to the contraceptive action. The efficacy is lower (96–98%) compared to 98–99.9% with combined pill.

4. Postcoital (emergency) contraception

Currently 3 regimens are available:
(a) Levonorgestrel 0.5 mg + ethinylestradiol 0.1 mg (2 OVRAL tablets) taken as early as possible, but within 72 hours of unprotected intercourse and repeated after 12 hours. Till recently, this regimen called the 'Yuzpe method' has been most popular.
(b) Levonorgestrel alone 0.75 mg taken twice at 12-hour gap within 72 hours of intercourse.

The WHO essential drug list (2001) has recommended replacement of Yuzpe method by this regimen.
(c) Mifepristone 600 mg single dose taken within 72 hours of intercourse.

Emergency postcoital contraception should be reserved for unexpected or accidental exposure (rape, condom rupture) only.

Injectable These have been developed to obviate need for daily ingestion of pills. They are given i.m. as oily solution; are highly effective.

Two types of preparations have been tested:
(i) *Long acting progestin alone*:
(a) Depot medroxyprogesterone acetate (DMPA) 150 mg at 3-month intervals.
(b) Norethindrone (Norethisterone) enanthate (NEE) 200 mg at 2-month intervals.

The most important undesirable property is complete disruption of menstrual bleeding pattern and total amenorrhoea in many cases.
(ii) *Long acting progestin + long acting estrogen* — once a month.

These have been tested to a more limited extent. Main advantage is that they allow a reasonable menstrual bleeding pattern in most cases. Their obvious disadvantage is that they contain a long-acting estrogen which has potential to harm.

MECHANISM OF ACTION

Hormonal contraceptives interfere with fertility in many ways; the relative importance depends on the type of method.

1. Inhibition of Gn release from pituitary. When the combined pill is taken, both FSH and LH are reduced and the midcycle surge is abolished. As a result, follicles fail to develop and fail to rupture—*ovulation does not occur*.
2. Thick *cervical mucus* secretion *hostile to sperm penetration* is evoked by progestin action.
3. Even if ovulation and fertilization occur, the blastocyst may fail to implant because *endometrium* is *out of phase* with fertilization—not suitable for nidation.
4. *Uterine and tubal contractions* may be modified to disfavour fertilization.
5. The postcoital pill may *dislodge* a just implanted blastocyst.

ADVERSE EFFECTS

Since contraceptives are used in otherwise healthy and young women, adverse effects, especially long-term consequences assume great significance. The present-day low-dose preparations carry relatively minor risk.

A. Nonserious side effects These are frequent, especially in the first 1–3 cycles and then disappear gradually.

1. Nausea and vomiting.
2. Headache; migraine may be precipitated or worsened.
3. Breakthrough bleeding or spotting. Amenorrhoea may occur in few.
4. Breast discomfort.

B. Side effects that appear later

1. Weight gain, acne and increased body hair.
2. Chloasma: pigmentation of cheeks.
3. Pruritus vulvae.
4. Carbohydrate intolerance and precipitation of diabetes.
5. Mood swings, abdominal distention.

C. Serious complications

1. *Leg vein and pulmonary thrombosis:* Significant risk in women >35 years of age, diabetics, hypertensives and in those who smoke.
2. *Coronary and cerebral thrombosis* resulting in *myocardial infarction or stroke:* A 2 to 6-fold increase in risk was estimated earlier, but recent studies have found no increased incidence with the low dose pills in the absence of other risk factors.
3. *Rise in BP*: This again is less frequent and smaller in magnitude with the low-dose pills of today.
4. *Genital carcinoma:* Risk is increased in predisposed individuals but not in general population. Growth of already existing hormone-dependent tumour may be hastened.

   Epidemiological data has recorded minor increase in breast cancer incidence among current OC users.
5. *Gallstones:* Incidence of gallstones is slightly higher in women on OCs.

Contraindications

The combined oral contraceptive pill is absolutely contraindicated in:

1. Thromboembolic, coronary and cerebrovascular disease or a history of it.
2. Moderate-to-severe hypertension; hyperlipidaemia.
3. Active liver disease, hepatoma or h/o jaundice during past pregnancy.
4. Suspected/overt malignancy of genitals/breast.
5. Impending major surgery—to avoid postoperative thromboembolism.

Interactions Contraceptive failure may occur if the following drugs are used concurrently:

(a) *Enzyme inducers:* phenytoin, phenobarbitone, primidone, carbamazepine, rifampin.
(b) *Suppression of intestinal microflora:* tetracyclines, ampicillin, etc. No deconjugation of estrogens excreted in bile → their enterohepatic circulation is interrupted → blood levels fall.

Centchroman It is a nonsteroidal estrogen antagonist or SERM developed at CDRI, India and introduced in the National Family Welfare Programme as an oral contraceptive. It probably acts as an anti-implantation agent by inducing embryo-uterine asynchrony, accelerated tubal transport and suppression of decidualization. It prevents conception as long as taken, with return of fertility on withdrawal. Failure rate of 1–3% has been recorded.

UTERINE STIMULANTS (Oxytocics, Abortifacients)

These drugs increase uterine motility, especially at term.

1. *Posterior pituitary hormone* Oxytocin
2. *Ergot alkaloids* Ergometrine (Ergonovine), Methylergometrine
3. *Prostaglandins* PGE_2, $PGF_{2\alpha}$, 15-methyl $PGF_{2\alpha}$, Misoprostol
4. *Miscellaneous* Ethacridine, Quinine.

Oxytocin

Oxytocin is a nonapeptide secreted by the posterior pituitary along with ADH.

Both oxytocin and ADH are synthesized within the nerve cell bodies in supraoptic and paraventricular nuclei of hypothalamus; are transported down the axon and stored in the nerve endings within the neurohypophysis. Both are released by stimuli appropriate for oxytocin—coitus, parturition, suckling; or for ADH—hypertonic saline infusion, water deprivation, haemorrhage, etc.

Oxytocin increases the force and frequency of uterine contractions. With low doses, full relaxation occurs inbetween contractions.

The increased contractility is restricted to the fundus and body; lower segment is not contracted, may even be relaxed at term. Oxytocin plays a facilitatory role in labour, but does not appear to be essential for its initiation.

Initiated by suckling, oxytocin plays an essential role in 'milk ejection reflex' by contracting myoepithelium of mammary alveoli which forces milk into the bigger milk sinusoids.

Conventional doses used in obstetrics have no effect on BP, but higher doses cause vasodilatation → brief fall in BP, reflex tachycardia and flushing. Oxytocin in high doses exerts an ADH-like action—urine output is decreased.

Being a peptide, oxytocin is inactive orally and is administered by i.m. or i.v. routes. It is used to induce labour in case of postmaturity or to augment it in case of uterine inertia. It can also be used to control postpartum haemorrhage as an alternative to ergometrine. Intranasal spray of oxytocin may be employed to relieve breast engorgement in women with inadequate milk ejection reflex.

Injudicious use of oxytocin during labour can produce too strong uterine contractions forcing the presenting part through incompletely dilated birth canal, causing maternal and foetal soft tissue injury, rupture of uterus, foetal asphyxia and death.

Ergometrine, Methylergometrine

The amine ergot alkaloid ergometrine (ergonovine) and its derivative methylergometrine increase force, frequency and duration of uterine contractions. At low doses, contractions are phasic with normal relaxation in between, but only moderate increase in dose raises the basal tone, contracture occurs with high doses. Gravid uterus is more sensitive, especially at term and in early puerparium. Their stimulant action involves the lower segment also. The uterotonic action is believed to result from partial agonistic action on 5-HT_2 and α adrenergic receptors.

They are much weaker vasoconstrictors than the amino acid ergot alkaloid ergotamine.

Methylergometrine is 1½ times more potent than ergometrine on uterus and has replaced ergometrine at many obstetric units.

Ergometrine and methylergometrine are rapidly and nearly completely absorbed from the oral route. They are partly metabolized in liver and excreted in urine. Plasma t½ is 1–2 hours.

Use

1. The primary indication of ergometrine/methylergometrine is to control and prevent postpartum haemorrhage (PPH).

These drugs are preferred over oxytocin because they produce sustained tonic contraction: perforating uterine arteries are compressed by the myometrial meshwork—bleeding stops.

2. After cesarean section/instrumental delivery—to prevent uterine atony.
3. To ensure normal involution: because a firm and active uterus involutes rapidly.

Prostaglandins PGE_2, $PGF_{2\alpha}$ and 15-methyl $PGF_{2\alpha}$ are potent uterine stimulants, especially in the later part of pregnancy and cause ripening of cervix. Their actions and use in obstetrics are described in Ch. 7.

UTERINE RELAXANTS (Tocolytics)

These are drugs which decrease uterine motility. They have been used to delay or postpone labour and arrest threatened abortion. Suppression of labour may be needed to allow foetus to mature, to initiate glucocorticoid therapy for foetal lung maturation or to transfer the mother in labour to a centre with proper facilities.

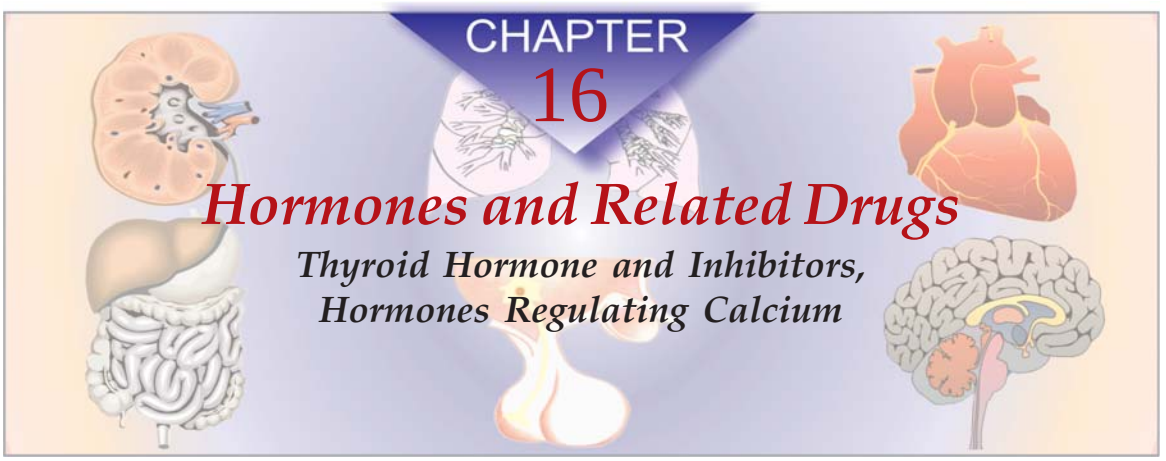
1. Adrenergic agonists (*see* Ch. 6) Ritodrine, the β_2 selective agonist having major uterine relaxant action is preferred to suppress premature labour and to delay delivery in case of some exigency or acute foetal distress. For dependable action, it is given by i.v. infusion. However, cardiovascular (hypotension, tachycardia, arrhythmia, pulmonary edema) and metabolic (hyperglycaemia, hyperinsulinaemia, hypokalaemia) complications occur frequently.

Salbutamol and terbutaline are the alternatives. Isoxsuprine oral/i.m. has been used to stop threatened abortion, but efficacy is uncertain.

2. Magnesium sulfate Given by i.v. infusion, it has been used to control convulsions and to reduce BP in toxaemia of pregnancy. It also suppresses uterine contraction effectively, but can cause cardiac arrhythmias, muscular paralysis, CNS and respiratory depression.

3. Calcium channel blockers Because influx of Ca^{2+} ions plays an important role in uterine contractions, Ca^{2+} channel blockers (*see* Ch. 11) reduce the tone of myometrium and oppose contractions. These drugs, especially nifedipine, which has prominent smooth muscle relaxant action, can postpone labour if used early enough. Tachycardia and hypotension are prominent at doses which suppress uterine contractions.

Ethyl alcohol, nitrates, progesterone, general anaesthetics (especially halothane) and PG synthesis inhibitors are other drugs which can depress uterine contractions.



CHAPTER 16

Hormones and Related Drugs

Thyroid Hormone and Inhibitors, Hormones Regulating Calcium

THYROID HORMONE

The thyroid gland secretes 3 hormones—thyroxine (T_4), triiodothyronine (T_3) and calcitonin. The former 2 are produced by thyroid follicles, have similar biological activity and the term 'thyroid hormone' is restricted to these only. *Calcitonin* produced by interfollicular 'C' cells is chemically and biologically entirely different: regulates calcium metabolism.

Chemistry and synthesis

Both T_4 and T_3 are iodine containing derivatives of *thyronine* which is a condensation product of two molecules of the amino acid *tyrosine*.

The thyroid hormones are synthesized and stored in the thyroid follicles as part of *thyroglobulin* molecule—which is a glycoprotein. The synthesis, storage and release of T_4 and T_3 is summarized in Fig. 16.1 and involves the following processes:

1. Iodide uptake into the thyroid by active transport (Na^+:I^- symporter) which is activated by TSH.
2. Oxidation of the trapped iodide by thyroid peroxidase enzyme to forms of iodine which combine avidly with tyrosil residues of thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT).
3. Coupling of MIT and DIT with the aid of the same peroxidase to form T_3 and T_4.
4. Storage of thyroglobulin containing T_3, T_4, MIT and DIT residues as thyroid colloid in the interior of the follicles till it is taken back into the cells by endocytosis and broken down by lysosomal proteases. The T_4 and T_3 so released are secreted into circulation.
5. Peripheral conversion of T_4 and T_3 in several tissues, especially liver and kidney.

Thyroid hormones are avidly bound to plasma proteins—only 0.03–0.08% of T_4 and 0.2–0.5% of T_3 are in the free form.

Only the free hormone is available for action as well as for metabolism and excretion. Metabolic inactivation of T_4 and T_3 occurs by deiodination and glucuronide/sulfate conjugation of the hormones as well as of their deiodinated products. Liver is the primary site. The conjugates are excreted in bile. A significant fraction is deconjugated in intestines and reabsorbed (enterohepatic circulation) to be finally excreted in urine.

Plasma t½ of T_4 is 6–7 days, while that of T_3 is 1–2 days.

Actions

The actions of T_4 and T_3 are qualitatively similar and are nicely depicted in the features of hypo- and hyperthyroidism. They affect the function of practically all body cells.

1. Growth and development T_4 and T_3 are essential for normal growth and development.

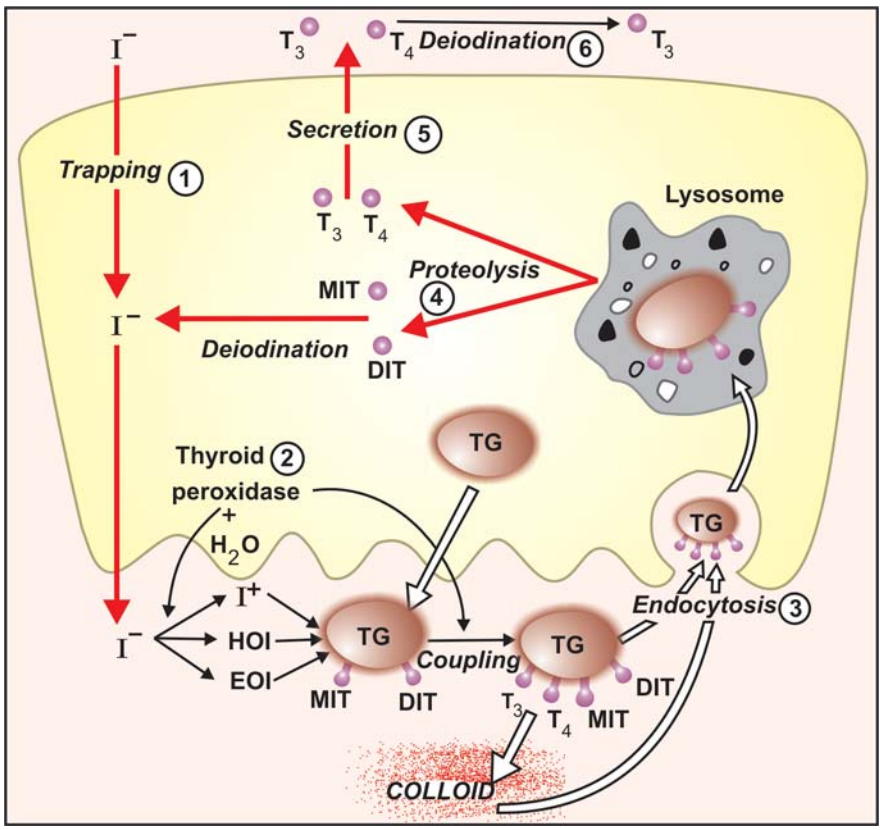


Fig. 16.1: Synthesis, storage and secretion of thyroid hormone
TG—Thyroglobulin; MIT—Monoiodotyrosine; DIT—Diiodotyrosine; T_3—Triiodothyronine; T_4—Thyroxine (Tetraiodothyronine); HOI—Hypoiodous acid; EOI—Enzyme-linked hypoiodate
Thyroid-stimulating hormone (TSH) activates steps 1, 2, 3, 4, and 5; Ionic inhibitors block step 1; Excess iodide interferes with steps 1, 2, 3 and 5 with primary action on step 3 and 5; Propylthiouracil inhibits steps 2 and 6; Carbimazole inhibits step 2 only.

The action is exerted through a critical control of protein synthesis in the translation of the genetic code. Congenital deficiency of T_4 and T_3 resulting in cretinism emphasizes their importance. The milestones of development are delayed and practically every organ and tissue of the body suffers. The greatest sufferer, however, is the nervous system. Retardation and nervous deficit is a consequence of paucity of axonal and dendritic ramification, synapse formation and impaired myelination. In adult hypothyroidism also, intelligence is impaired and movements are slow.

2. *Intermediary metabolism* Thyroid hormones have marked effect on lipid, carbohydrate and protein metabolism. Lipolysis and cholesterol metabolism are accelerated, more cholesterol is converted to bile acids.

Though utilization of sugar by tissues is increased, glycogenolysis and gluconeogenesis in liver more than compensate it → hyperglycaemia and diabetic like state results.

Synthesis of certain proteins is increased, but the overall effect of T_3 is catabolic—increased amounts of protein being used as energy source.

Prolonged action results in negative nitrogen balance and tissue wasting.

3. *Calorigenesis* T_3/T_4 increase BMR by stimulation of cellular metabolism and resetting of the energystat. This is important for maintaining body temperature.

4. *Organ systems* Heart rate, contractility and output are increased resulting in a fast, bounding pulse. T_3/T_4 stimulate heart by direct action on contractile elements as well as by upregulation of β adrenergic receptors. Atrial fibrillation and other irregularities are common in hyperthyroidism. T_3/T_4 have profound functional effect on CNS. Mental retardation is the hallmark of cretinism; sluggishness and other behavioral features are seen in myxoedema. Hyperthyroid individuals are anxious, nervous, excitable, exhibit tremors and hyperreflexia.

Muscles are flabby and weak in myxoedema, while thyrotoxicosis produces increased muscle tone and propulsive activity of gut is increased by T_3/T_4. Hypothyroid patients are often constipated, while diarrhoea is common in hyperthyroidism. Thyroid hormones are facilitatory to erythropoiesis and reproduction.

Mechanism of action T_3 (and T_4) penetrate cells and combine with a nuclear receptor. A specific DNA sequence called '*thyroid hormone response element*' has been identified in the regulatory region of specific genes to which the T_3-receptor complex binds → derepression of gene transcription or in some cases direct activation of gene transcription occurs. This results in expression of predetermined genetically coded pattern of protein synthesis.

Many of the manifestations, e.g. tachycardia, arrhythmias, raised BP, tremor, hyperglycaemia are mediated, at least partly, by sensitization of adrenergic receptors to catecholamines. In the thyrotoxic patient, Adr mixed local anaesthetic should be avoided for dental anaesthesia.

Because T_3 binds more avidly to the intracellular receptor and is 5 times more potent as well as faster acting than T_4, in most tissues, it is the major active hormone, while T_4 is only the transport form or prohormone.

Uses The most important uses of thyroid hormone are as *replacement therapy* in cretinism (congenital hypothyroidism) and myxoedema (adult hypothyroidism). Levothyroxine (T_4) given orally is the preparation of choice and benefits are most gratifying. Nontoxic goiter is due to relative thyroid hormone deficiency resulting in excess TSH → thyroid enlargement, more efficient iodide trapping and T_3 synthesis → enough hormone to meet peripheral demand is produced → the patient is clinically not hypothyroid. Treatment with T_4 normalises TSH level and tends to regress the goiter if the enlargement was recent and diffuse. Endemic goiter and endemic cretinism can be prevented by iodizing table salt. T_4 has palliative effect in certain benign functioning thyroid nodules and in papillary carcinoma of thyroid by lowering TSH levels. Myxoedema coma is an emergency that is treated with liothyronine (T_3) injected i.v.

THYROID INHIBITORS

These are drugs used to lower the functional capacity of the hyperactive thyroid gland.

Thyrotoxicosis is due to excessive secretion of thyroid hormones. The two main causes are *Graves' disease* and *toxic nodular goiter*. Graves' disease is an autoimmune disorder: IgG class of antibodies to the TSH receptor bind to and stimulate thyroid cells, and produce other TSH like effects. Due to feedback inhibition, TSH levels are low.

Toxic nodular goiter, which produces thyroid hormone independent of TSH, mostly supervenes on old nontoxic goiters.

CLASSIFICATION

1. *Inhibit hormone synthesis (Antithyroid drugs)*
   Propylthiouracil, Methimazole, Carbimazole.
2. *Inhibit hormone release*
   Iodine, Iodides of Na and K.
3. *Destroy thyroid tissue*
   Radioactive iodine (^{131}I).

ANTITHYROID DRUGS

By convention, only the synthesis inhibitors are called antithyroid drugs, though this term has also been applied to all thyroid inhibitors.

Antithyroid drugs bind to thyroid peroxidase and prevent oxidation of iodide/iodotyrosyl residues, thereby;

(i) Inhibit iodination of tyrosine residues in thyroglobulin
(ii) Inhibit coupling of iodotyrosine residues to form T_3 and T_4.

Effects of antithyroid drugs are not apparent till thyroid is depleted of its hormone content.

Propylthiouracil also inhibits peripheral conversion of T_4 to T_3: this may partly contribute to its effects. Methimazole and carbimazole do not have this action.

Pharmacokinetics All antithyroid drugs are quickly absorbed orally, widely distributed in the body, enter milk and cross placenta, are metabolized in liver and excreted in urine, primarily as metabolites.

Adverse effects Hypothyroidism and goiter can occur due to overtreatment, but is reversible on stopping the drug.
Important side effects are: g.i. intolerance, skin rashes and joint pain.
A rare but serious adverse effect is agranulocytosis.

Use Antithyroid drugs control thyrotoxicosis in both Graves' disease and toxic nodular goiter. Clinical improvement starts after 1–2 weeks or more and may take 1–3 months for full control. These drugs may be used for short periods before partial thyroidectomy (surgery in thyrotoxic patient is risky) or while awaiting response to radioactive iodine. They can also be used as definitive therapy at lower (maintenance) doses.

IODINE AND IODIDES

Though iodine is a constituent of thyroid hormones, it is the fastest acting thyroid inhibitor. It is reduced in the intestines to iodide and the response to iodine or iodides is identical. The gland, if enlarged, shrinks, becomes firm and less vascular. The thyroid status starts returning to normal at a rate commensurate with complete stoppage of hormone release from the gland. Peak effects are seen in 10–15 days, after which 'thyroid escape' occurs and thyrotoxicosis may return with greater vengeance.

All facets of thyroid function seem to be affected, but the most important action is inhibition of hormone release. Endocytosis of colloid and proteolysis of thyroglobulin comes to a halt.

In thyrotoxicosis, iodine is primarily used for about 10 days just preceding thyroid surgery to make the gland firm, less vascular and easier to operate on. It may also be given to stop thyroid storm. Incidence of endemic goiter in iodine deficient areas has been reduced by iodizing table salt.

Potassium iodide is an expectorant. Tincture iodine is used externally as an antiseptic.

Adverse effects Long-term ingestion of high doses of iodine/iodides can cause hypothyroidism and goiter. Chronic overdose also results in inflammation of mucous membranes. An acute reaction consisting of swelling of lips, eyes, angioedema, fever, thrombocytopenia, etc. can develop in sensitive individuals.

RADIOACTIVE IODINE

The stable isotope of iodine is ^{127}I. Its radioactive isotope ^{131}I has a physical half-life of 8 days—most commonly used in medicine.

^{131}I emits X-rays as well as β particles. The former are useful in tracer studies, while the latter are utilized for their destructive effect on thyroid cells. ^{131}I is concentrated by thyroid, incorporated in colloid—emits radiation from within the follicles. The β particles penetrate only 0.5–2 mm of tissue. The thyroid follicular cells are affected from within, undergo pyknosis and necrosis followed by fibrosis when a sufficiently large dose has been administered, without damage to neighbouring tissues. With carefully selected doses, it is possible to achieve partial ablation of thyroid.

It is used as sodium salt of ^{131}I dissolved in water and taken orally.

Diagnostic 25–100 μ curie is given; counting or scanning is done at intervals. No damage to thyroid cells occurs at this dose.

Therapeutic The most common indication is *hyperthyroidism*. The average therapeutic dose is 3–6 m curie—calculated on the basis of previous tracer studies and thyroid size. The response is slow—starts after 2 weeks and gradually increases, reaching peak at 3 months or so.

Treatment with ^{131}I is simple, conveniently given on outpatient basis and inexpensive. Once hyperthyroidism is controlled, cure is permanent.

The biggest disadvantage of ^{131}I therapy is development of life-long hypothyroidism in many recipients. Long latent period of response is another drawback. Radioactive iodine may be palliative in metastatic carcinoma of thyroid.

β ADRENERGIC BLOCKERS

Propranolol (and other nonselective β blockers) have emerged as an important form of therapy to rapidly alleviate manifestations of thyrotoxicosis that are due to sympathetic overactivity: palpitation, tremor, nervousness, severe myopathy, sweating. They have little effect on thyroid function and the hypermetabolic state; are used for symptomatic relief only.

HORMONES REGULATING CALCIUM

CALCIUM

After C, O, H and N, calcium is the most abundant body constituent, making up about 2% of body weight: 1–1.5 kg in an adult. Over 99% of this is stored in bones (and teeth), the rest being distributed in plasma, all tissues and cells, and serves important physiological roles.

1. Controls excitability of nerves and muscles and regulates permeability of cell membranes.
2. Ca^{2+} ions are essential for excitation-contraction coupling in all types of muscle and excitation-secretion coupling in exocrine and endocrine glands, release of transmitters from nerve ending and other release reactions.
3. Intracellular messenger for hormones, autacoids and transmitters.
4. Impulse generation in heart—determines level of automaticity and A-V conduction.
5. Coagulation of blood.
6. Calcium serves structural function in bone and teeth; abnormalities of calcium balance affect teeth indirectly.

Plasma calcium level is precisely regulated by 3 hormones almost exclusively devoted to this function viz. *parathormone* (PTH), *calcitonin* and *calcitriol* (active form of vit D). These regulators control its intestinal absorption, exchange with bone and renal excretion as summarized in Fig. 16.2.

Normal plasma calcium is 9–11 mg/dl. Of this, about 40% is bound to plasma proteins—chiefly albumin; 10% is complexed with citrate, phosphate and carbonate in an undissociable form; the remaining (about 50%) is ionized and physiologically important.

Calcium turnover Major fraction of calcium in the bone is stored as crystalline hydroxyapatite deposited on the organic bone matrix *osteoid*, while a small labile pool is in dynamic equilibrium with plasma. Even the fully laid down parts of the bone undergo constant *remodeling* by way of two closely coupled but directionally opposite processes of resorption and new bone formation (Fig. 16.3). Millions of tiny remodeling units are working on the surface of bone trabeculae and Haversian canals to dig micropits by osteoclastic activity and then repair by osteoblastic activity in which first collagen and other proteins (osteoid) are deposited followed by mineralization; the full cycle taking 4–6 months.

Absorption and excretion Calcium is absorbed by facilitated diffusion from the entire small intestine as well as from duodenum by a carrier-mediated active transport under the influence of vit D. Phytates, phosphates, oxalates, tetracyclines, glucocorticoids and phenytoin reduce calcium absorption.

All ionized calcium is filtered at the glomerulus and most of it is reabsorbed in the tubules. Vit D increases and calcitonin decreases proximal tubular reabsorption, while PTH increases distal

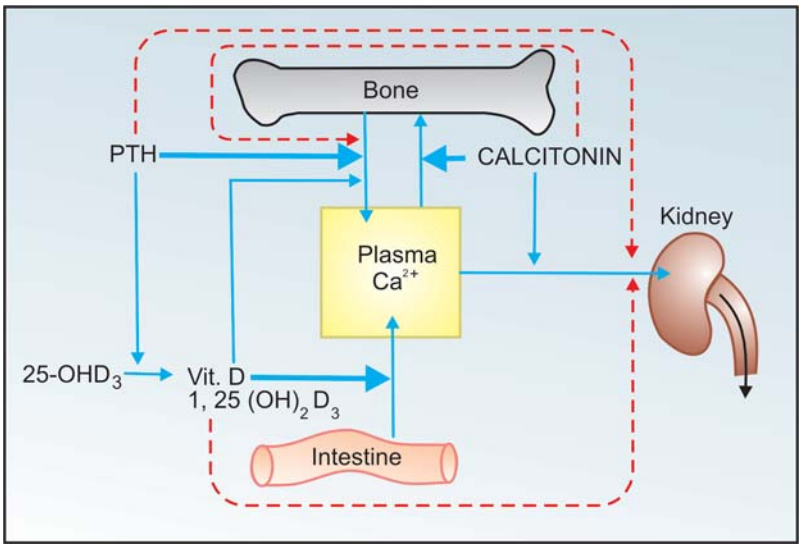


Fig. 16.2: Regulation of plasma level of calcium.
————→ stimulation, - - - - - - →Inhibition; Bold arrow—major action.
PTH—Parathormone; 25-OHD_3—Calcifediol; 1,25 $(OH)_2D_3$—Calcitriol

tubular reabsorption of Ca^{2+}. About 300 mg of endogenous calcium is excreted daily: half in urine and half in faeces. To maintain calcium balance, the same amount has to be absorbed in the small intestine from the diet. Because normally only 1/3rd of ingested calcium is absorbed, the dietary allowance for calcium is 0.8–1.5 g per day.

Side effects Calcium supplements are usually well tolerated; only g.i. side effects like constipation, bloating and excess gas have been reported.

Use

1. *As dietary supplement* especially in growing children, pregnant, lactating and menopausal women. Abnormalities of dentition can be reduced by avoiding calcium deficiency.
2. *Osteoporosis* Calcium + vit D_3 have adjuvant role to HRT/raloxifene/alendronate in prevention and treatment of osteoporosis.
3. To prevent and treat tetany which occurs due to hypocalcaemia.

PARATHYROID HORMONE (Parathormone)

Parathyroid hormone (PTH) is a single chain 84 amino acid polypeptide, MW 9,500. Secretion of PTH is regulated by plasma Ca^{2+} concentration; there is no trophic hormone for it. Fall in plasma Ca^{2+} induces PTH release and rise inhibits secretion. Changes in phosphate concentration in plasma affect PTH secretion indirectly by altering Ca^{2+} concentration.

PTH increases plasma calcium levels by:

1. Increasing resorption of calcium from bone. This is the most prominent action of PTH.
2. Increasing calcium reabsorption in the distal tubule. It also promotes phosphate excretion which tends to supplement the hypercalcaemic effect.
3. Enhancing the formation of calcitriol (active form of vit D) in the kidney, which then increases intestinal absorption of calcium.

Hypoparathyroidism Manifestations are:
Low plasma calcium levels, tetany, convulsions, laryngospasm, paresthesias, cataract and psy-

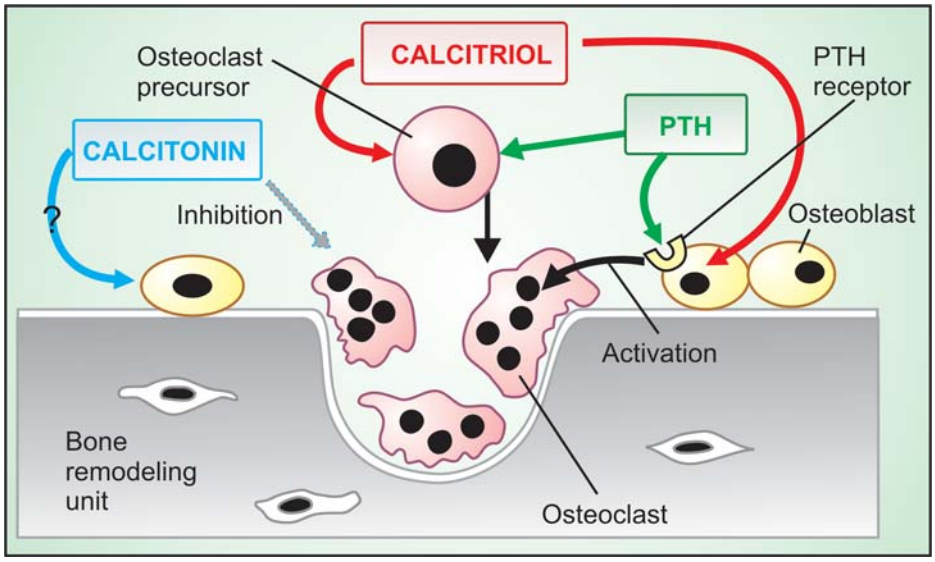


Fig. 16.3: Hormonal regulation of bone remodeling units.
Parathyroid hormone (PTH) acts on osteoblasts and indirectly activates osteoclasts, as well as recruits osteoclast precursors in bone remodeling units. Calcitriol promotes differentiation of osteoclast precursors. Facilitated by PTH, calcitriol increases osteoblast-mediated activation of osteoclasts. Calcitonin inhibits osteoclastic activity and probably increases osteoblastic activity

chiatric changes. Pseudohypoparathyroidism occurs due to reduced sensitivity of target cells to PTH. Hypoparathyroidism is treated with Vit D.

Hyperparathyroidism It is mostly due to parathyroid tumour. It produces:
Hypercalcaemia, decalcification of bone—deformities and fractures (osteitis fibrosa generalisata), metastatic calcification, renal stones, muscle weakness, constipation and anorexia.

Treatment is surgical removal of the parathyroid tumour.

CALCITONIN

Calcitonin is the hypocalcaemic hormone. It is a 32 amino acid single chain polypeptide (MW 3,600) produced by parafollicular 'C' cells of thyroid.

Synthesis and secretion of calcitonin is regulated by plasma Ca^{2+} concentration itself: rise in plasma Ca^{2+} increases, while fall in plasma Ca^{2+} decreases calcitonin release. However, the physiological role of calcitonin in regulating plasma Ca^{2+} appears to be minor. The plasma t½ of calcitonin is 10 min, but its action lasts for several hours.

The actions of calcitonin are generally opposite to that of PTH.

It inhibits bone resorption by direct action on osteoclasts—decreasing their ruffled surface which forms contact with the resorptive pit.

Calcitonin inhibits proximal tubular calcium and phosphate reabsorption by direct action on kidney.

Calcitonin is rarely used clinically; indications are Paget's disease of bone and hypercalcaemic states like hypervitaminosis D, osteolytic bony metastasis, etc. It has to be injected i.m. or s.c.

VITAMIN D

Vitamin D is the collective name given to antirachitic substances synthesized in the body and found in foods activated by UV radiation.

D3 : cholecalciferol — synthesized in the skin under the influence of UV rays.
D2 : calciferol—present in irradiated food—yeasts, fungi, bread, milk.

In man, vit D_2 and D_3 are equally active and *calcitriol* (active form of D_3) is more important physiologically; 25-OH D_3 is released in blood from liver. Its final hydroxylation in kidney is rate limiting and controlled by many factors. This step is activated or induced by calcium/vit D deficiency as well as by PTH, estrogens and prolactin, while calcitriol inhibits it in a feedback manner.

Thus, vit D should be considered a hormone because:
(a) It is synthesized in skin: (under ideal conditions, it is not required in diet).
(b) It is transported by blood, activated and then acts on specific receptors in target tissues.
(c) Feedback regulation of vit D activation occurs by plasma Ca^{2+} level and by the active form itself.

Actions

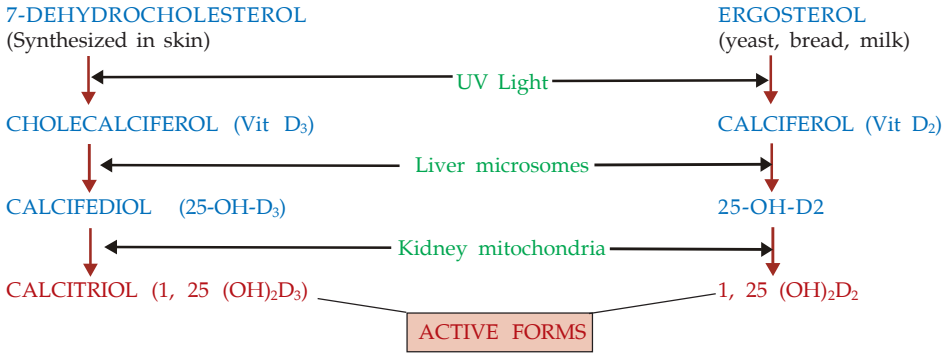
1. Calcitriol enhances absorption of calcium and phosphate from *intestine*. This is brought about probably by increasing synthesis of a carrier protein for Ca^{2+} called 'calcium binding protein' (Ca BP) or *Calbindin*. The action of calcitriol is analogous to that of steroid hormones which bind to a cytoplasmic receptor → translocate to the nucleus → increase synthesis of specific mRNA → regulation of protein synthesis. At least part of vit D action is quick (within minutes) and, therefore, appears to be exerted by mechanisms not involving gene regulation.
2. Calcitriol enhances resorption of calcium and phosphate from *bone*. It appears to help bone mineralization indirectly by maintaining normal plasma calcium and phosphate concentration. Its action is independent of but facilitated by PTH.
3. It enhances proximal tubular reabsorption of both calcium and phosphate in *kidney*.

Vit D deficiency Plasma calcium and phosphate tend to fall due to inadequate intestinal absorption. As a consequence, PTH is secreted → calcium is mobilized from bone in order to restore plasma Ca^{2+}. The bone fails to mineralize normally in the newly laid area, becomes soft → rickets in children and osteomalacia in adults. However, in contrast to *osteoporosis*, the organic matrix (osteoid) is normal in osteomalacia.

Retarded development of mandible, delayed/faulty eruption of teeth and defective tooth enamel are the dental complications of vit D deficiency.

Hypervitaminosis D It may occur due to chronic ingestion of large doses (~50,000 IU/day) or due to increased sensitivity of tissues to vit D. Manifestations are due to elevated plasma calcium and its ectopic deposition.

Hypercalcaemia, weakness, fatigue, vomiting, diarrhoea, sluggishness, polyuria, albuminuria, ectopic Ca^{2+} deposition (in soft tissues, blood vessels, parenchymal organs), renal stones hypertension, growth retardation in children.



Treatment: consists of withholding the vitamin, low calcium diet, plenty of fluid and corticosteroids.

Pharmacokinetics Vit D is well absorbed from intestines in the presence of bile salts. Malabsorption and steatorrhoea interfere with its absorption.

In the circulation, it is bound to a specific α globulin and is stored in the body, mostly in adipose tissues, for many months. It is hydroxylated in liver to active and inactive metabolites. The t½ of different forms varies from 1–18 days: 25-OHD$_3$, having the longest t½ , constitutes the primary circulating form.

Metabolites of vit D are excreted mainly in bile.

1 µg of cholecalciferol = 40 IU of vit D.

The daily requirement varies, depending on exposure to sunlight. It is estimated that if no vit D$_3$ is synthesized in the body, a dietary allowance of 400 IU/day will prevent deficiency symptoms.

Use

1. *Prophylaxis* (400 IU/day) and *treatment* (3,000–4,000 IU/day) of *nutritional vit D deficiency* which causes rickets in children and osteomalacia in adults.

2. *Metabolic rickets* These are a group of conditions in which tissues do not respond to normal doses of vit D. The active forms of vit D *Calcitriol* or *Alfacalcidol*, which do not need hydroxylation by kidney, are effective in these conditions.

3. *Senile or postmenopausal osteoporosis* Age-related decrease in calcium absorption from gut has been noted. Vit D$_3$ + calcium have been shown to improve calcium balance in osteoporotic females and elderly males.

4. *Hypoparathyroidism* Calcitriol/alfacalcidol are more effective than vit D$_2$ or D$_3$ because they act quickly and directly without the need for hydroxylation in kidney which needs PTH.

BISPHOSPHONATES

Bisphosphonates (BPNs e.g. *Etidronate, Pamidronate, Alendronate*) are analogues of pyrophosphate: carbon atom replacing oxygen in the P-O-P skeleton. They inhibit bone resorption and have recently attracted considerable attention because of their ability to prevent osteoporosis in addition to their usefulness in metabolic bone diseases and hypercalcemia.

The BPNs have strong affinity for calcium phosphate, therefore exert selective action in calcified tissue. They have also been shown to affect isoprenoid lipid synthesis. The net result is:

- Accelerated apoptosis of osteoclasts reducing their number.
- Disruption of cytoskeleton and ruffled border of osteoclasts.

In addition, BPNs appear to affect osteoclast precursors and inhibit their differentiation by suppressing IL-6.

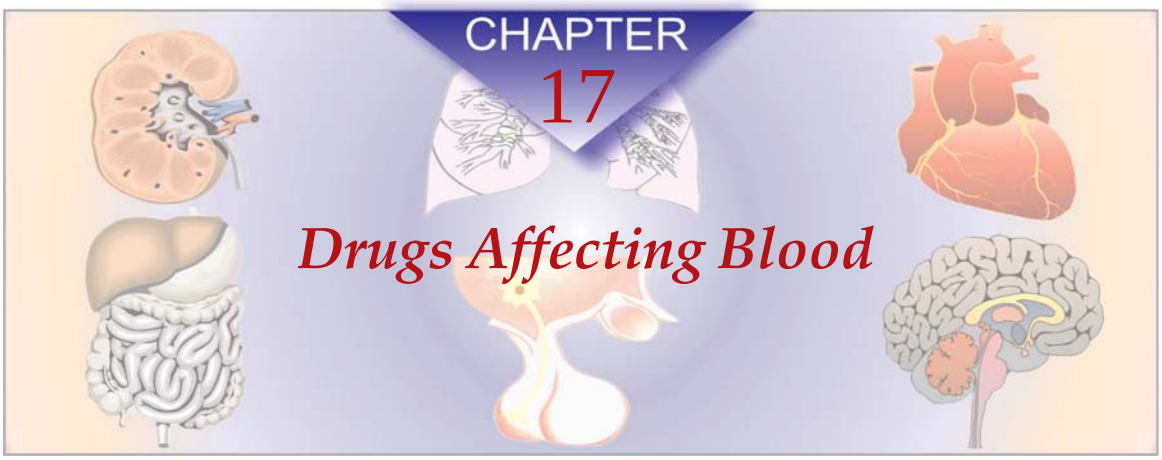
The BPNs are useful in conditions characterized by enhanced bone turnover.

1. *Osteoporosis* The second generation BPNs (alendronate) are effective in preventing and treating postmenopausal osteoporosis in women as well as idiopathic and steroid-induced osteoporosis in both men and women.

2. *Paget's disease* This disease due to abnormal osteoclast function producing disordered bone architecture is benefited by BPNs. They arrest osteolytic lesions, reduce bone pain and improve secondary symptoms.

3. *Osteolytic bone metastasis* Parenteral pamidronate arrests osteolytic lesions and reduces bone pain.

4. *Hypercalcaemia of malignancy* Pamidronate and etidronate injected i.v. normalise plasma Ca^{2+} level.



CHAPTER 17

Drugs Affecting Blood

HAEMATINICS

Haematinics are substances required in the formation of blood, and are used for treatment of anaemias.

Anaemia occurs when the balance between production and destruction of RBCs is disturbed by:

(a) Blood loss (acute or chronic).
(b) Impaired red cell formation due to:
i. Deficiency of essential factors, i.e. iron, vitamin B_{12}, folic acid.
ii. Bone marrow depression (hypoplastic anaemia), erythropoietin deficiency.
(c) Increased destruction of RBCs (haemolytic anaemia).

IRON

Iron is an essential body constituent. Total body iron in an adult is 2.5–5 g (average 3.5 g). It is more in men (50 mg/kg) than in women (38 mg/kg) and is distributed into:

Haemoglobin (Hb)	66%
Iron stores as ferritin and haemosiderin	25%
Myoglobin (in muscles)	3%
Parenchymal iron (enzymes, etc.)	6%

To raise the Hb level of blood by 1 g/dl—about 200 mg of iron is needed. Though the primary reflection of iron deficiency occurs in blood, severe deficiency affects practically every cell. Oral ulceration, stomatitis, glossitis may even be early manifestations of iron deficiency. The daily iron requirement is:

Adult male	:	0.5–1 mg (13 µg/kg)
Adult female	:	1–2 mg (21 µg/kg)
Infants	:	60 µg/kg
Children	:	25 µg/kg
Pregnancy	:	3–5 mg (80 µg/kg).

Iron absorption, transport and excretion

Iron absorption occurs all over the intestine, but majority in the upper part. Dietary iron is present either as haeme or as inorganic iron. Haeme iron is better absorbed (up to 35%) than inorganic (~5%), but the former is a smaller fraction of the dietary iron. Inorganic iron is mostly in the ferric form; needs to be reduced to ferrous form before absorption can take place (Fig. 17.1). Two distinct iron transporters appear to function at the luminal surface and at the basolateral membrane of mucosal cells to regulate iron absorption. Gastric acid, reducing substances (ascorbic acid) and amino acids facilitate iron absorption, while antacids, tetracyclines, phosphates and phytates impede iron absorption.

Mucosal block The gut has a mechanism to prevent entry of excess iron in the body. Iron reaching inside mucosal cell is either transported to plasma or oxidised to ferric form and complexed with apoferritin to form ferritin (Fig. 17.1). This ferritin generally remains stored in the mucosal cells and is lost when they are shed (lifespan 2–4 days). This is called the 'Ferritin Curtain'.

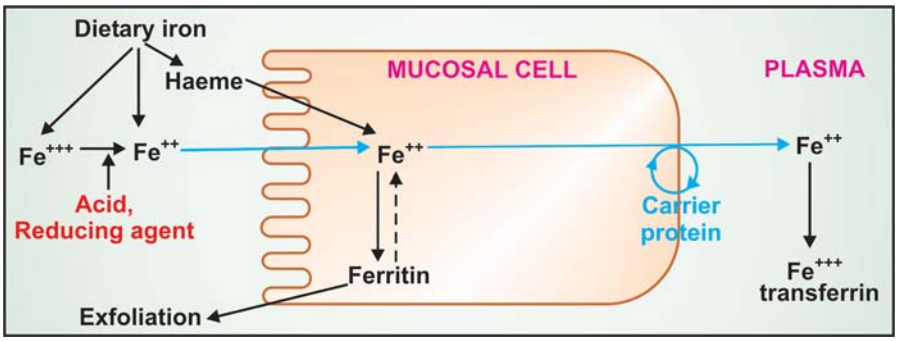


Fig. 17.1: Schematic representation of intestinal absorption of iron and the 'mucosal block'

The iron status of the body and erythropoietic activity govern the balance between these two processes, a larger percentage is absorbed during iron deficiency.

Iron is transported in blood in combination with a glycoprotein *transferrin*. It is transported into cells through attachment of transferrin to specific membrane bound receptors. In iron deficiency the erythron becomes selectively more efficient in trapping iron. Iron is stored in RE cells in liver, spleen, bone marrow, also in hepatocytes and myocytes as ferritin and haemosiderin. Plasma iron derived from destruction of old RBCs (lifespan–120 days), from stores and from intestinal absorption forms a common pool that is available for erythropoiesis, to all other cells and for restorage.

Oral iron The preferred route of iron administration is oral in the form of dissociable ferrous salts.

1. Ferrous sulfate: (hydrated salt 20% iron, dried salt 32% iron) is the cheapest. It often leaves a metallic taste in mouth.
2. Ferrous gluconate (12% iron).
3. Ferrous fumarate (33% iron): is less water soluble than ferrous sulfate and tasteless.
4. Colloidal ferric hydroxide (50% iron).

Other forms of iron present in oral formulations are:

Ferrous succinate (35% iron)
Iron calcium complex (5% iron)
Ferric ammonium citrate (scale iron)
Iron hydroxy polymaltose

These are claimed to be better absorbed and/or produce less bowel upset, but this is primarily due to lower iron content.

The elemental iron content and not the quantity of iron compound per dose unit should be taken into consideration.

A total of 200 mg elemental iron (infants and children 3–5 mg/kg) given daily in 3 divided doses produces the maximal haemopoietic response. Prophylactic dose is 30 mg iron daily.

Adverse effects of oral iron These are common, but individuals differ in susceptibility.

Epigastric pain, heart burn, nausea, vomiting, staining of teeth, metallic taste.

Constipation is more common (believed to be due to astringent action of iron) than diarrhoea (thought to reflect irritant action). However, these may be caused by alteration of intestinal flora as well.

Parenteral iron

Iron therapy by injection is indicated only when:

1. Oral iron is not tolerated: bowel upset is too much.
2. Failure to absorb oral iron.
3. Non-compliance to oral iron.
4. In presence of severe deficiency with chronic bleeding.

Rate of response with parenteral iron is not faster than that with optimal doses given orally. However, stores can be replenished in a shorter time by parenteral therapy.

Two organically complexed preparations for parenteral use are:

(i) Iron-dextran: as a colloidal solution containing 50 mg elemental iron/ml is the preparation of choice.

(ii) Iron-sorbitol-citric acid complex: 50 mg iron/ml.

Both are injected i.m. using Z track technique. Iron dextran can also be infused i.v., but this is more risky.

Pain at site of i.m. injection, pigmentation of skin, sterile abscess are the local complications.

Fever, headache, joint pains, flushing, palpitation, chest pain, dyspnoea are the systemic adverse effects.

An anaphylactoid reaction resulting in vascular collapse and death occurs rarely.

Use

Prophylaxis and treatment of iron deficiency anaemia is the most important indication for medicinal iron. A rise in Hb level by 0.5–1 g/dl per week is an optimum response to iron therapy. Treatment should be continued till normal Hb level is attained (generally takes 1–3 months depending on the severity) and 2–4 months thereafter to replenish the stores because after correction of anaemia, iron absorption is slow.

Iron is given in megaloblastic anaemia along with vit B_{12}/folic acid so that existing iron deficiency may not be unmasked when brisk haemopoiesis is induced by the maturation factors.

Ferric chloride is used in throat paint as an astringent.

VITAMIN B_{12}

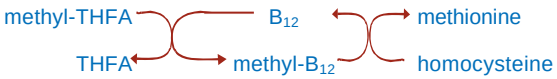
Cyanocobalamin and hydroxocobalamin are complex cobalt containing compounds present in the diet and referred to as vit B_{12}.

Vit B_{12} occurs as water soluble, thermostable red crystals. It is synthesized in nature only by microorganisms; plants and animals acquire it from them. Vit B_{12} is synthesized by the colonic microflora, but this is not available for absorption in man.

Daily requirement: is 1–3 µg; in pregnancy and lactation it is 3–5 µg.

Metabolic functions Vit B_{12} is intricately linked with folate metabolism in many ways; megaloblastic anaemia occurring due to deficiency of either is indistinguishable. In addition, vit B_{12} has some independent metabolic functions as well. The active coenzyme forms of B_{12} generated in the body are *deoxyadenosyl-cobalamin* (DAB_{12}) and *methyl-cobalamin* (methyl B_{12}).

(i) Vit B_{12} is essential for the conversion of homocysteine to methionine



Methionine is needed as a methyl group donor in many metabolic reactions and for protein synthesis. This reaction is also critical in making tetrahydrofolic acid (THFA) available for reutilization. In B_{12} deficiency THFA gets trapped in the methyl form and a number of *one carbon* transfer reactions suffer.

(ii) Purine and pyrimidine synthesis is affected primarily due to defective 'one carbon' transfer because of 'folate trap'.

(iii) Malonic acid $\xrightarrow{DAB_{12}}$ Succinic acid:
is an important step in propionic acid metabolism. This reaction does not require folate and has been considered to be responsible for demyelination seen in B_{12} deficiency, but not in pure folate deficiency.

(iv) Now it appears that interference with the reaction:

Methionine $\xrightarrow{DAB_{12}}$ S-adenosyl methionine

may be more important in the neurological damage of B_{12} deficiency, because it is needed in the synthesis of phospholipids and myelin.

(v) Vit B_{12} is essential for cell growth and multiplication.

Utilization of vit B_{12} Intrinsic factor (a glycoprotein) secreted by stomach is essential for absorption of B_{12} ingested in physiological amounts. Vit B_{12} is transported in blood in combination with a specific β globulin *transcobalamin II* (TCII).

Vit B_{12} is not degraded in the body. It is excreted mainly in bile (3–7 µg/day), all but 0.5–1 µg of this is reabsorbed. Thus, in the absence of intrinsic factor or when there is malabsorption, B_{12} deficiency develops much more rapidly than when it is due to nutritional deficiency.

Vit B_{12} is completely absorbed after i.m. or deep s.c. injection. Normally, only traces of B_{12} are excreted in urine, but when pharmacological doses (> 100 µg) are given orally or parenterally—a large part is excreted in urine.

Deficiency B_{12} deficiency occurs due to absence of intrinsic factor secretion by stomach (pernicious anaemia in which there is autoimmune gastric mucosal damage, or chronic gastritis, gastric carcinoma, etc.), malabsorption, increased demand or nutritional deficiency.

Manifestations of deficiency are:

(a) Megaloblastic anaemia, neutrophils with hypersegmented nuclei, giant platelets.
(b) Glossitis, g.i. disturbances: damage to epithelial structures.
(c) Neurological: subacute combined degeneration of spinal cord; peripheral neuritis, paresthesias, depressed stretch reflexes; mental changes—poor memory, mood changes, hallucinations, etc.

Uses

1. Prevention and treatment of B_{12} deficiency. It is wise to add 1–5 mg of oral folic acid and an iron preparation, because reinstitution of brisk haemopoiesis may unmask deficiency of these factors.
2. Mega doses of B_{12} have been used in neuropathies, psychiatric disorders, cutaneous sarcoid and as a general tonic to allay fatigue, improve growth—value is questionable.

FOLIC ACID

Chemically, it is *Pteroyl glutamic acid (PGA)* consisting of pteridine + paraaminobenzoic acid (PABA) + glutamic acid, which occurs as yellow crystals.

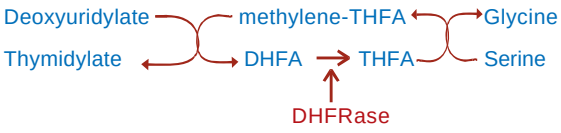
Daily requirement of an adult is < 0.1 mg, but dietary allowance of 0.2 mg/day is recommended. During pregnancy, lactation or any condition of high metabolic activity, 0.8 mg/ day is considered appropriate.

Utilization Small, physiological amounts of folic acid are absorbed by specific carrier-mediated active transport in the intestinal mucosa. Large pharmacological doses may gain entry by passive diffusion, but only a fraction is absorbed.

Folic acid is rapidly extracted by tissues and stored in cells as polyglutamates. Liver takes up a large part and secretes methyl-THFA in bile which is mostly reabsorbed. Normally, only traces are excreted, but when pharmacological doses are given, 50–90% of a dose may be excreted in urine.

Metabolic functions Folic acid is inactive as such and is reduced to the coenzyme form in two steps: FA → DHFA → THFA by folate reductase (FRase) and dihydrofolate reductase (DHFRase). THFA mediates a number of *one carbon* transfer reactions by carrying a methyl group as an adduct.

1. Conversion of homocysteine to methionine.
2. Generation of thymidylate, an essential constituent of DNA:



3. Conversion of serine to glycine: needs THFA and results in the formation of methylene-THFA which is utilized in thymidylate synthesis.
4. Purine synthesis: *de novo* building of purine ring requires formyl-THFA and methenyl-THFA.
5. Generation and utilization of 'formate pool'.
6. Histidine metabolism.

Deficiency Folate deficiency occurs due to:
(a) Inadequate dietary intake
(b) Malabsorption: coeliac disease, tropical sprue, regional ileitis, etc.
(c) Chronic alcoholism.
(d) Increased demand: pregnancy, lactation, rapid growth periods, haemolytic anaemia.
(e) Drug induced: prolonged therapy with anticonvulsants (phenytoin, phenobarbitone, primidone) and oral contraceptives—interfere with absorption and storage of folate.

Manifestations of deficiency are:
(i) Megaloblastic anaemia, indistinguishable from that due to B_{12} deficiency.
(ii) Epithelial damage: glossitis, enteritis, diarrhoea, steatorrhoea.
(iii) General debility, weight loss, sterility.

Uses

1. *Megaloblastic anaemias* due to nutritional folate deficiency, periods of increased folate demand, malabsorption or antiepileptic therapy.

Folic acid should never be given alone to patients with B_{12} deficiency—haematological response may occur, but neurological defect may progress due to diversion of meagre amount of B_{12} present in body to haemopoiesis.

2. *Prophylaxis* of folate deficiency: only when definite predisposing factors are present.

3. *Methotrexate toxicity*: Folinic acid (Leucovorin, citrovorum factor, 5-formyl-THFA) an active coenzyme form is used. Methotrexate is a DHFRase inhibitor; its toxicity is not counteracted by folic acid, but antagonized by folinic acid.

4. *Citrovorum factor rescue*: In certain malignancies, high dose of methotrexate is injected i.v. and is followed within ½–2 hours with 1–3 mg i.v. of folinic acid to rescue the normal cells.

COAGULANTS

These are agents which promote coagulation, and are indicated in haemorrhagic states.

Haemostasis and blood coagulation involve complex interactions between the injured vessel wall, platelets and coagulation factors. A cascading series of proteolytic reactions (Fig. 17.2) is started by:
(i) Contact activation of Hageman factor: *intrinsic system*, in which all factors needed for coagulation are present in plasma. This is slow and takes several minutes to activate factor X.
(ii) Tissue thromboplastin: *extrinsic system*, needs a tissue factor, but activates factor X in seconds.

The subsequent events are common in the two systems and result in the formation of fibrin meshwork in which blood cells are trapped and clot is formed.

Most clotting factors are proteins present in plasma in the inactive (zymogen) form. By partial proteolysis, they themselves become active proteases and activate the next factor. On the other hand, factors like *antithrombin*, *protein C*, *antithromboplastin* and the *fibrinolysin system* tend to oppose coagulation and lyse formed clot. Thus, a check and balance system operates to maintain blood in a fluid state while in circulation and allows rapid haemostasis following injury.

Fresh whole blood or plasma provide all the factors needed for coagulation and are the best therapy for deficiency of any clotting factor; also they act immediately. Drugs used to restore haemostasis are:

1. *Vitamin K*
   K_1 : Phytonadione (Phylloquinone)
   K_3 (synthetic)
   - Fat soluble : Menadione, Acetomenaphthone
   - Water soluble : Menadione sod. bisulfite, Menadione sod. diphosphate
2. Fibrinogen (human)
3. Antihaemophilic factor
4. Ethamsylate.

Vitamin K

It is a fat-soluble dietary principle required for the synthesis of clotting factors.

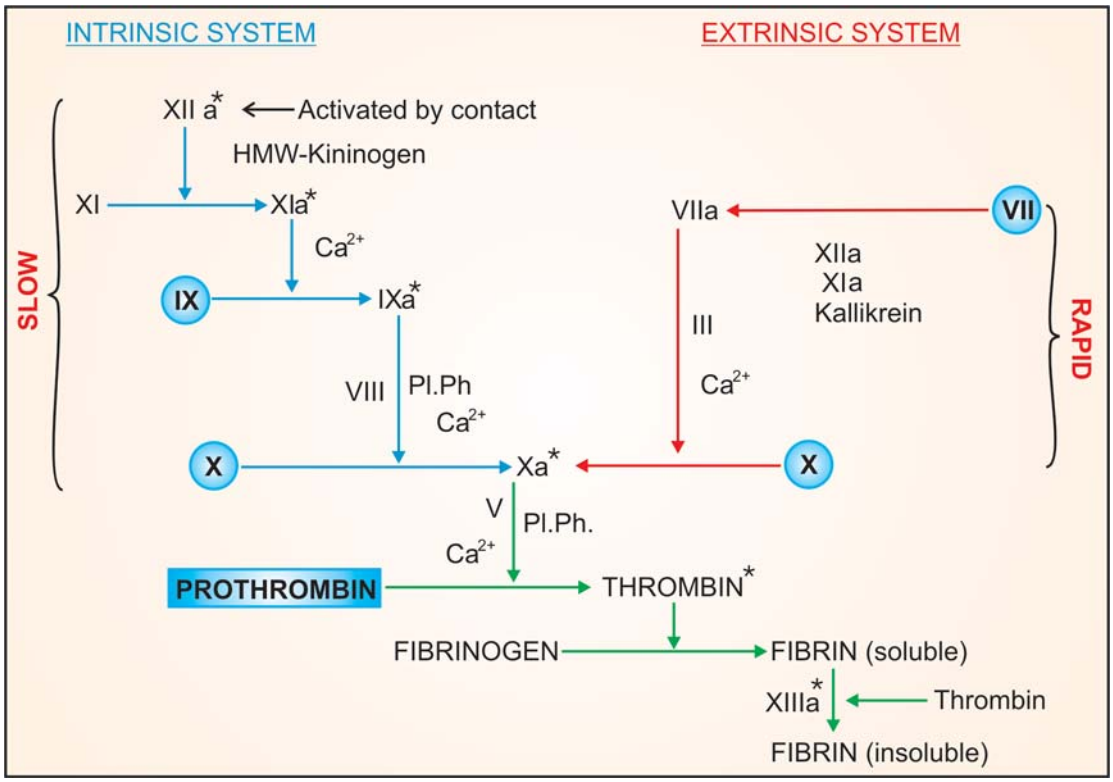


Fig. 17.2: The coagulation cascade. The vit. K dependent factors have been encircled;* Inactivated by heparin; a—activated form; Pl.Ph.—Platelet phospholipid; HMW—High molecular weight

Vit K has a basic naphthoquinone structure, with or without a side chain.

Daily requirement of vit K is uncertain, because a variable amount becomes available from colonic bacteria. Even 3–10 µg/day external source may be sufficient. However, the total requirement of an adult has been estimated to be 50–100 µg/day.

Vit K acts as a cofactor at a late stage in the synthesis by liver of coagulation proteins—prothrombin, factors VII, IX and X. The vit K dependent change (γ carboxylation of glutamate residues of these zymogen proteins; *see* Fig. 17.3) confers on them the capacity to bind Ca^{2+} and to get bound to phospholipid surfaces—properties essential for participation in the coagulation cascade.

Fat-soluble forms of vit K are absorbed from intestine *via* lymph and require bile salts for absorption, while water-soluble forms are absorbed directly into portal blood. Vit K is only temporarily concentrated in liver, but there are no significant stores in the body. It is metabolized in liver by side chain cleavage and glucuronide conjugation; metabolites are excreted in bile and urine.

Deficiency Deficiency of vit K occurs due to liver disease, obstructive jaundice, malabsorption, long-term antimicrobial therapy which alters intestinal flora. However, deficient diet is rarely responsible. The most important manifestation is bleeding tendency due to lowering of the levels of prothrombin and other clotting factors in blood. Haematuria is usually first to occur; other common sites of bleeding are g.i.t., nose and under the skin—ecchymoses.

Use The only use of vit K is in prophylaxis and treatment of bleeding due to deficiency of clotting factors in the above situations.

All newborns have low levels of prothrombin and other clotting factors. Vit K 1 mg i.m. soon after birth has been recommended routinely. Menadione (K_3) should not be used for this purpose (*see* below).

Another important indication of vit K is to reverse the effect of overdose of oral anticoagulants: Phytonadione (K_1) is the preparation of choice, because it acts most rapidly; dose depends on the severity of hypoprothrombinaemia (measured INR) and bleeding. Unnecessary high dose is to be avoided because it will render the patient unresponsive to oral anticoagulants for several days.

Menadione and its water-soluble derivatives can cause haemolysis in a dose-dependent manner. Patients with G-6-PD deficiency and neonates are specially susceptible. In the newborn menadione or its salts can precipitate kernicterus:
(a) by inducing haemolysis and increasing bilirubin load.
(b) by competitively inhibiting glucuronidation of bilirubin.

Fibrinogen The fibrinogen fraction of human plasma is employed to control bleeding in haemophilia, antihaemophilic globulin (AHG) deficiency and acute afibrinogenemic states; 0.5 g is infused i.v.

Antihaemophilic factor It is concentrated human AHG prepared from pooled human plasma. It is indicated (along with human fibrinogen) in haemophilia and AHG deficiency. It is highly effective in controlling bleeding episodes, but action is short lasting (1 to 2 days).

Ethamsylate It reduces capillary bleeding when platelets are adequate; probably exerts antihyaluronidase action—improves capillary wall stability. It is also claimed to inhibit PGI_2 production and correct abnormal platelet function, but does not stabilize fibrin (not an antifibrinolytic). It has been used in the prevention and treatment of capillary bleeding in menorrhagia, after abortion, epistaxis, malena, hematuria and after tooth extraction. Side effects are nausea, rash, headache, and fall in BP (only after i.v. injection).

Haemostasis in dentistry

Many dental procedures cause at least some bleeding: the dentist has to routinely deal with haemostasis (arrest of blood loss). After tooth extraction or similar procedures, bleeding occurs due to disruption of arterioles and smaller blood vessels, which cannot be sutured. Normal haemostasis occurs successively by contraction of injured vessel wall (lasting few minutes), adhesion and aggregation of platelets to form a plug, formation of a blood clot, and finally in due course dissolution of the clot by fibrinolysis.

Postextraction bleeding from the tooth socket is usually arrested by a cotton-gauze pressure pack held for 20 to 30 min. Suturing may be required if bleeding is due to tear around the socket. Control of bleeding may need to be aided by the use of local haemostatics.

Local Haemostatics (styptics) are substances used to stop bleeding from a local and approachable site. They are particularly effective on oozing surfaces, e.g. tooth socket, abrasions, etc. Absorbable materials like *fibrin* (prepared from human plasma and dryed as sheet or foam), *gelatin foam*, *oxidized cellulose* (as strips which can be cut and placed in the socket) provide a meshwork which activates the clotting mechanism and checks bleeding. Left *in situ* these materials are absorbed in 1–4 weeks and generally cause no foreign body reaction. *Thrombin* obtained from bovine plasma may be applied as dry powder or freshly prepared solution to the bleeding surface in haemophiliacs. *Vasoconstrictors* like 1% Adr solution may be soaked in sterile cotton-gauze and packed in the bleeding socket (or nose in case of epistaxis) to check bleeding when vasoconstriction is inadequate. *Astringents* such as tannic acid or metallic salts are occasionally applied for bleeding gums, bleeding piles, etc.

Many diseases and drugs can affect the vascular response to injury, platelet function or coagulation to create haemostatic problems. When dental surgery is contemplated in patients with such defects, careful planning and consultation with their physician are needed.

1. Vitamin C deficiency impairs collagen synthesis and causes bleeding gums, excessive postextraction blood loss. Scurvy should be corrected before elective dental surgery. In case of emergency surgery, careful packing and pressure can stop the bleed. Long-term corticosteroid therapy can also compromise haemostasis by impairing vessel retraction as well as by reducing platelet count.
2. Platelet function may be deficient due to thrombocytopenia (count<100,000/mL) or use of drugs which inhibit platelet aggregation. Transfusion of platelet-rich plasma is indicated before dental surgery in patients with low platelet count. Corticosteroid therapy helps to restore platelet count in idiopathic thrombocytopenic purpura. Aspirin and other NSAIDs are the most important drugs that inhibit platelet aggregation. A large number of older individuals now receive long-term low-dose aspirin prophylaxis for ischaemic heart disease or stroke. Many arthritis patients regularly take NSAIDs. Discontinuation of aspirin for 5 days (other antiplatelet drugs for periods appropriate to their duration of action) before dental surgery should be considered. In case this is not possible, proper packing and use of local haemostatics is needed to prevent excess bleeding.
3. Even minor dental procedures (like scaling) put the haemophiliac patient at great risk of bleeding. The patient should be covered before and after the procedure with i.v. infusion of antihaemophilic factor (AHG or factor VIII) along with fibrinogen. The antifibrinolytic drug tranexaemic acid has adjuvant value by reducing the requirement of AHG. Desmopressin injected i.v. also helps in checking dental bleeding in haemophiliacs as well as in von Willebrand's disease by releasing factor VIII and von Willebrand's factor from vascular endothelium.
4. Any oral surgery in patients on anticoagulant medication requires due care to avoid excessive bleeding. Since the action of i.v. heparin lasts for only 4–6 hours, the extraction can be scheduled at a time when anticoagulation is minimal. Low dose s.c. heparin and LMW heparin therapy ordinarily does not increase dental surgery associated bleeding. The heparin antagonist protamine may be given i.v. in case of emergency bleed.

In patients treated with oral anticoagulants, due consultation with their physician and monitoring of their INR prior to dental surgery is essential. An INR of <3 generally does not increase bleeding due to simple extractions, but in case of more invasive procedures, it may be advisable to stop the anticoagulant for 2–3 days or temporarily switch over the patient to heparin. In case of emergency dental bleed, the effect of oral anticoagulant is reversed by i.v. infusion of fresh frozen plasma (containing all coagulation factors) with or without vit K. Adequate packing and local measures must be applied.

ANTICOAGULANTS

These are drugs used to reduce the coagulability of blood. They may be classified into:

1. Used *in vivo*

A. *Parenteral anticoagulant*
Heparin, Low molecular weight heparin.

B. *Oral anticoagulants*

(i) *Coumarin derivatives*: Bishydroxycoumarin (Dicumarol), Warfarin sod, Acenocoumarol (Nicoumalone), Ethylbiscoumacetate

(ii) *Indandione derivative*: Phenindione.

2. Used *in vitro*

A. Heparin

B. Calcium complexing agents:
Sodium citrate: used to keep blood in the fluid state for transfusion;

Sodium oxalate, Sodium edetate } used in blood taken for investigations

HEPARIN

Heparin is a non-uniform mixture of straight chain mucopolysaccharides with MW 10,000 to 20,000. It contains polymers of two sulfated disaccharide units:

D-glucosamine-L-iduronic acid, D-glucosamine-D-glucuronic acid } chain length and proportion of the two disaccharide units varies. Some glucosamine residues are N-acetylated.

It carries strong electronegative charges and is the strongest organic acid present in the body. It occurs in mast cells loosely bound to the granular protein. Commercially, it is produced from ox lung and pig intestinal mucosa.

Actions

1. *Anticoagulant* Heparin is a powerful and instantaneously acting anticoagulant, effective both *in vivo* and *in vitro*. It acts indirectly by activating plasma antithrombin III (AT III, a serine proteinase inhibitor). The heparin-AT III complex then binds to clotting factors of the intrinsic and common pathways (Xa, IIa, IXa, XIa, XIIa and XIIIa) and inactivates them but not factor VIIa operative in the extrinsic pathway. At low concentrations of heparin, factor Xa mediated conversion of prothrombin to thrombin is selectively affected. The anticoagulant action is exerted mainly by inhibition of factor Xa as well as thrombin (IIa) mediated conversion of fibrinogen to fibrin.

Low concentrations of heparin prolong activated partial thromboplastin time (aPTT) without significantly prolonging prothrombin time (PT). High concentrations prolong both. Thus, low concentrations interfere selectively with the intrinsic pathway, while high concentrations affect the common pathway as well.

2. *Antiplatelet* Heparin in higher doses inhibits platelet aggregation and prolongs bleeding time.

3. *Lipaemia clearing* Injection of heparin clears turbid post-prandial lipaemic plasma by releasing a lipoprotein lipase from the vessel wall and tissues, which hydrolyses triglycerides of chylomicra and very low density lipoproteins to free fatty acids; these then pass into tissues and the plasma looks clear.

Pharmacokinetics: Heparin is a large, highly ionized molecule; therefore not absorbed orally. Injected i.v. it acts instantaneously, but after s.c. injection anticoagulant effect develops after ~60 min. Heparin does not cross blood-brain barrier or placenta. It is metabolized in liver by heparinase and fragments are excreted in urine. Heparin is not a physiologically circulating anticoagulant.

After i.v. injection, dose-dependent inactivation is seen and t½ varies from 1–4 hours.

Heparin is conventionally given i.v. in bolus doses of 5,000–10,000 U every 4–6 hours, or the initial bolus dose is followed by continuous infusion. The dose and frequency is controlled by aPTT measurement which is kept at 50–80 sec. or 1.5–2.5 times the patient's pretreatment value.

Low dose (s.c.) regimen 5,000 U is injected s.c. every 8–12 hours; started before surgery and continued for 7–10 days or till the patient starts moving about. This regimen has been found to prevent postoperative deep vein thrombosis without increasing surgical bleeding. It also does not prolong aPTT or clotting time.

Adverse effects

1. Bleeding due to overdose is the most serious complication of heparin therapy. Aspirin, other NSAIDs and antiplatelet drugs enhance heparin-induced bleeding. They should be used very cautiously in heparinized patients.
2. Thrombocytopenia is another common problem.
3. Osteoporosis and alopecia are infrequent.

Low molecular weight (LMW) heparins

Heparin has been fractionated into LMW forms (MW 3,000–7,000) by different techniques. LMW heparins have a different anticoagulant profile; selectively inhibit factor Xa with little effect on IIa. As a result, LMW heparins have smaller effect on aPTT and whole blood clotting time than unfractionated heparin (UFH) relative to

antifactor Xa activity. Also, they appear to have lesser antiplatelet action—less interference with haemostasis. The more important advantages of LMW heparins are pharmacokinetic:

- Better subcutaneous bioavailability.
- Longer and more consistent monoexponential t½: once daily s.c. administration.
- Since aPTT/clotting times are not prolonged, laboratory monitoring is not needed.

Indications of LMW heparins are:

1. Prophylaxis of deep vein thrombosis and pulmonary embolism in high-risk patients undergoing surgery, stroke or other immobilized patients.
2. Treatment of established deep vein thrombosis.
3. Unstable angina.
4. To maintain patency of cannulae and shunts in dialysis patients, and in extracorporeal circulation.

A number of LMW heparins (Enoxaparin, Raviparin, Dalteparin, Nadroparin, etc.) have been marketed.

Heparin antagonist

Protamine sulfate is a strongly basic, low molecular weight protein obtained from the sperm of certain fish. Given i.v. it neutralises heparin weight for weight, i.e. 1 mg is needed for every 100 U of heparin. It is used when heparin action needs to be terminated rapidly, e.g. after cardiac or vascular surgery and for heparin-induced bleeding.

ORAL ANTICOAGULANTS

Warfarin and its congeners act as anticoagulants only *in vivo*, not *in vitro*. This is so because they act indirectly by interfering with the synthesis of vit K dependent clotting factors in liver. They apparently behave as competitive antagonists of vit K and reduce the plasma levels of functional clotting factors in a dose-dependent manner. In fact, they interfere with regeneration of the active hydroquinone form of vit K (Fig. 17.3) which carries out the final step of γ carboxylating

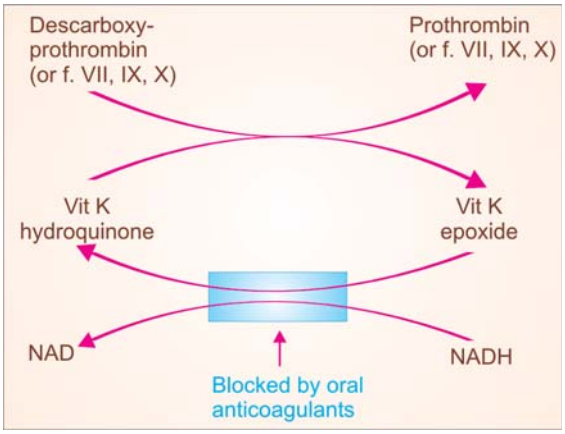


Fig. 17.3: Mechanism of action of oral anticoagulants
NAD—Nicotinamide adenine dinucleotide; NADH—its reduced form

glutamate residues of prothrombin and factors VII, IX and X. This carboxylation is essential for the ability of the clotting factors to bind Ca^{2+} and to get bound to phospholipid surfaces, necessary for coagulation sequence to proceed.

Factor VII has the shortest plasma t½ (6 hr), its level falls first when warfarin is given, followed by factor IX (t½ 24 hr), factor X (t½ 40 hr) and prothrombin (t½ 60 hr). The anticoagulant effect develops gradually over 1–3 days as the levels of the clotting factors already present in plasma decline progressively. Thus, there is always a delay between administration of the drug and the anticoagulant effect.

The differences between different oral anticoagulants are primarily pharmacokinetic and in the adverse side effects produced by them. These are summarized in Table 17.1.

Bleeding as a result of extension of the desired pharmacological action is the most important problem: ecchymosis, epistaxis, hematuria, bleeding in the g.i.t., intracranial or other internal haemorrhages may be fatal.

Treatment: of bleeding due to oral anticoagulants consists of:

- Withhold the anticoagulant.
- Give fresh blood transfusion. Alternatively, fresh frozen plasma may be used as a source of clotting factors.

Table 17.1: Pharmacokinetic and adverse effect profile of oral anticoagulants

Drug	t½	Duration of action	Dose (mg)		Adverse side effects (other than bleeding)
			Loading	Maintenance*	
1. Bishydroxycoumarin	25–100 hr (dose dependent)	4–7 days	200 for 2 days	50–100	Frequent g.i.t. disturbances
2. Warfarin sod.	36–48 hr	3–6 days	10–15	2–10	Alopecia, dermatitis, diarrhoea
3. Acenocoumarol (Nicoumalone)	18–24 hr	2–3 days	8–12	2–8	Oral ulceration, g.i.t. disturbances, dermatitis, urticaria, alopecia
4. Ethylbiscoumacetate	2 hr	1–3 days	900	300–600	Alopecia, bad taste
5. Phenindione	5 hr	1–3 days	200	50–100	Orange urine, rashes, fever, leukopenia, hepatitis, nephropathy, agranulocytosis

* Daily maintenance dose: to be adjusted by measurement of prothrombin time.

- Give vit K_1—specific antidote, but it takes 6–24 hours for the clotting factors to be resynthesized and released in blood after vit K administration.

Dose regulation The dose of oral anticoagulant must be individualized by repeated measurement of *prothrombin time*; the aim is to achieve a therapeutic effect without unduly increasing the chances of bleeding. A standardized system called the International Normalized Ratio (INR) based on the use of human brain thromboplastin has been developed by WHO to quantify the effect of oral anticoagulants. An INR of 2–4.5 is considered therapeutic for different indications. Many factors like diet, liver/kidney/bowel/thyroid disease, alcoholism, pregnancy and genetics affect the activity of oral anticoagulants.

Drug interactions A large number of drugs interact with oral anticoagulants and either enhance or depress their effect. These interactions are clinically important (may be fatal if bleeding occurs).

A. *Enhanced anticoagulant action*

1. Broad-spectrum antibiotics, inhibit gut flora and reduce vit K production.
2. Newer cephalosporins (cefamandole, moxalactam, cefoperazone) cause hypoprothrombinaemia by the same mechanism as warfarin —additive action.
3. Aspirin: inhibits platelet aggregation and causes g.i. bleeding—this may be hazardous in anticoagulated patients.
4. Sulfonamides, indomethacin, phenytoin displace warfarin from plasma protein binding.
5. Metronidazole, chloramphenicol, erythromycin, celecoxib, cimetidine, allopurinol and amiodarone inhibit warfarin metabolism.

B. *Reduced anticoagulant action*

1. Barbiturates and other hypnotics (but not benzodiazepines), rifampin and griseofulvin induce the metabolism of oral anticoagulants.
2. Oral contraceptives: increase blood levels of clotting factors.

Uses of anticoagulants The aim of using anticoagulants is to prevent thrombus extension and embolic complications by reducing the rate of fibrin formation. They do not dissolve already formed clot, but prevent recurrences.

1. *Deep vein thrombosis and pulmonary embolism* Because venous thrombi are mainly fibrin thrombi, anticoagulants are highly effective. Prophylaxis is needed by bedridden, old, postoperative, postpartum, poststroke and leg fracture patients. When deep vein thrombosis/pulmonary embolism has occurred, 3 months anticoagulant therapy has been recommended.

2. *Myocardial infarction (MI)* Arterial thrombi are mainly platelet thrombi; anticoagulants are

of questionable value. Their use in acute MI has declined.

Heparin (followed by oral anticoagulant) is generally given after recanalization of coronary artery by fibrinolytic therapy.

3. *Unstable angina* Short-term use of heparin has reduced the occurrence of MI. Current recommendation is to use aspirin + heparin followed by warfarin.

4. *Rheumatic heart disease, atrial fibrillation (AF)* Warfarin/low dose heparin/low dose aspirin are effective in preventing stroke (due to embolism from fibrillating atria). Anticoagulants are given for 3–4 weeks before and after attempting conversion of AF to sinus rhythm.

5. *Vascular surgery, prosthetic heart valves, retinal vessel thrombosis, extracorporeal circulation, haemodialysis* Anticoagulants are indicated along with antiplatelet drugs for prevention of thromboembolism.

The important features of heparin and oral anticoagulants are compared in Table 17.2.

FIBRINOLYTICS (Thrombolytics)

These are drugs used to lyse thrombi/clot to recanalize occluded blood vessels (mainly coronary artery). They are curative rather than prophylactic; work by activating the natural fibrinolytic system.

Haemostatic plug of platelets formed at the site of injury to blood vessels is reinforced by fibrin deposition to form a thrombus. Once repair is over, the fibrinolytic system is activated to remove fibrin. The enzyme responsible for digesting fibrin is a serine protease *Plasmin* generated from *plasminogen* by tissue plasminogen activator (t-PA), which is produced primarily by vascular endothelium. Plasminogen circulates in plasma as well as remains bound to fibrin. The t-PA selectively activates fibrin bound plasminogen within the thrombus.

Three fibrinolytics *Streptokinase, Urokinase* and *Alteplase* (rt-PA) are available. All are administered by i.v. injection. Haemorrhage is their major complication.

Streptokinase It is obtained from β haemolytic *Streptococci* group C and is inactive as such: combines with circulating plasminogen to form

Table 17.2: Some comparative aspects of heparin and oral anticoagulants

	Heparin	*Warfarin*
1. Chemistry	Mucopolysaccharide	Coumarin derivative
2. Source	Hog lung, pig intestine	Synthetic
3. Route of admin.	Parenteral (i.v., s.c.)	Oral
4. Onset of action	Immediate	Delayed (1–3 days)
5. Duration of action	4–6 hrs	3–6 days
6. Activity	*In vitro* and *in vivo*	*In vivo* only
7. Mechanism	Blocks action of factor X and thrombin	Inhibits synthesis of clotting factors
8. Antagonist	Protamine sulphate	Vit K
9. Variability in response	Little	Marked
10. Lab. control	aPTT/clotting time (desirable)	Prothrombin time/INR (essential)
11. Drug interactions	Few and not significant	Many and significant
12. Use	To initiate therapy	For maintenance

an activator complex which then causes limited proteolysis of other plasminogen molecules to plasmin. Its t½ is estimated to be 30–80 min.

Streptokinase is antigenic; can cause hypersensitivity reactions and anaphylaxis. Fever is common, hypotension and arrhythmias are reported.

Urokinase It is an enzyme isolated from human urine; now prepared from cultured human kidney cells which activates plasminogen directly and has a plasma t½ of 10–15 min. It is nonantigenic. Fever occurs during treatment, but hypotension and allergic phenomena are rare.

Alteplase (recombinant tissue plasminogen activator (r t-PA) Produced by recombinant DNA technology from human tissue culture, it specifically activates gel-phase plasminogen already bound to fibrin, and has little action on circulating plasminogen. It is rapidly cleared by liver and has a plasma t½ of 4–8 min. It is nonantigenic, but nausea, mild hypotension and fever may occur.

Uses of fibrinolytics

1. *Acute myocardial infarction* is the chief indication; now considered a first line approach if fibrinolytic therapy can be instituted within 12 hours of symptom onset. Time lag in starting infusion is critical for reducing area of necrosis, preserving ventricular function and reducing mortality. Heparin with or without aspirin is generally started concurrently or soon after thrombolysis to prevent reocclusion.

Fibrinolytic therapy has also been used in unstable angina.

2. *Deep vein thrombosis* in leg, pelvis, shoulder, etc.; up to 60% patients can be successfully treated.

3. *Pulmonary embolism* Fibrinolytic therapy is indicated in large, life-threatening pulmonary embolism.

ANTIFIBRINOLYTICS

These are drugs which inhibit plasminogen activation and dissolution of clot.

Epsilon amino-caproic acid (EACA) It is an analogue of the amino acid lysine: combines with the lysine binding sites of plasminogen and plasmin so that the latter is not able to bind to fibrin and lyse it. It is a specific antidote for fibrinolytic agents and has been used in many hyperplasminaemic states associated with excessive intravascular fibrinolysis resulting in bleeding.

Tranexaemic acid Like EACA, it binds to the lysine binding site on plasminogen and prevents its combination with fibrin and is 7 times more potent. Antifibrinolytics are used to prevent/control excessive bleeding in the following situations:

- Overdose of fibrinolytics
- After cardio-pulmonary bypass surgery.
- After tooth extraction, tonsillectomy, prostatic surgery in haemophiliacs.
- Menorrhagia, especially due to IUCD.
- Recurrent epistaxis, ocular trauma, bleeding peptic ulcer.

Main side effects are nausea and diarrhoea. Headache, giddiness and thromboflebitis of injected vein are other adverse effects.

ANTIPLATELET DRUGS (Antithrombotic drugs)

These are drugs which interfere with platelet function and may be useful in the prophylaxis of thromboembolic disorders. However, all of them are likely to accentuate dental surgery related bleeding.

Platelets stick to the damaged vessel wall, then they stick to each other (aggregate) and release ADP, thromboxane A_2 (TXA_2) which promote further aggregation. Thus, a 'platelet plug' is formed.

Prostacyclin (PGI_2), synthesized in the intima of blood vessels, is a strong inhibitor of platelet aggregation. A balance between TXA_2 released from platelets and PGI_2 released from vessel wall appears to control intravascular thrombus formation.

Drugs interfering with platelet function are:

Aspirin	Clopidogrel
(other NSAIDs)	Abciximab
Dipyridamole	(GP II_b/III_a antagonist)
Ticlopidine	

Aspirin It acetylates the enzyme cyclooxygenase (COX) and TX-synthetase—inactivating them irreversibly. Because platelets are exposed to aspirin in the portal circulation before it is deacetylated during first pass in liver, and because platelets cannot synthesize fresh enzyme (have no nuclei), TXA_2 formation is suppressed at very low doses and till fresh platelets are formed. Thus, aspirin induced prolongation of bleeding time lasts for 5–7 days. Effect of daily doses cumulates and it has now been shown that doses as low as 40 mg/day have an effect on platelet aggregation. Maximal inhibition of platelet function occurs at ~160 mg aspirin per day.

Aspirin also inhibits PGI_2 synthesis in vessel wall. However, since intimal cells can synthesize fresh enzyme, activity returns rapidly. It is possible that at low doses (75–150 mg/day), TXA_2 formation by platelets is selectively suppressed, whereas higher doses (> 900 mg/day) may decrease both TXA_2 and PGI_2 production.

Aspirin inhibits the release of ADP from platelets and their sticking to each other. However, it has no effect on platelet survival time and their adhesion to damaged vessel wall.

Other NSAIDs are reversible inhibitors of COX, produce short-lasting inhibition of platelet function—are not clinically useful but can prolong bleeding time for variable periods.

Dipyridamole It is a vasodilator which was introduced for angina pectoris (*see* Ch.11). It inhibits phosphodiesterase and blocks uptake of adenosine to increase platelet cAMP which potentiates PGI_2 and interferes with aggregation. Levels of TXA_2 or PGI_2, are not altered, but platelet survival time reduced by disease is normalized.

Dipyridamole used along with warfarin decreases the incidence of thromboembolism in patients with prosthetic heart valves.

It has also been used to enhance the antiplatelet action of aspirin. Risk of stroke in patients with transient ischaemic attacks (TIAs) may be additively reduced.

Ticlopidine It is the first thienopyridine which alters surface receptors on platelets and inhibits ADP as well as fibrinogen-induced platelet aggregation. It prevents fibrinogen binding to platelets without modifying $GPII_b/IIIa$ receptor. There is no effect on platelet TXA_2, but bleeding time is prolonged and platelet survival in extracorporeal circulation is increased. Because of different mechanism of action, it has synergistic effect on platelets with aspirin: combination is a potent platelet inhibitor.

Ticlopidine has produced beneficial effects in stroke prevention, TIAs, intermittent claudication, unstable angina, coronary artery bypass grafts and secondary prophylaxis of MI. Combined with aspirin, it has markedly lowered incidence of restenosis after percutaneous transluminal coronary angioplasty (PTCA) and stent thrombosis.

Side effects: Diarrhoea, vomiting, abdominal pain, headache, tinnitus, skin rash, bleeding, rarely neutropenia, thrombocytopenia and jaundice.

Clopidogrel This newer congener of ticlopidine has similar mechanism of action, ability to inhibit platelet function and therapeutic efficacy, but appears to be better tolerated. Side effects are diarrhoea, epigastric pain and rashes.

Glycoprotein (GP) II_b/III_a receptor antagonists

GP II_b/III_a antagonists are a new class of potent platelet aggregation inhibitors which act by blocking the key receptor involved in platelet aggregation. The GP II_b/III_a is an adhesive receptor (integrin) for fibrinogen and von Willebrand's factor through which agonists like collagen, thrombin, TXA_2, ADP, etc. induce platelet aggregation. Thus, GP II_b/III_a antagonists block aggregation induced by all platelet agonists.

Abciximab It is the Fab fragment of a chimeric monoclonal antibody against GP II_b/III_a. Given along with aspirin + heparin during PTCA, it has markedly reduced the incidence of restenosis, subsequent MI and death.

Abciximab is nonantigenic. The main risk is haemorrhage. Thrombocytopenia is another complication.

Uses of antiplatelet drugs

1. *Coronary artery disease*

MI: Low dose aspirin started immediately after MI has been found to reduce mortality and prevent reinfarction. Ticlopidine and clopidogrel are alternatives. Aspirin is now routinely used to prevent reocclusion after thrombolytic therapy. It is also given along with heparin to cover PTCA.

Unstable angina Aspirin reduces the risk of MI and sudden death.

Primary and secondary prevention of MI It has been recommended that aspirin 75–150 mg/day be given to all individuals with evidence of coronary artery disease and in those with risk factors for the same, but routine use in the whole population is not warranted.

2. *Cerebrovascular disease* Antiplatelet drugs do not alter the course of stroke due to cerebral thrombosis. However, aspirin has reduced the incidence of TIAs, of stroke in patients with TIAs or persistent atrial fibrillation and in those with history of stroke in the past. Ticlopidine and clopidogrel also reduce TIAs and stroke.

3. *Coronary bypass implants* The patency of implanted bypass vessel is improved and incidence of reocclusion is reduced by aspirin and/or ticlopidine/clopidogrel.

4. *Prosthetic heart valves and arteriovenous shunts* Antiplatelet drugs, used with warfarin reduce formation of microthrombi on artificial heart valves and the incidence of embolism. Antiplatelet drugs also prolong the patency of chronic arteriovenous shunts.

5. *Peripheral vascular disease* Aspirin/ticlopidine/clopidogrel may produce some improvement in intermittent claudication and reduce the incidence of thromboembolism.

HYPOLIPIDAEMIC DRUGS

These are drugs which lower the levels of lipids and lipoproteins in blood.

The hypolipidaemic drugs have attracted considerable attention because of their potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis in hyperlipidaemic individuals.

Whereas, raised low density lipoprotein-cholesterol (LDL-CH) is atherogenic, a higher high density lipoprotein-cholesterol (HDL-CH) is either itself protective or indicates a low atherogenic state. It is now recognized that elevated plasma triglyceride (TG) level poses independent risk of coronary artery disease (CAD) and stroke.

CLASSIFICATION

1. *HMG-CoA reductase inhibitors (Statins)*: Lovastatin, Simvastatin, Pravastatin, Atorvastatin.
2. *Bile acid sequestrants (Resins)*: Cholestyramine, Colestipol
3. *Activate lipoprotein lipase (Fibric acid derivatives):* Clofibrate, Gemfibrozil, Bezafibrate, Fenofibrate.
4. *Inhibit triglyceride synthesis and lipolysis*: Nicotinic acid.

The mechanism of action and profile of lipid lowering effect of important hypolipidaemic drugs is summarized in Table 17.3.

HMG-CoA reductase inhibitors (Statins)

These are the most efficacious and best tolerated hypolipidaemic drugs. They competitively inhibit conversion of 3-Hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) to mevalonate, the rate limiting step in cholesterol (CH) synthesis, by the

Table 17.3: Mechanism of action and pattern of lipid lowering effect of important hypolipidaemic drugs

Drug (daily dose)	*Mechanism of action*	*Effect on lipids (%)*
HMG-CoA reductase inhibitors		
Lovastatin (10–80 mg) Simvastatin (5–40 mg) Atorvastatin (10–80 mg)	↓ CH synthesis by inhibition of rate limiting HMG-CoA reductase	LDL ↓ 20–55 HDL↑ 5–15 TG ↓ 7–30
Bile acid sequestrants		
Cholestyramine (4–16 g) Colestipol (5–30 g)	↓ bile acid absorption, ↑ hepatic conversion of CH to bile acids, ↑ LDL receptors on hepatocytes	LDL ↓ 15–30 HDL ↑ 3–5 TG not affected, may ↑ in some
Fibric acid derivatives		
Gemfibrozil (1,200 mg) Bezafibrate (600 mg)	↑ Activity of lipoprotein lipase, ↓ release of fatty acids from adipose tissue	LDL ↓ 5–20 may ↑ LDL when TG is high HDL ↑ 10–20 TG ↓ 20–50
Nicotinic acid (2–6 g)	↓ Production of VLDL, ↓ lipolysis in adipocytes	LDL ↓ 5–25 HDL↑ 15–35 TG ↓ 20–50

enzyme HMG-CoA reductase. Therapeutic doses reduce CH synthesis by 20–50%. This results in compensatory increase in LDL receptor expression on liver cells → increased receptor mediated uptake and catabolism of intermediate density lipoprotein (IDL) and LDL. They cause dose-dependent lowering of LDL-CH levels.

At their maximum recommended doses, simvastatin and atorvastatin can reduce LDL-CH by up to 45–55%, while the ceiling effect of lovastatin and pravastatin is 35–40% LDL-CH reduction.

A concurrent fall by 10–20% in plasma TG level, probably due to reduction of very low density lipoprotein (VLDL) occurs. A rise in HDL-CH by 5–15% is also noted. Statins are not useful when TG alone is markedly raised.

All statins are remarkably well tolerated; overall incidence of side effects not differing from placebo.

- Headache, nausea, bowel upset, rashes, sleep disturbances.
- Rise in serum transaminase can occur, but liver damage is rare.
- Muscle tenderness and rise in CPK levels occurs infrequently. Myopathy is the only serious reaction, but is rare.

Statins are the first choice drugs for primary hyperlipidaemias with raised LDL and total CH levels, with or without raised TG levels. Efficacy of statins in reducing raised LDL-CH associated mortality and morbidity is now well established.

Improvement in endothelial function, reduction in LDL oxidation and an antiinflammatory effect are proposed as additional mechanisms by which statins may exert antiatherosclerotic action.

Bile acid sequestrants (Resins)

Cholestyramine and Colestipol are basic ion exchange resins supplied in the chloride form. They bind bile acids in the intestine interrupting their enterohepatic circulation. Faecal excretion of bile salts and CH (which is absorbed with the help of bile salts) is increased. This indirectly leads to enhanced hepatic metabolism of CH to bile acids. More LDL receptors are expressed on liver cells: clearance of plasma IDL, LDL and indirectly that of VLDL is increased.

Resins can retard atherosclerosis but are not popular clinically because they are unpalatable, inconvenient, cause

flatulence and other g.i. symptoms, interfere with absorption of many drugs, and have poor patient acceptability.

Fibric acid derivatives

The fibrates (isobutyric acid derivatives) primarily activate lipoprotein lipase which is a key enzyme in the degradation of VLDL resulting in lowering of circulating TGs. This effect appears to be exerted through paroxisome proliferator-activated receptor α (PPARα) which enhances lipoprotein lipase synthesis and fatty acid oxidation. PPARα may also mediate enhanced LDL receptor expression in liver. Fibrates also decrease hepatic TG synthesis. Drugs in this class primarily lower TG levels by 20–50% generally accompanied by 10–15% decrease in LDL-CH and a 10–15% increase in HDL-CH.

Fibrates are the hypolipidaemic drugs of choice for patients with raised TG levels, whether or not CH levels are also raised. They may be used as adjuvants to statins in hypercholesterolaemia. Reduction in coronary events and slowing of atherosclerotic process has been noted in post-MI subjects. Their main side effects are g.i. upset, rashes, bodyache, rarely myopathy (particularly when combined with statins).

Nicotinic acid

It is a B group vitamin which in much higher doses reduces plasma lipids. This action is unrelated to its vitamin activity and not present in nicotinamide. When nicotinic acid is given, TGs and VLDL decrease rapidly, followed by a modest fall in LDL-CH and total CH. A 20–50% reduction in plasma TGs and 15–25% reduction in CH levels has been recorded. It is the most effective drug to raise HDL-CH; a 15–30% increase is generally obtained.

Nicotinic acid reduces production of VLDL in liver by inhibiting TG synthesis. It inhibits lipolysis in adipose tissue and increases activity of lipoprotein lipase that clears TGs.

Adverse effects The large doses needed for hypolipidaemic action are poorly tolerated. Marked flushing, heat and itching (especially in the blush area) occur after every dose. Aspirin taken daily largely prevents the reaction (PGs may be involved).

Dyspepsia is very common; vomiting and diarrhoea occur when full doses are given. Peptic ulcer may be activated.

Dryness and hyperpigmentation of skin can be troublesome. Other long-term effects are: liver dysfunction and jaundice, hyperglycaemia, precipitation of diabetes.

Risk of myopathy due to lovastatin is increased.

Use Nicotinic acid is highly efficacious in hypertriglyceridaemia whether associated with raised CH level or not. It is mostly used to lower VLDL and raise HDL levels, and as an adjunctive drug to statins/fibrates.

However, because of marked side effects, use of nicotinic acid is restricted to high-risk cases only.

CHAPTER 18

Gastrointestinal Drugs*

DRUGS FOR PEPTIC ULCER

Peptic ulcer occurs in that part of the gastrointestinal tract (g.i.t.) which is exposed to gastric acid and pepsin, i.e., the stomach and duodenum. The etiology of peptic ulcer is not clearly known. It results probably due to an imbalance between the *aggressive* (acid, pepsin and *H. pylori*) and the *defensive* (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of the mucosal cells) factors. A variety of psychosomatic, humoral and vascular derangements have been implicated and the importance of *Helicobacter pylori* infection as a contributor to ulcer formation and recurrence has been recognized.

In *gastric ulcer*, generally acid secretion is normal or low. In *duodenal ulcer*, acid secretion is high in half of the patients but normal in the rest. Notwithstanding whether production of acid is normal or high, it does contribute to ulceration as an aggressive factor, reduction of which is the main approach to ulcer treatment.

Regulation of gastric acid secretion The mechanisms operating at the gastric parietal cells are summarized in Fig. 18.1. The terminal enzyme H^+K^+ATPase (proton pump) which secretes H^+ ions in the apical canaliculi of parietal cells can be activated by histamine, ACh and gastrin acting *via* their own receptors located on the basolateral membrane of these cells. Out of the three physiological secretagogues, histamine, acting through H_2 receptors, plays the dominant role, because the other two, gastrin and ACh act partly directly and partly indirectly by releasing histamine from paracrine enterochromaffin-like cells called "histaminocytes" located in the oxyntic glands.

Approaches for the treatment of peptic ulcer are:

1. *Reduction of gastric acid secretion*
   (a) *H_2 antihistamines*: Cimetidine, Ranitidine, Famotidine, Roxatidine, Loxatidine
   (b) *Proton pump inhibitors*: Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole
   (c) *Anticholinergics*: Pirenzepine, Propantheline, Oxyphenonium
   (d) *Prostaglandin analogues*: Misoprostol.

2. *Neutralization of gastric acid (Antacids)*
   (a) *Systemic*: Sodium bicarbonate, Sod. citrate
   (b) *Nonsystemic*: Magnesium hydroxide, Mag. trisilicate, Aluminium hydroxide gel, Magaldrate, Calcium carbonate.

3. *Ulcer protectives*: Sucralfate, Colloidal bismuth subcitrate (CBS).

4. *Anti-H. pylori drugs*: Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline.

* These are drugs used to treat gastrointestinal (g.i.) disorders. The common g.i. disorders are: peptic ulcer, gastroesophageal reflux, vomiting, constipation and diarrhoea.

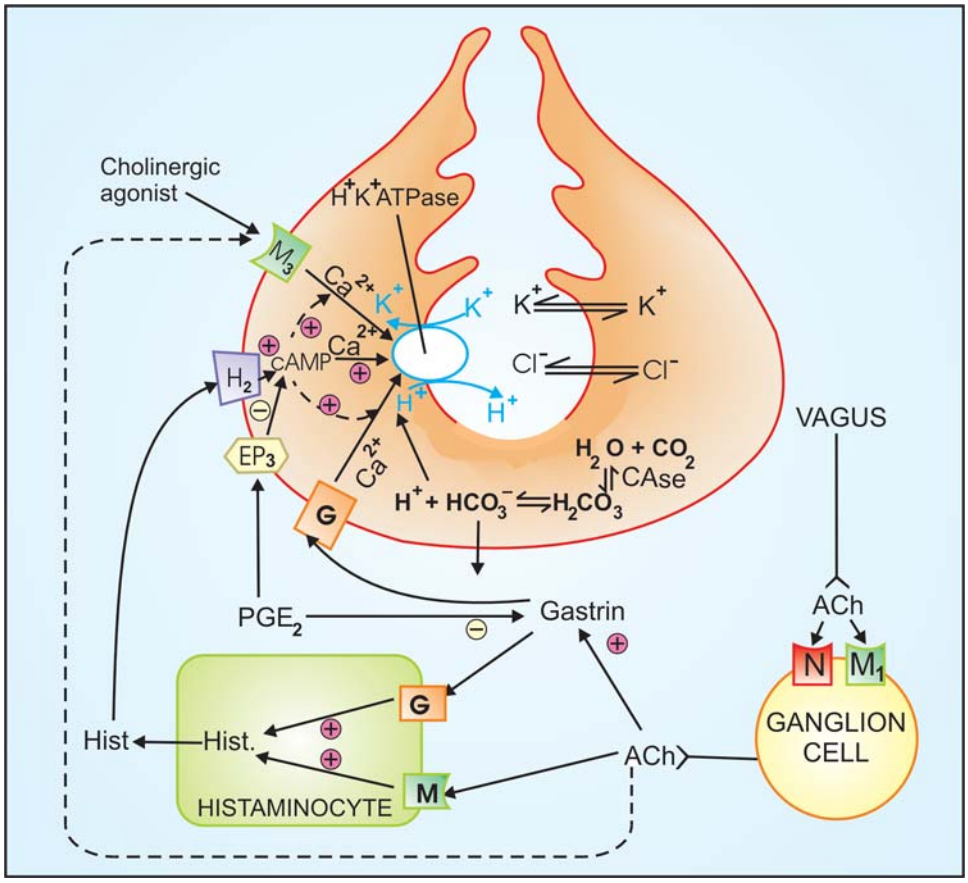


Fig. 18.1: Secretion of HCl by gastric parietal cell and its regulation
C.Ase.—Carbonic anhydrase; Hist.—Histamine; ACh.—Acetylcholine; G—Gastrin/cholecystokinin(CCK_2) receptor; M.—Muscarinic receptor; N—Nicotinic receptor; H_2—Histamine H_2 receptor; EP_3—Prostaglandin receptor; + = Stimulation; — = Inhibition. Probable, but unconfirmed actions are shown by broken lines.

H_2 ANTAGONISTS

These are the first class of highly effective drugs for acid-peptic disease. Cimetidine was the first H_2 blocker to be introduced clinically and is described as the prototype.

Pharmacological actions

1. *H_2 blockade* Cimetidine and all other H_2 antagonists block histamine-induced gastric secretion, cardiac stimulation (prominent in isolated preparations, especially in guinea pig), uterine relaxation (in rat) and bronchial relaxation. They attenuate fall in BP due to histamine, especially the late phase response seen with high doses. They are highly selective: have no effect on H_1 mediated responses or on action of other transmitters/autacoids.

2. *Gastric secretion* The only significant *in vivo* action of H_2 blockers is marked inhibition of gastric secretion. All phases (basal, psychic, neurogenic, gastric) of secretion are suppressed dose-dependently. Secretory responses to not only histamine but also all other stimuli (ACh, gastrin, insulin, alcohol, food) are attenuated. This reflects the permissive role of histamine in amplifying responses to other secretagogues.

The usual ulcer healing doses produce 60–70% inhibition of 24-hour acid output. The H_2 blockers have antiulcerogenic effect. Gastric ulceration due to stress and drugs (NSAIDs, cholinergic, histaminergic) is prevented. They do not have any direct effect on gastric or esophageal motility or on lower esophageal sphincter (LES) tone.

Pharmacokinetics Cimetidine is adequately absorbed orally, though bioavailability is 60–80% due to first pass hepatic metabolism. About 2/3rd of a dose is excreted unchanged in urine and bile, the rest as oxidized metabolites. The elimination t½ is 2–3 hr.

Adverse effects Cimetidine is well tolerated by most patients: adverse effects occur in ~5%. These are generally mild.

- Headache, dizziness, bowel upset, dry mouth, rashes.
- CNS effects like confusional state, restlessness, hallucinations can occur with high dose.
- Cimetidine (but not other H_2 blockers) has antiandrogenic action; increases plasma prolactin and inhibits degradation of estradiol by liver. High doses given for long periods have produced gynaecomastia, loss of libido, impotence and temporary decrease in sperm count.

Interactions Cimetidine inhibits cytochrome P-450 and reduces hepatic blood flow. It inhibits the metabolism of many drugs so that they can accumulate to toxic levels, e.g. metronidazole, theophylline, phenytoin, phenobarbitone, sulfonylureas, warfarin, imipramine, lignocaine, quinidine.

Antacids reduce absorption of all H_2 blockers.

Ketoconazole absorption is decreased by cimetidine (probably by other H_2 blockers also).

Uses The H_2 blockers are widely used in conditions in which it is profitable to suppress gastric acid secretion. Used in appropriate doses, all available agents have similar efficacy.

1. *Duodenal ulcer* Cimetidine 400 mg BD produces rapid and marked pain relief (within 2–3 days). It heals 60–85% ulcers at 4 weeks and 70–95% ulcers at 8 weeks.

Maintenance therapy with 400 mg at bedtime reduces ulcer relapse.

2. *Gastric ulcer* Healing rates obtained in gastric ulcer are somewhat lower (50–75% at 8 weeks). H_2 blockers can heal NSAID associated ulcers, but are less effective than proton pump inhibitors (PPIs) or misoprostol.

3. *Stress ulcers and gastritis* Acutely stressful situations like hepatic coma, severe burns and trauma, prolonged surgery, etc. are associated with gastric erosions and bleeding. Intravenous infusion of cimetidine (50 mg/hr) or equivalent H_2 blockade successfully prevents the gastric lesions and haemorrhage.

4. *Zollinger-Ellison syndrome* It is a gastric hypersecretory state due to a rare tumour secreting gastrin. Cimetidine in high doses controls hyperacidity and symptoms in many patients, but PPIs are the drugs of choice.

5. *Gastroesophageal reflux disease (GERD)* H_2 blockers afford symptomatic relief and facilitate healing of esophageal erosions by reducing acidity of gastric contents that are refluxed. However, they are less effective in this condition than PPIs.

6. *Prophylaxis of aspiration pneumonia* H_2 blockers given preoperatively (preferably evening before also) reduce the risk of aspiration of acidic gastric contents during anaesthesia and surgery.

Ranitidine It has several desirable features compared to cimetidine:

- About 5 times more potent than cimetidine.
- No antiandrogenic action, does not increase prolactin secretion or spare estradiol from hepatic metabolism—no effect on male sexual function or gynaecomastia.
- Lesser permeability into the brain: lower propensity to cause CNS effects.
- Does not significantly inhibit hepatic metabolism of other drugs; drug interactions mostly have no clinical relevance.
- Overall incidence of side effects is lower.

Famotidine It is 5–8 times more potent than ranitidine and has no antiandrogenic action. Because of low affinity for cytochrome P450 and the low dose, drug metabolism modifying propensity is minimal.

PROTON PUMP INHIBITORS (PPIs)

Omeprazole It is the prototype member of substituted benzimidazoles which inhibit the final common step in gastric acid secretion and have overtaken H_2 blockers for acid-peptic disorders. The only significant pharmacological action of omeprazole is dose-dependent suppression of gastric acid secretion; without anticholinergic or H_2 blocking action. It is a powerful inhibitor of gastric acid: can totally abolish HCl secretion, both resting as well as that stimulated by any of the secretagogues, without much effect on pepsin, intrinsic factor, juice volume and gastric motility.

Omeprazole is inactive at neutral pH, but at pH < 5 rearranges to two charged cationic forms that react covalently with SH groups of the H^+K^+ATPase enzyme and inactivate it irreversibly, especially when two molecules of omeprazole react with one molecule of the enzyme. After diffusing into the parietal cell from blood, it gets concentrated in the acidic pH of the canaliculi because the charged forms generated there at the acidic pH are unable to diffuse back. Moreover, it gets tightly bound to the enzyme. These features and the specific localization of H^+K^+ATPase to the apical membrane of parietal cells confer high degree of selectivity of action to omeprazole. Acid secretion resumes only when new H^+K^+ATPase molecules are synthesized.

The oral absorption of omeprazole is ~50%, because of instability at acidic pH. As the gastric pH rises, a higher fraction (up to 3/4) may be absorbed. It is highly plasma protein bound, rapidly metabolised in liver by CYP2C19 and CYP3A4 (plasma t½ ~1 hr) and metabolites are excreted in urine. Inhibition of HCl secretion occurs within 1 hr, reaches maximum at 2 hr, is still half maximal at 24 hr and lasts for 3 days.

Uses

1. *Peptic ulcer* Omeprazole is equally or more effective than H_2 blockers. Relief of pain is rapid and excellent; some duodenal ulcers heal even at 2 weeks and the remaining at 4 weeks. Gastric ulcer generally requires 4–8 weeks. Continued treatment can prevent relapse. PPIs are an integral component of anti-*H. pylori* therapy. PPIs are the drugs of choice for NSAID induced gastric/duodenal ulcers.

PPIs may help control bleeding from peptic ulcer; i.v. pantoprazole is preferred.

2. *Gastroesophageal reflux disease (GERD)* Omeprazole produces rapid symptom relief and is more effective than H_2 blockers in promoting healing of esophageal lesions. PPIs are the drugs of choice for patients with frequent or chronic symptoms and/or esophagitis/erosions; i.e. stage-2 or stage-3 GERD.

3. *Zollinger-Ellison syndrome* Omeprazole is more effective than H_2 blockers.

Adverse effects These are minimal: nausea, loose stools, headache, abdominal pain, muscle and joint pain, dizziness are complained by 3–5%. Rashes, leucopenia and hepatic dysfunction are infrequent.

Interactions Omeprazole inhibits oxidation of certain drugs: diazepam, phenytoin and warfarin levels may be increased.

Lansoprazole, *pantoprazole* and *rabeprazole* are other PPIs with only minor differences from omeprazole.

ANTICHOLINERGICS (*See* Ch.7)

Atropinic drugs reduce gastric secretion and can help healing of peptic ulcer, but frequently produce antimuscarinic side effects. Availability of H_2 blockers and PPIs has sent them into oblivion.

Pirenzepine is a selective M_1 anticholinergic that has been used in Europe for peptic ulcer. Gastric secretion is reduced without producing intolerable side effects.

PROSTAGLANDIN ANALOGUES

PGE_2 and PGI_2 are produced in the gastric mucosa and appear to serve a protective role by

inhibiting acid secretion and promoting mucus + HCO_3^- secretion. In addition, PGs inhibit gastrin production, increase mucosal blood flow and probably have an ill-defined "cytoprotective" action.

Natural PGs have very short t½. A number of stable PG analogues which exert action for hours rather than minutes have been developed for use in peptic ulcer and *misoprostol* (methyl-PGE_1 ester) is commercially available. Ulcer healing rates comparable to cimetidine have been obtained in 4–8 weeks, but misoprostol is poorer in relieving ulcer pain. Some patients may even complain of increased pain during the first week of therapy.

Major problems in the use of PG analogues are—diarrhoea, abdominal cramps, uterine bleeding, abortion, and need for multiple daily doses. Patient acceptability is poor.

The primary use of PG analogues is in the prevention and treatment of NSAID associated gastrointestinal injury and blood loss.

In ulcer patients, dentists should take care not to prescribe aspirin or other NSAIDs; instead choose paracetamol/codeine/selective COX-2 inhibitor for pain relief.

ANTACIDS

These are basic substances which neutralize gastric acid and raise pH of gastric contents. Peptic activity is indirectly reduced if the pH rises above 4.

Antacids do not decrease acid production; rather, agents that raise the antral pH to > 4 evoke reflex gastrin release → more acid is secreted, especially in patients with hyperacidity and duodenal ulcer; "acid rebound" occurs and gastric motility is increased.

The potency of an antacid is generally expressed in terms of its *acid neutralizing capacity* (ANC), which is defined as number of mEq of 1N HCl that are brought to pH 3.5 in 15 min (or 60 min in some tests) by a unit dose of the antacid preparation.

SYSTEMIC ANTACIDS

Sodium bicarbonate It is water soluble, acts instantaneously, but the duration of action is short. It is a potent neutralizer (1 g → 12 mEq HCl), pH may rise above 7. However, it has several demerits:

(a) Absorbed systemically: large doses will induce alkalosis.
(b) Produces CO_2 in stomach → distention, discomfort, belching, risk of ulcer perforation.
(c) Acid rebound occurs, but is usually short lasting.
(d) Increases Na^+ load: may worsen edema and CHF.

Use of sod. bicarbonate is restricted to casual treatment of heart burn: provides quick symptomatic relief. Other uses are to alkalinize urine and to treat acidosis.

Sodium citrate Properties similar to sod. bicarbonate; 1 g neutralizes 10 mEq HCl; CO_2 is not evolved.

NONSYSTEMIC ANTACIDS

These are insoluble and poorly absorbed basic compounds that react in stomach to form the corresponding chloride salt. The chloride salt again reacts with the intestinal bicarbonate so that HCO_3^- is not spared for absorption—no acid-base disturbance occurs.

Mag. hydroxide has low water solubility but reacts with HCl promptly and is an efficacious antacid (1 g → 30 mEq HCl).

Magnesium trisilicate has low solubility and reactivity; clinically neutralizes only about 1 mEq acid per gram due to slow action. All Mg salts have a laxative action—by generating osmotically active $MgCl_2$ in the stomach and through Mg^{2+} ion induced cholecystokinin release.

Aluminium hydroxide gel It is a bland, weak and slowly reacting antacid. On keeping it slowly polymerizes to variable extents into still less reactive forms. Thus, the ANC of a preparation gradually declines on storage. ANC usually varies from 1–2.5 mEq/g. Thus, 5 ml of its suspension may neutralize just 1 mEq HCl.

The Al^{3+} ions relax smooth muscle. Thus, it delays gastric emptying. Alum. hydrox. frequently causes constipation due to its smooth muscle relaxant and mucosal astringent action.

Magaldrate It is a hydrated complex of hydroxymagnesium aluminate that initially reacts rapidly with acid and releases alum. hydrox. which then reacts more slowly. Thus, magaldrate cannot be equated to a physical mixture of mag. and alum. hydroxides. It is a good antacid with prompt and sustained neutralizing action.

Antacid combinations A combination of two or more antacids is frequently used. These may be superior to any single agent on the following accounts:

(a) Fast (Mag. hydrox.) and slow (Alum. hydrox.) acting components yield prompt as well as sustained effect.
(b) Mag. salts are laxative, while Alum. salts are constipating: combination may annul each other's action and bowel movement may be least affected.
(c) Dose of individual components is reduced; systemic toxicity (dependent on fractional absorption) is minimized.

Drug interactions By raising gastric pH and by forming complexes, the non-absorbable antacids decrease the absorption of many drugs, especially tetracyclines, iron salts, fluoroquinolones, ketoconazole, H_2 blockers, diazepam, phenothiazines, indomethacin, phenytoin, isoniazid, ethambutol and nitrofurantoin. Stagger their administration by 2 hours. The efficacy of nitrofurantoin is also reduced by alkalinization of urine.

Uses Antacids are no longer used for healing peptic ulcer because they are needed in large and frequent doses, are inconvenient, can cause acid rebound and bowel upset, afford little nocturnal protection and have poor patient acceptability. They are now employed only for intercurrent pain relief and acidity, mostly self-prescribed by the patients. They continue to be used for nonulcer dyspepsia and minor episodes of heartburn, acid eructation.

ULCER PROTECTIVES

Sucralfate It is a basic aluminium salt of sulfated sucrose; a drug of its own kind. Sucralfate polymerizes at pH < 4 by cross linking of molecules, assuming a sticky gel-like consistency. It preferentially and strongly adheres to ulcer base, especially duodenal ulcer; has been seen endoscopically to remain there for ~ 6 hours. It precipitates surface proteins at ulcer base and acts as a physical barrier preventing acid, pepsin and bile from coming in contact with the ulcer base. Dietary proteins get deposited on this coat, forming another layer.

Sucralfate has no acid neutralizing action, but delays gastric emptying—its own stay in stomach is prolonged. Augmented gastric mucosal PG synthesis may supplement physical protective action of sucralfate.

Sucralfate is minimally absorbed after oral administration. It promotes healing of both duodenal and gastric ulcers, especially the former: efficacy similar to cimetidine at 4 weeks. However, sucralfate is infrequently used now because of need for 4 large well-timed daily doses and the availability of simpler H_2 blockers/PPIs.

Side effects are few; constipation is reported by 2% patients.

Interactions Sucralfate adsorbs many drugs and interferes with the absorption of tetracyclines, fluoroquinolones, cimetidine, phenytoin and digoxin. Antacids given concurrently reduce the efficacy of sucralfate.

Colloidal bismuth subcitrate (CBS; Tripotassium dicitratobismuthate)

It is a colloidal bismuth compound; water soluble but precipitates at pH < 5. It is not an antacid, but heals 60% ulcers at 4 weeks and 80–90% at 8 weeks. The mechanism of action of CBS is not clear; probabilities are:

(i) Increased secretion of mucus and bicarbonate through stimulation of mucosal PGE_2 production.
(ii) CBS and mucus form a glycoprotein-Bi complex which coats the ulcer and acts as a diffusion barrier to HCl.
(iii) Detaches *H. pylori* from the surface of mucosa and directly kills this organism involved in causation of ulcers and relapses.

Gastritis and nonulcer dyspepsia associated with *H. pylori* are also improved by CBS. Recommended regimen for CBS is 120 mg (as Bi_2O_3) taken ½ an hour before 3 major meals and at bedtime for 4–8 weeks.

Most of the ingested CBS passes in the faeces. Small amounts absorbed are excreted in urine.

Side effects reported are diarrhoea, headache and dizziness. Patient acceptance of CBS is compromised by blackening of tongue, dentures and stools; by variable and delayed symptom control and inconvenience of dosing schedule. Presently, it is used occasionally as a component of triple drug anti-*H.pylori* regimen.

ANTI-*HELICOBACTER PYLORI* DRUGS

H. pylori is a gram-negative bacillus uniquely adapted to survival in the hostile environment of stomach. It attaches to the surface epithelium beneath the mucus, has high urease activity—produces ammonia which maintains a neutral microenvironment around the bacteria, and promotes back diffusion of H^+ ions. It has been found as a commensal in 20–70% normal individuals, and is now accepted as an important contributor to the causation of chronic gastritis, dyspepsia, peptic ulcer, gastric lymphoma and gastric carcinoma. Up to 90% patients of duodenal and gastric ulcer have tested positive for *H. pylori*.

Eradication of *H. pylori* concurrently with H_2 blocker/PPI therapy of peptic ulcer has been associated with faster ulcer healing and lower relapse rate. Anti-*H. pylori* therapy is, therefore, now recommended in all ulcer patients who test positive for *H. pylori.* In the absence of such testing, all cases with failed conventional ulcer therapy and relapse cases may be given the benefit of *H. pylori* eradication.

Antimicrobials that have been found clinically effective against *H. pylori* are: amoxicillin, clarithromycin, tetracycline and metronidazole/tinidazole. However, any single drug is relatively ineffective. Resistance develops rapidly, especially to metronidazole/tinidazole. Since bismuth (CBS) is active against *H. pylori* and resistance does not develop to it, early combination regimens included bismuth, but had poor patient acceptability; are infrequently used now. In the meantime, it was observed that omeprazole monotherapy reduces population of *H. pylori* in the gastric antrum, probably by altering the acid environment as well as direct inhibitory effect. A number of 2-drug and 3-drug regimens of 1 or 2 weeks duration have been tested reporting 60–96% eradication rates, but the optimum regimen is difficult to proclaim.

The US-FDA approved regimen is: lansoprazole 30 mg + amoxicillin 1000 mg + clarithromycin 500 mg all given twice daily for 2 weeks. It has achieved 86–92% eradication rate.

All regimens are complex and expensive, side effects are frequent and compliance is poor. Long-term benefits of anti-*H. pylori* therapy include lowering of ulcer disease prevalence and prevention of gastric carcinoma/lymphoma; but benefits in nonulcer dyspepsia are equivocal.

ANTIEMETICS

These are drugs used to prevent or suppress vomiting (emesis).

Emesis Vomiting occurs due to stimulation of the *emetic (vomiting) centre* situated in the medulla oblongata. Multiple pathways can elicit vomiting (Fig. 18.2). The *chemoreceptor trigger zone (CTZ)* located in the area postrema and the *nucleus tractus solitarius (NTS)* are the most important relay areas for afferent impulses arising in the g.i.t, throat and other viscera. The CTZ is also accessible to blood-borne drugs, mediators, hormones, toxins, etc., because it is unprotected by the blood-brain barrier. Cytotoxic drugs, radiation and other g.i. irritants release 5-HT from enterochromaffin cells → acts on 5-HT_3 receptors present on vagal afferents and sends impulses to NTS and CTZ. However, 5-HT is not the only mediator of such signals: many peptides and other messengers are also involved.

The CTZ and NTS express a variety of receptors, e.g. histamine H_1, dopamine D2, serotonin 5-HT_3, cholinergic M and opioid μ through which the emetic signals are relayed and which could be targets of antiemetic drug action.

The vestibular apparatus generates impulses when body is rotated or equilibrium is disturbed or when ototoxic drugs act. These impulses reach the vomiting centre mainly relayed from the cerebellum and utilize muscarinic as well as H_1 receptors.

CLASSIFICATION

1. *Anticholinergics*	Hyoscine, Dicyclomine
2. *H_1 antihistaminics*	Promethazine, Diphenhydramine, Dimenhydrinate,

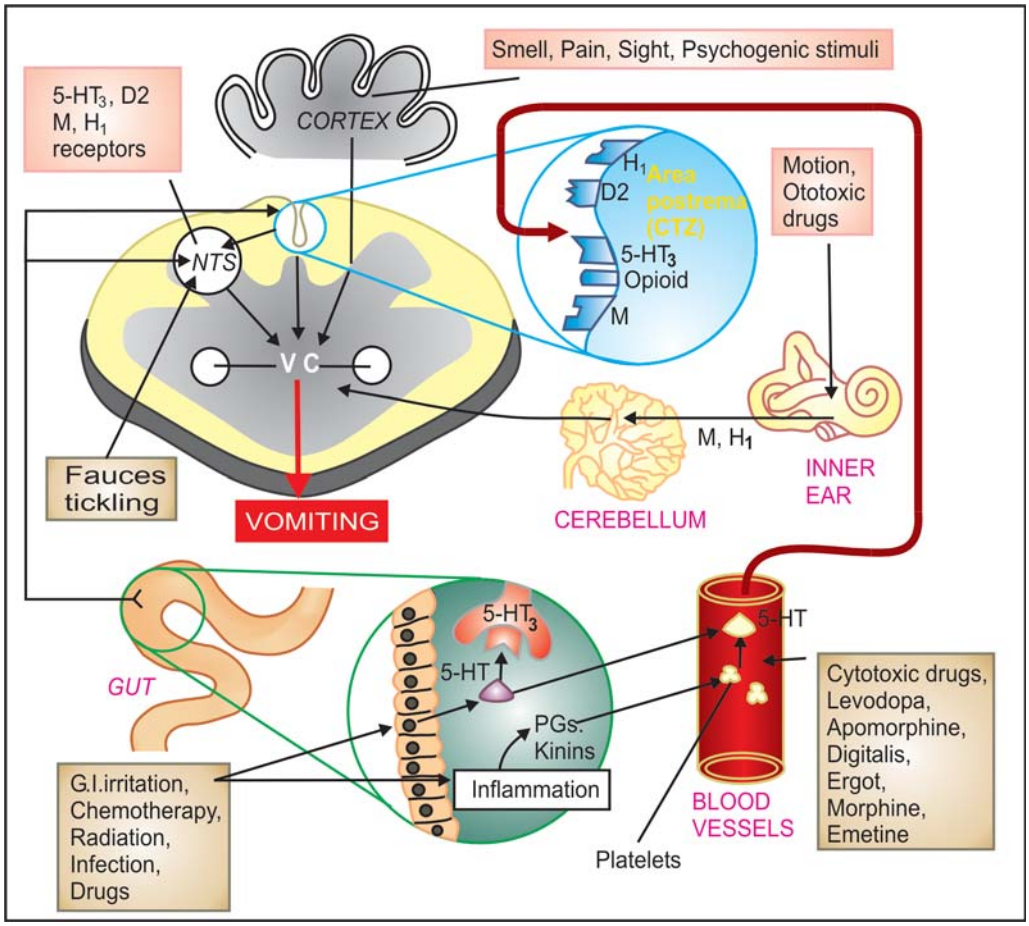


Fig. 18.2: Major central and visceral structures involved in emesis and the neurohumoral receptors mediating the emetic response. NTS: Nucleus tractus solitarius; VC: vomiting centre

	Cyclizine, Meclozine, Cinnarizine.
3. *Neuroleptics*	Chlorpromazine, Prochlorperazine, Haloperidol, etc.
4. *Prokinetic drugs*	Metoclopramide, Domperidone Cisapride, Mosapride
5. *5-HT$_3$ antagonists*	Ondansetron, Granisetron
6. *Adjuvant antiemetics*	Dexamethasone, Benzodiazepines, Cannabinoids.

ANTICHOLINERGICS (*See* Ch. 5)

Hyoscine is the most effective drug for motion sickness. However, it has a brief duration of action; produces sedation and other anticholinergic side effects; suitable only for short brisk journies. It acts probably by blocking conduction of nerve impulses across a cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre. It is not effective in vomiting of other etiologies.

Dicyclomine has been used for prophylaxis of motion sickness and for morning sickness.

H_1 ANTIHISTAMINICS (*See* Ch. 7)

Some antihistaminics are antiemetic. They are useful mainly in motion sickness and to a lesser extent in morning sickness, postoperative and some other forms of vomiting. Their antiemetic effect appears to be based on anticholinergic, antihistaminic and sedative properties.

Promethazine, diphenhydramine, dimenhydrinate afford protection of motion sickness for 4–6 hours, but produce sedation and dryness of mouth.

Cyclizine, meclozine are less sedative and less anticholinergic. Meclozine is long acting, protects against sea sickness for nearly 24 hours.

Cinnarizine is an antivertigo drug, and is also protective for motion sickness. It probably acts by inhibiting influx of Ca^{2+} from endolymph into the vestibular sensory cells.

All antimotion sickness drugs are more effective when taken ½–1 hour before commencing journey. Once sickness has started, it is more difficult to control; higher doses/parenteral administration may be needed.

NEUROLEPTICS (*see* Ch. 10)

These are potent antiemetics; act by blocking D2 receptors in the CTZ. They have broad-spectrum antiemetic action in:

(a) Drug induced and postanaesthetic nausea and vomiting.
(b) Disease induced vomiting: gastroenteritis, uraemia, liver disease, migraine, etc.
(c) Malignancy associated and cancer chemotherapy (mildly emetogenic) induced vomiting.
(d) Radiation sickness vomiting (less effective).
(e) Morning sickness: should not be used except in hyperemesis gravidarum.

They are *not* effective in motion sickness: the vestibular pathway probably does not involve dopaminergic link.

Most of these drugs produce significant degree of sedation. Acute muscle dystonia may occur after a single dose, especially in children and girls. The antiemetic dose is generally much lower than antipsychotic doses.

Prochlorperazine is a labyrinthine suppressant, has selective antivertigo and antiemetic actions. It is highly effective when given by injection in vertigo associated with vomiting and is not used as antipsychotic.

PROKINETIC DRUGS

These are drugs which promote gastrointestinal transit and speed gastric emptying.

Metoclopramide

Introduced in early 1970s as a 'gastric hurrying' agent, metoclopramide is now a widely used antiemetic.

Metoclopramide increases gastric peristalsis while relaxing the pylorus and the first part of duodenum → speeds gastric emptying, especially if it was slow.

Lower esophageal sphincter (LES) tone is increased and gastroesophageal reflux is opposed. It also increases intestinal peristalsis to some extent, but has no significant action on colonic motility and gastric secretion.

Metoclopramide is an effective antiemetic; by blocking D_2 receptors in CTZ. The gastrokinetic action may contribute to the antiemetic effect.

Other manifestations of D2 receptor blockade are chlorpromazine like extrapyramidal side effects and hyperprolactinaemia, but no antipsychotic effect is exerted. The gastric hurrying and LES tonic effects are mainly due to activation of 5-HT_4 receptors on myenteric interneurones, which enhance ACh, release from primary motor neurone innervating the gastric and LES smooth muscles (Fig. 18.3). Because dopamine acts as an inhibitory transmitter in the g.i.t., the D2 receptor blocking action also contributes to the gastrokinetic effects. At high concentrations, metoclopramide can block 5-HT_3 receptors present on inhibitory myenteric interneurones and in NTS/CTZ. The peripheral action can augment ACh release in the gut, but

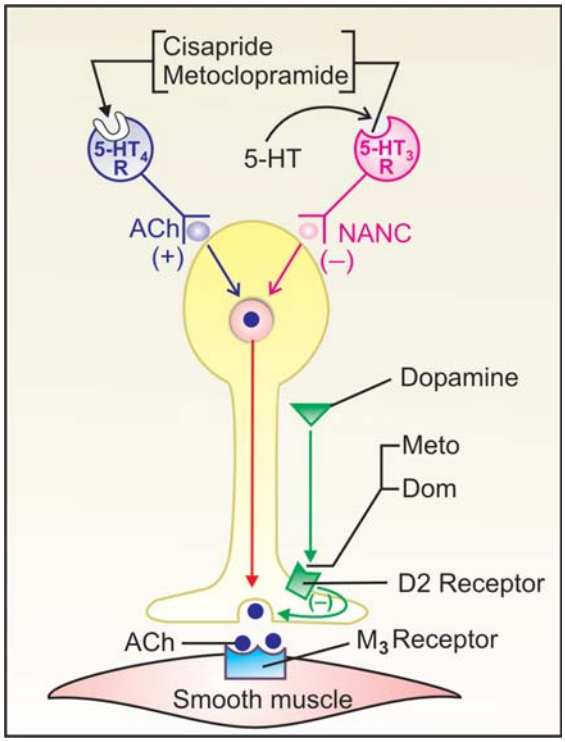


Fig. 18.3: Mechanism of action of prokinetic drugs. Cisapride and metoclopramide (Meto) activate 5-HT_4 receptors on excitatory interneurones which enhance acetylcholine (ACh) release from primary motor neurones in myenteric plexus (major action). They probably also block 5-HT_3 receptors on inhibitory interneurones that cause relaxation through release of nonadrenergic-noncholinergic (NANC) transmitter (most likely NO), adding to the augmentation of ACh release from primary motor neurone. Domperidone (Dom) and metoclopramide block D2 receptor which normally inhibits ACh release from the primary motor neurone

appears to be minor. The central action appears to be significant only when large doses are used to control chemotherapy induced vomiting.

Pharmacokinetics Metoclopramide is rapidly absorbed orally, enters brain, crosses placenta and is secreted in milk. It is partly conjugated in liver and excreted in urine within 24 hours; t½ is 3–6 hours. Orally, it acts in ½–1 hr, but within 10 min after i.m. and 2 min after i.v. injection. Action lasts for 4–6 hours.

Interactions It hastens the absorption of many drugs, e.g. aspirin, diazepam, etc. by facilitating gastric emptying. It reduces the extent of absorption of digoxin by allowing less time for it.

By blocking DA receptors in basal ganglia, it abolishes the therapeutic effect of levodopa.

Adverse effects Metoclopramide is generally well tolerated.

Sedation, dizziness, diarrhoea, muscle dystonias (especially in children) are the main side effects. Long-term use can cause parkinsonism, galactorrhoea and gynaecomastia.

Uses

1. *Antiemetic:* Metoclopramide is an effective and popular drug for many types of vomiting—postoperative, drug induced, disease associated (especially migraine), radiation sickness, etc. but is less effective in motion sickness. Though ondansetron is being preferred, metoclopramide continues to be used for prophylaxis and treatment of vomiting induced by highly emetic anticancer drugs.

2. *Gastrokinetic:* to accelerate gastric emptying:
   (a) When emergency general anaesthesia has to be given and the patient has taken food less than 4 hours before.
   (b) To relieve postvagotomy or diabetes associated gastric stasis.
   (c) To facilitate duodenal intubation.

3. *Dyspepsia* and other functional g.i. disorders.

4. *Gastroesophageal reflux disease (GERD)* Metoclopramide may afford symptomatic relief in milder cases of GERD, but is much less effective than PPIs/H_2 blockers, and does not aid healing of esophagitis.

Domperidone It is a D2 antagonist, chemically related to haloperidol, but pharmacologically related to metoclopramide. It has lower ceiling antiemetic and prokinetic actions. Unlike meto-

clopramide, its prokinetic action is not blocked by atropine and is based only on D2 receptor blockade in upper g.i.t. Domperidone crosses blood-brain barrier poorly. Accordingly, extrapyramidal side effects are rare, but hyperprolactinaemia can occur. However, it does act on CTZ which is not protected by blood-brain barrier, though antiemetic efficacy is lower than metoclopramide.

Side effects of domperidone are much less than with metoclopramide: dry mouth, loose stools, headache, rashes, galactorrhoea.

Cisapride It is a prokinetic drug with little antiemetic property, because it lacs D2 receptor antagonism. Effects of cisapride on gastric motility resemble metoclopramide—gastric emptying is accelerated, LES tone is improved and esophageal peristalsis is augmented. It restores and facilitates motility throughout the g.i.t., including colon (metoclopramide/domperidone do not accelerate colonic transit). Cisapride often produces loose stools. Its prokinetic action is exerted mainly through 5-HT_4 agonism which promotes ACh release from myenteric neurones, aided by 5-HT_3 antagonism which suppresses inhibitory transmission in myenteric plexus. Cisapride is devoid of action on CTZ and does not produce extrapyramidal symptoms or hyperprolactinaemia.

Oral bioavailability of cisapride is ~33%. It is primarily inactivated by hepatic metabolism by CYP3A4 with a t½ of ~10 hours.

Cisapride is a prokinetic drug without antidopaminergic side effects, but abdominal cramps and diarrhoea can occur.

Primary indication of cisapride has been GERD. Some patients derive symptomatic relief, but this is less complete compared to PPIs/H_2 blockers. Other indications of cisapride are nonulcer dyspepsia, impaired gastric emptying and chronic constipation, though usefulness in these conditions also is limited.

Safety of cisapride has been challenged by reports of serious ventricular arrhythmias and death, mainly among patients who took CYP3A4 inhibitors like azole antifungals, macrolide antibiotics, antidepressants, HIV protease inhibitors, etc. concurrently. At high concentrations, cisapride blocks delayed rectifying K^+ channels in heart—prolongs Q-Tc interval and predisposes to *torsades de pointes*/ventricular fibrillation. It has been withdrawn in many countries.

Mosapride A newer congener of cisapride with similar gastrokinetic and LES tonic action due to 5-HT_4 agonistic (major) and 5-HT_3 antagonistic (minor) action in the myenteric plexus, but has not caused Q-Tc prolongation or arrhythmias. Like cisapride, it has no clinically useful antiemetic action and does not produce extrapyramidal/hyperprolactinaemic side effects due to absence of D2 blocking property. Indications and side effects are similar to cisapride.

Gastroesophageal reflux disease (GERD)

It is a very common problem presenting as 'heartburn', acid eructation, sensation of stomach contents coming back in foodpipe, especially after a large meal, aggravated by stooping or lying flat. Some cases have an anatomical defect (hiatus hernia) but majority are only functional (LES relaxation in the absence of swallowing). Repeated reflux of acid gastric contents into lower $^1/_3$rd of esophagus causes esophagitis, erosions, ulcers, strictures, and increases the risk of esophageal carcinoma.

Though GERD is primarily a g.i. motility disorder, acidity of gastric contents is the most important aggressive factor in causing symptoms and esophageal lesions. The functional abnormality is persistent; dietary and other lifestyle measures (light early dinner, raising head end of bed, weight reduction and avoidance of precipitating factors) must be taken.

Treatment of GERD is to be individualized according to severity and stage of the disorder. The site and mechanism of benefit afforded by different classes of drugs in GERD is depicted in Fig. 18.4.

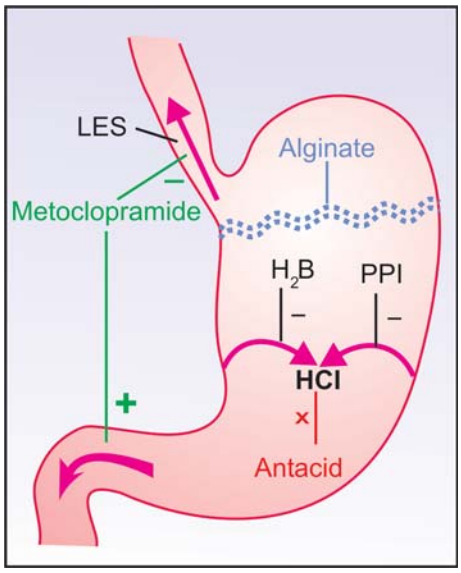


Fig. 18.4: Sites and mechanisms of drug action in gastroesophageal reflux disease.
Metoclopramide increases lower esophageal sphincter (LES) tone and promotes gastric emptying. Proton pump inhibitor (PPI) and H_2 blocker (H_2B) inhibit acid secretion, while antacids neutralize it. Alginate floats on gastric contents and prevents contact of esophageal mucosa with gastric acid

1. *Proton pump inhibitors (PPIs)* These are the most effective drugs, both for symptomatic relief as well as for healing of esophageal lesions. Intragastric pH >4 maintained for ~18 hr/day is considered optimal for healing of esophagitis. This level of acid suppression can be consistently achieved only by PPIs. Therefore, PPIs are the drugs of choice for all stages of GERD patients, particularly severe cases. Prolonged (often indefinite) therapy is required in chronic cases because symptoms recur a few days after drug stoppage.

2. *H_2 blockers* H_2 blockers cause less complete acid suppression than PPIs—adequate symptom relief is obtained only in mild cases; healing of esophagitis may occur in 50–70% patients.

3. *Antacids* Their use in GERD is limited to occasional or intercurrent relief of heartburn.

4. *Sodium alginate* It forms a thick frothy layer which floats on the gastric contents—may prevent contact of acid with esophageal mucosa. It has no effect on LES tone. Combination of alginate with antacids may be used in place of antacids alone, but real benefit is marginal.

5. *Prokinetic drugs* Metoclopramide and other prokinetic drugs may relieve regurgitation and heartburn by increasing LES tone, improving esophageal clearance and facilitating gastric emptying, but do not affect gastric acidity or promote healing of esophagitis. Symptom control afforded by prokinetic drugs is inferior to that by PPIs/H_2 blockers. Prokinetic drugs are occasionally added to PPI/H_2 blocker therapy, but whether this improves outcome is not clear.

5-HT_3 ANTAGONISTS

Ondansetron It is the prototype of a new class of antiemetic drugs developed to control cancer chemotherapy/radiotherapy induced vomiting and later found to be highly effective in postoperative nausea and vomiting as well. It blocks the depolarizing action of 5-HT through 5-HT_3 receptors on vagal afferents in the g.i.t. as well as in NTS and CTZ. Cytotoxic drugs/radiation produce nausea and vomiting by causing cellular damage → release of mediators including 5-HT from intestinal mucosa → activation of vagal afferents in the gut → emetogenic impulses to the NTS and CTZ. Ondansetron blocks emetogenic impulses both at their peripheral origin and their central relay.

Pharmacokinetics: Oral bioavailability of ondansetron is 60–70% due to first pass metabolism. No clinically significant drug interactions have been noted. It is eliminated in urine and faeces, mostly as metabolites; t½ being 3–5 hrs, and duration of action 4–12 hr.

Other types of vomiting: Efficacy of 5-HT_3 antagonists in prevention and treatment of postoperative nausea and vomiting is now well established.

Reports of efficacy in vomiting associated with drug overdosage, uraemia and certain neurological injuries are also available.

Side effects: Ondansetron is generally well tolerated: the only common side effect is headache. Mild constipation or diarrhoea and abdominal discomfort occur in a few patients. Rashes and allergic reactions are possible, especially after i.v. injection.

Granisetron It is 10–15 times more potent than ondansetron and probably more effective during the repeat cycle of chemotherapy.

ADJUVANT ANTIEMETICS

Corticosteroids (e.g. dexamethasone 8–20 mg i.v.) can alleviate nausea and vomiting due to moderately emetogenic chemotherapy, but are more often employed to augment the efficacy of other primary antiemetic drugs like metoclopramide and ondansetron.

Benzodiazepines Their weak antiemetic property is primarily based on the sedative action. Used as adjuvant to metoclopramide/ondansetron, they help by relieving anxiety, anticipatory vomiting and produce amnesia for the unpleasant procedure.

Cannabinoids Δ^9 Tetrahydrocannabinol (Δ^9 THC) is the active principle of the hallucinogen *Cannabis indica*. It possesses antiemetic activity. Nabilone and dronabinol are less hallucinogenic and more antiemetic than Δ^9 THC. Dronabinol has been used for chemotherapy induced vomiting in patients who cannot tolerate other antiemetics or are unresponsive to them.

LAXATIVES
(Aperients, Purgatives, Cathartics)

These are drugs that promote evacuation of bowels. A distinction is sometimes made according to the intensity of action.
(a) *Laxative or aperient*: milder action, elimination of soft but formed stools.
(b) *Purgative or cathartic*: stronger action resulting in more fluid evacuation.
Many drugs in low doses act as laxative and in larger doses as purgative.

CLASSIFICATION

1. *Bulk forming*
   Dietary fibre: Bran, Psyllium (Plantago) Ispaghula, Methylcellulose
2. *Stool softener*
   Docusates (DOSS), Liquid paraffin
3. *Stimulant purgatives*
   (a) *Diphenylmethanes*
   Phenolphthalein, Bisacodyl
   (b) *Anthraquinones (Emodins)*
   Senna, Cascara sagrada
4. *Osmotic purgatives*
   Magnesium salts: sulfate, hydroxide
   Sodium salts: sulfate, phosphate
   Sod. pot. tartrate
   Lactulose.

MECHANISM OF ACTION

All purgatives increase the water content of faeces by:
(a) A hydrophilic or osmotic action, retaining water and electrolytes in the intestinal lumen—increase volume of colonic content and make it easily propelled.
(b) Acting on intestinal mucosa to decrease net absorption of water and electrolyte; intestinal transit is enhanced indirectly by the fluid bulk.
(c) Increasing propulsive activity as primary action—allowing less time for absorption of salt and water as a secondary effect.

Bulk purgatives

Dietary fibre (*bran*) consists of unabsorbable cell wall and other constituents of vegetable food—cellulose, pectins, glycoproteins and other polysaccharides, while psyllium and ispaghula husk contain natural colloidal mucilage which absorbs water, swells and forms a gelatinous mass. This increases water content of faeces—softens it and facilitates colonic transit.

Bulk forming laxatives are the most appropriate method for prevention and treatment of functional constipation. It is the first line approach for most patients of simple constipation. Full effect requires daily administration for at least 3–4 days.

Generous amounts of water must be taken with all bulk forming agents.

Stool softener

Docusates (Dioctyl sodium sulfosuccinate: DOSS) is an anionic detergent; softens the stools by net water accumulation in the lumen due to an action on the intestinal mucosa. It emulsifies the colonic contents and increases penetration of water into faeces. It is a mild laxative; especially indicated when straining at stools must be avoided.

Liquid paraffin is a viscous liquid; a mixture of petroleum hydrocarbons. It is pharmacologically inert. Taken for 2–3 days, it softens stools and is said to lubricate hard scybali by coating them. However, it is unpleasant to swallow and has many drawbacks such as interference with absorption of fat-soluble vitamins, likelihood of leakage past the anus, lipid pneumonia if it trickles into the airway, or foreign body granulomas in mesenteric lymph nodes if it is absorbed.

Stimulant purgatives

They are powerful purgatives: often produce griping. They were thought to irritate the intestinal mucosa and thus stimulate motor activity. Though some of them do primarily increase motility by acting on myenteric plexuses, the more important mechanism of action is accumulation of water and electrolytes in the lumen by altering absorptive and secretory activity of the mucosal cell. They inhibit Na^+K^+ATPase at the basolateral membrane of villous cells—transport of Na^+ and accompanying water into the interstitium is reduced. Secretion is enhanced by activation of cAMP in crypt cells and by increased PG synthesis.

Larger doses of stimulant purgatives can cause excess purgation → fluid and electrolyte imbalance. Hypokalaemia can occur on regular use. Routine and long-term use must be discouraged; produces colonic atony.

Phenolphthalein and *bisacodyl* are synthetic diphenylmethanes which primarily act in the colon and at optimum doses produce one or two semiformed motions after 6–8 hours. However, the same dose may be ineffective in some, but cause fluid evacuations and cramps in other individuals. Bisacodyl can also be used as suppository.

Senna and *Cascara sagrada* are plant products containing anthraquinone glycosides (also called emodins). Unabsorbed in the small intestine, they are passed to the colon where bacteria liberate the active *anthrol* form, which either acts locally or is absorbed into circulation—excreted in bile to act on small intestine. Thus, they take 6–8 hours to produce action.

Taken at bedtime—a single, soft but formed evacuation generally occurs in the morning. Cramps and excessive purging occur in some cases. The active principle is believed to act on the myenteric plexus to increase peristalsis and decrease segmentation. They also inhibit salt and water absorption in the colon.

Skin rashes, fixed drug eruption are seen occasionally with both anthraquinones and diphenyl methanes.

Osmotic purgatives

Solutes that are not absorbed in the intestine retain water osmotically and distend the bowel—increasing peristalsis indirectly. Magnesium ions release cholecystokinin which may aid purgative action of Mag. salts. All inorganic salts used as osmotic (saline) purgatives have similar action—produce 1–2 fluid evacuations within 1–3 hours with mild cramping; cause nearly complete emptying of bowels. Smaller doses may have a milder laxative action.

They are not used for the treatment of constipation, because afterconstipation is quite common. However, they may be preferred for preparation of bowel before surgery and colonoscopy; in food/drug poisoning and as after-purge in treatment of tapeworm infestation.

Lactulose It is a semisynthetic disaccharide of fructose and lactose which is neither digested nor absorbed in the small intestine—retains water. Further, it is broken down in the colon by bacteria to osmotically more active products. In a dose of 10 g BD taken with plenty of water, it produces

soft formed stools in 1–3 days. Flatulence is common, cramps occur in few. Some patients feel nauseated by its peculiar sweet taste. It is not a favoured purgative for treatment of constipation.

Lactulose is also used to lower blood NH_3 in hepatic encephalopathy, because its acidic breakdown products generated in the colon react with NH_3 to form ionized NH_4 salts that are not absorbed.

USES OF PURGATIVES

Laxatives are as important for their harmfulness as they are for their value in medicine.
Valid indications of laxatives are:

1. *Functional constipation* Constipation is infrequent production of hard stools requiring straining to pass, or a sense of incomplete evacuation.

Constipation may be spastic or atonic.

(i) *Spastic constipation* (irritable bowel): The stools are hard, rounded, stone like and difficult to pass. The first choice laxative is dietary fibre or any of the bulk forming agents taken over weeks/months; stimulant purgatives are contraindicated.

(ii) *Atonic constipation* (sluggish bowel): Non-drug measures like plenty of fluids, exercise, regular habits and reassurance should be tried. In resistant cases a bulk forming agent should be prescribed. In case of poor compliance or if the patient is not satisfied—bisacodyl or senna may be given once or twice a week for as short a period as possible.

2. *Bedridden patients* (myocardial infarction, stroke, fractures, postoperative).
To prevent constipation: Give bulk forming agents on a regular schedule; docusates is an alternative.
To treat constipation: Enema (soap-water/glycerine) is preferred; bisacodyl or senna may be used otherwise.

3. *To avoid straining at stools* (hernia, cardiovascular disease, eye surgery) and in perianal afflictions (piles, fissure, anal surgery) use adequate dose of a bulk forming agent or docusates.

4. *Preparation of bowel for surgery, colonoscopy, abdominal X-ray* The bowel needs to be emptied of the contents including gas. Saline purgative, bisacodyl or senna may be used.

5. *After certain anthelmintics* (especially for tape-worm) Saline purgative or senna may be used to flush out the worm and the anthelmintic drug.

The choice of a purgative depends on the latency of action and type of stools desired. This is given in Table 18.1.

Table 18.1: Type of stools and latency of action of purgatives employed in usually recommended doses

Soft, formed faeces (take 1–3 days)	*Semifluid stools (take 6–8 hr)*	*Watery evacuation (within 1–3 hr)*
Bulk forming Docusates Liquid paraffin Lactulose	Phenolphthalein Bisacodyl Senna	Saline purgatives

TREATMENT OF DIARRHOEAS

Diarrhoea is too frequent, often too precipitate passage of poorly formed stools. In pathological terms, it occurs due to passage of excess water in faeces.

Diarrhoeal diseases constitute a major cause of morbidity and mortality worldwide; especially in developing countries. More than 5 million children under the age of 5 years die every year of diarrhoea. Even mild diarrhoea, and that in adults, is a disabling symptom and an inconvenience.

Principles of management

Rational management of diarrhoea depends on establishing the underlying cause and instituting specific therapy only if necessary, since most diarrhoeas are self-limiting. Majority of enteropathogens are taken care of by motility and other defence mechanisms of the gut. Therapeutic measures may be grouped into:

(a) Treatment of fluid depletion and acidosis.
(b) Antimicrobial drugs.
(c) Nonspecific antidiarrhoeal drugs.

ORAL REHYDRATION

In majority of cases this is the only measure needed, especially if the fluid loss is mild (5–7% BW) or moderate (7.5–10% BW).

Oral rehydration is possible if glucose is added with salt. It capitalizes on the intactness of glucose facilitated Na^+ absorption, even when other mechanisms have failed or when intestinal secretion is excessive—the secreted fluid lacks glucose and cannot be reabsorbed. The general principles governing composition of oral rehydration solution (ORS) are:

(a) It should be isotonic or somewhat hypotonic, i.e. total osmolarity 200–310 mOsm/L (diarrhoea fluids are approximately isotonic with plasma).

(b) The molar ratio of glucose should be equal to or somewhat higher than Na^+, but not exceed 110 mM.

(c) Enough K^+ (15–25 mM) and bicarbonate/citrate (8–12 mM) should be provided to make up the losses in stool.

The WHO recommended a standard formula:

NaCl	60 mM = 3.5 g	to be dissolved in 1 L of water
KCl	20 mM = 1.5 g	
Trisod. citrate	30 mM = 2.9 g	
Glucose	110 mM = 20 g	

This provides Na^+ 90 mM, K^+ 20 mM, Cl^- 80 mM, citrate (base) 10 mM, glucose 110 mM and has a total osmolarity of 310 mOsm/L. It is based on the composition of cholera stools, particularly in children.

New formula WHO-ORS In 2002, a new formula low Na^+ low glucose ORS has been released by the WHO based on studies carried out in several developing countries among children and adults suffering from diarrhoeas.

The WHO and UNICEF have recommended replacement of standard (310 mOsm/L) ORS formula by the new (245 mOsm/L) formula.

Oral rehydration therapy (ORT) is not designed to stop diarrhoea, but to restore and maintain hydration, electrolyte and pH balance until diarrhoea ceases, mostly spontaneously.

New formula WHO-ORS

Content		*Concentrations*	
NaCl	: 2.6 g	Na^+	— 75 mM
KCl	: 1.5 g	K^+	— 20 mM
Trisod. citrate	: 2.9 g	Cl^-	— 65 mM
Glucose	: 13.5 g	Citrate	— 10 mM
Water	: 1 L	Glucose	— 75 mM

Total osmolarity 245 mOsm/L

ANTIMICROBIALS

One or more antimicrobial agent is almost routinely prescribed to every patient of diarrhoea. However, such drugs have a limited role in the overall treatment of diarrhoeal patients; the reasons are:

(i) Bacterial pathogen is responsible for only a fraction of cases.

(ii) Even in bacterial diarrhoea, antimicrobials alter the course of illness only in selected cases.

(iii) Antimicrobials may prolong the carrier state.

A. Antimicrobials are of no value In diarrhoea due to *noninfective causes*, such as irritable bowel syndrome, coeliac disease, pancreatic enzyme deficiency, tropical sprue (except when there is secondary infection), thyrotoxicosis as well as in *infective* diarrhoea due to rotavirus or *Salmonella* food poisoning.

B. Antimicrobials are useful only in severe disease (but not in mild cases) in case of:

(i) Travellers' diarrhoea: mostly due to enterotoxigenic *E.coli* (ETEC), *Campylobacter* or virus: cotrimoxazole, norfloxacin, doxycycline and erythromycin reduce the duration and total fluid needed only in severe cases.

(ii) Enteropathogenic *E. coli (EPEC):* is less common, but causes *Shigella*-like invasive illness. Cotrimoxazole, colistin, nalidixic acid or norfloxacin may be used.

(iii) *Shigella* enteritis: only when associated with blood and mucus in stools may be treated with ciprofloxacin, norfloxacin or nalidixic acid.

(iv) *Salmonella typhimurium* enteritis is often invasive; severe cases may be treated with a fluoroquinolone, cotrimoxazole or ampicillin.

(v) *Yersinia enterocolitica:* common in colder places, not in tropics. Cotrimoxazole is the most suitable drug in severe cases; ciprofloxacin is an alternative.

C. Antimicrobials are regularly useful in:

(i) Cholera: Though not life saving, tetracyclines reduce stool volume to nearly ½. Cotrimoxazole is an alternative, especially in children.

(ii) *Campylobacter jejuni:* Norfloxacin and other fluoroquinolones control diarrhoea. Erythromycin is fairly effective.

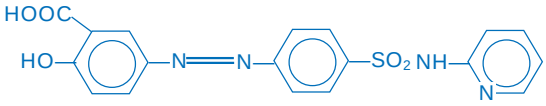
(iii) *Clostridium difficile:* produces antibiotic associated psuedo-membranous enterocolitis. The drug of choice for it is metronidazole.

(iv) Amoebiasis, (v) Giardiasis } metronidazole, diloxanide furoate are effective drugs.

NONSPECIFIC ANTIDIARRHOEAL AGENTS

1. Antisecretory drugs

Sulfasalazine (Salicylazosulfapyridine) It is a compound of 5-aminosalicylic acid (5-ASA) with sulfapyridine linked through an azo bond.



The azo bond is split by colonic bacteria to release 5-ASA and sulfapyridine. The former exerts a local antiinflammatory effect and is useful in ulcerative colitis and related inflammatory bowel diseases.

Mesalazine (Mesalamine) These are the official names given to 5-ASA. Realizing that 5-ASA is the active moiety in ulcerative colitis, it has been formulated as delayed release preparations by coating with acrylic polymer. Such preparations appear to be reliable for delivering 5-ASA to tge distal small bowel and colon: are as effective as sulfasalazine in inflammatory bowel disease and produce less side effects.

Drug interactions Coated mesalazine may enhance the gastric toxicity of glucocorticoids and hypoglycaemic action of sulfonylureas. Interaction with coumarins, furosemide, spironolactone, methotrexate and rifampicin are possible.

Corticosteroids Prednisolone (40 mg/day) or equivalent are highly effective in controlling symptoms/inducing remission in both ulcerative colitis and Crohn's disease.

2. Antimotility drugs

These are opioid drugs which increase small bowel tone and segmenting activity, reduce propulsive movements and diminish intestinal secretions while enhancing absorption. The major action appears to be mediated through μ opioid receptors located on enteric neuronal network, but direct action on intestinal smooth muscle and secretory/absorptive epithelium has also been demonstrated.

Codeine has prominent constipating action while its dependence producing liability is low. Side effects are nausea, vomiting and dizziness. It should be used only for short periods and with caution in children.

Diphenoxylate is a synthetic opioid used exclusively as constipating agent; action is similar to codeine. Because it is absorbed systemically and crosses blood-brain barrier—CNS effects do occur. Atropine is added in nonpharmacological dose to discourage abuse. It has caused respiratory depression, paralytic ileus and toxic megacolon in children—contraindicated below 6 years of age.

Loperamide is an opiate analogue with major peripheral μ opioid and additional weak anticholinergic property. As a constipating agent, it is much more potent than codeine. Because of poor water solubility—little is absorbed from the intestines. Entry into brain is negligible—CNS effects are rare, no abuse liability.

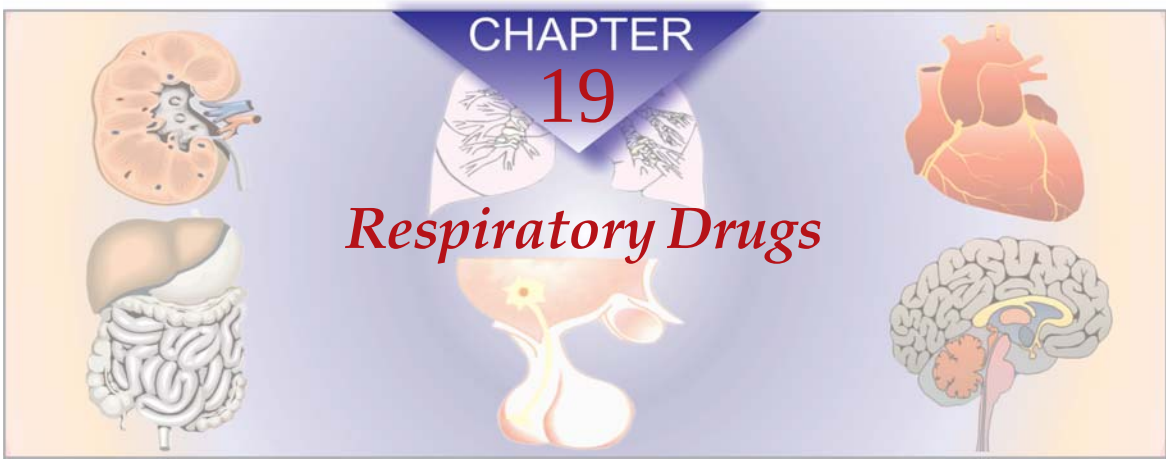
In addition to its opiate like action on motility, loperamide also inhibits secretion: directly interacts with calmodulin—this may be responsible for the antidiarrhoeal action.

Abdominal cramps and rashes are the most common side effects. Paralytic ileus, toxic megacolon with abdominal distension is a serious complication in young children—contraindicated in children < 4 years.

The utility of antimotility drugs in diarrhoea is limited to noninfective diarrhoea, mild travellers' diarrhoea and when diarrhoea is exhausting or idiopathic diarrhoea in AIDS patients. Their use is a short-term measure only.

Antimotility drugs are contraindicated in acute infective diarrhoeas because they delay clearance of the pathogen from the intestine. If invasive organisms (*Shigella*, EPEC, EH, etc.) are present, antimotility drugs can be disastrous.

Antimotility drugs can be used to induce deliberate short-term constipation, e.g. after anal surgery, and to reduce the volume, fluidity and bag cleaning frequency in ileostomy/colostomy patients.



CHAPTER 19

Respiratory Drugs

DRUGS FOR COUGH

Cough is a protective reflex, its purpose being expulsion of respiratory secretions or foreign particles from air passages. It occurs due to stimulation of mechano- or chemoreceptors in throat, respiratory passages or stretch receptors in the lungs. Cough may be useful or useless. Useless (nonproductive) cough should be suppressed. Useful (productive) cough serves to drain the airway, its suppression is not desirable, may even be harmful. Apart from specific remedies (antibiotics, etc.), cough may be treated as a symptom (nonspecific therapy) with:

1. *Pharyngeal Demulcents* Lozenges, cough drops, linctuses containing syrup, glycerine, liquorice.
2. *Expectorants (Mucokinetics)*
   Sodium and Potassium citrate or acetate, Potassium iodide, Guaiphenesin, balsum of Tolu, Vasaka, Ammonium chloride or carbonate. Bromhexine, Ambroxol, Carbocisteine
3. *Antitussives (Cough centre suppressants)*

(a) *Opioids* Codeine, Pholcodeine
(b) *Nonopioids* Noscapine, Dextromethorphan, Oxeladin, Chlophedianol.
(c) *Antihistamines* Chlorpheniramine, Diphenhydramine, Promethazine.

Pharyngeal demulcents sooth the throat and reduce afferent impulses from the inflamed/irritated pharyngeal mucosa, thus provide symptomatic relief in dry cough arising from throat.

Expectorants (Mucokinetics) are drugs believed to increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing.

Sodium and potassium citrate are considered to increase bronchial secretion by salt action. Potassium iodide is secreted by bronchial glands and can irritate the airway mucosa. Prolonged use can affect thyroid function. Guaiphenesin, vasaka, tolu balsum are plant products which are supposed to enhance bronchial secretion and mucociliary function while being secreted by tracheobronchial glands. Ammonium salts are nauseating—reflexly increase respiratory secretions. A variety of expectorant formulations containing an assortment of the above ingredients, often in combination with antitussives/antihistaminics are marketed and briskly promoted, but objective evidence of efficacy of these is nonconclusive.

Bromhexine A derivative of the alkaloid *vasicine,* obtained from vasaka, is a potent mucolytic and mucokinetic capable of inducing thin copious bronchial secretion. It depolymerises mucopolysaccharides directly as well as by liberating lysosomal enzymes. It is particularly useful if mucus plugs are present.

Side effects are rhinorrhoea, lacrimation, gastric irritation, hypersensitivity.

Ambroxol A metabolite of bromhexine having similar mucolytic action, uses and side effects.

Carbocisteine It liquefies viscid sputum by opening disulfide bonds in mucoproteins. Some patients of chronic bronchitis have been shown to benefit. Side effects are g.i. irritation and rashes.

ANTITUSSIVES

These are drugs that act in the CNS to raise the threshold of cough centre or act peripherally in the respiratory tract to reduce tussal impulses, or both these actions. Because they aim to control rather than eliminate cough, antitussives should be used only for dry unproductive cough or if it is unduly tiring, disturbs sleep or is hazardous (hernia, piles, cardiac disease, ocular surgery).

Codeine (*see* Ch. 24) An opium alkaloid, qualitatively similar to but less potent than morphine. It is more selective for cough centre and is treated as the standard antitussive; suppresses cough for about 6 hours. The antitussive action is blocked by naloxone indicating that it is exerted through opioid receptors in the brain. Abuse liability is low, but present; constipation is the chief drawback. Like morphine, it is contraindicated in asthmatics and in patients with diminished respiratory reserve.

Pholcodeine It has practically no analgesic or addicting property, but is similar in efficacy as antitussive to codeine and is longer acting—acts for 12 hours.

Noscapine (Narcotine) An opium alkaloid of the benzoisoquinoline series. It depresses cough but has no narcotic, analgesic or dependence inducing properties. It is nearly equipotent antitussive as codeine, especially useful in spasmodic cough. Headache and nausea occur occasionally as side effect. It can release histamine and produce bronchoconstriction in asthmatics.

Dextromethorphan A synthetic compound: the *d*-isomer has selective antitussive action (raises threshold of cough centre). As effective as codeine, does not depress mucociliary function of the airway mucosa and is practically devoid of constipating and addicting actions. Its antitussive action is not blocked by naloxone, therefore, not exerted through opioid receptors.
Side effect: Dizziness, nausea, drowsiness, ataxia.

Oxeladin Another synthetic centrally acting antitussive, devoid of opioid side effects.

Chlophedianol It is similar to oxeladin, has a slow onset and longer duration of antitussive action.
Side effect: Dryness of mouth, vertigo, irritability.

Antihistamines Many H_1 antihistamines have been conventionally added to antitussive/expectorant formulations. They afford relief in cough due to their sedative and anticholinergic actions, but lack selectivity for the cough centre. They have no expectorant property, may even reduce secretions by anticholinergic action. They have been specially promoted for cough in respiratory allergic states.

Bronchodilators Bronchospasm can induce or aggravate cough. Stimulation of pulmonary receptors can trigger both cough and bronchoconstriction, especially in individuals with bronchial hyperreactivity. Bronchodilators relieve cough in such individuals and improve the effectiveness of cough in clearing secretions by increasing surface velocity of airflow during cough. They should be used only when an element of bronchoconstriction is present and not routinely.

DRUGS FOR BRONCHIAL ASTHMA

Bronchial asthma is characterised by hyperresponsiveness of tracheobronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretion, mucosal edema and mucus plugging.

Asthma is now recognized to be a primarily inflammatory condition: inflammation underlying hyperreactivity. An allergic basis can be

demonstrated in many adult, and higher percentage of pediatric patients. In others, a variety of trigger factors (infection, irritants, pollution, exercise, exposure to cold air, psychogenic) may be involved:

Extrinsic asthma: It is mostly episodic, less prone to status asthmaticus.

Intrinsic asthma: It tends to be perennial, status asthmaticus is more common.

Mast cells (present in lungs) and inflammatory cells recruited as a result of initial reaction produce a multitude of mediators: histamine, TNFα, PGs, LTs, PAF, interleukins, etc. which constrict bronchial smooth muscle, cause mucosal edema, hyperemia and produce viscid secretions, all resulting in reversible airway obstruction. The inflammation perpetuates itself by cell-to-cell communication and recruitment of more and more inflammatory cells. Bronchial smooth muscle hypertrophy occurs over time and damage to bronchial epithelium accentuates the hyperreactivity. Vagal discharge to bronchial muscle is enhanced reflexly. Airway remodeling progressively worsens the disease.

Chronic obstructive pulmonary disease (COPD) is a progressive disease with emphysema (alveolar destruction) and bronchiolar fibrosis in variable proportions. The expiratory airflow limitation does not fluctuate markedly over long periods of time, but there are exacerbations precipitated by respiratory infections, pollutants, etc. It is clearly related to smoking and characteristically starts after the age of 40. Patients derive < 15% improvement in forced expiratory volume in 1 sec (FEV_1) following inhalation of a β agonist bronchodilator: airway obstruction is largely irreversible.

CLASSIFICATION

I. *Bronchodilators*

A. *Sympathomimetics:* Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol.
B. *Methylxanthines:* Theophylline, Aminophylline.
C. *Anticholinergics:* Ipratropium bromide, Tiotropium bromide.

II. *Leukotriene antagonists*

Montelukast, Zafirlukast.

III. *Mast cell stabilizers*

Sodium cromoglycate, Ketotifen.

IV. *Corticosteroids*

A. *Systemic:* Hydrocortisone, Prednisolone.
B. *Inhalational:* Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide.

SYMPATHOMIMETICS (*see* Ch. 6)

Adrenergic drugs cause bronchodilatation through β_2 receptor stimulation → increased cAMP formation in bronchial muscle cell → relaxation. In addition, increased cAMP in mast cells and other inflammatory cells decreases mediator release. Adrenergic drugs are the mainstay of treatment of reversible airway obstruction but should be cautiously used in hypertensives, heart patients and in those receiving digitalis. They are the fastest acting bronchodilators when inhaled.

The highly selective β_2 agonists like *salbutamol* and *terbutaline* are used in asthma to minimize cardiac side effects. Selectivity is further increased by inhaling the drug. Inhaled salbutamol produces bronchodilatation within 5 min and the action lasts for 2 to 4 hours. It is, therefore, used to abort and terminate attacks of asthma but is not suitable for round-the-clock prophylaxis. Muscle tremors are the dose-related side effect. Palpitation, restlessness, nervousness, throat irritation and ankle edema can also occur. Oral salbutamol acts for 4–6 hours, is longer acting and safer than isoprenaline, but similar in efficacy.

Because of more frequent side effects, oral β_2 agonist therapy is reserved for patients who cannot correctly use inhalers or during severe asthma exacerbations.

However, β_2 agonists do not reduce bronchial hyperreactivity: may even worsen it—this may be responsible for the diminished responsiveness seen after long-term use. Regular use also down-regulates bronchial β_2 receptors. It is felt that patients requiring regular β_2 agonists should be treated with inhaled steroids and use of β_2 agonist

inhalers should be restricted to symptomatic relief of wheezing.

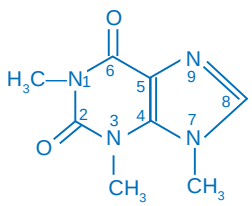
Salmeterol is the first long-acting selective β_2 agonist with a slow onset of action; used by inhalation on a twice daily schedule for maintenance therapy and for nocturnal asthma, but not for acute symptoms. Concern of asthma worsening due to regular use of inhaled β_2 agonists applies to salmeterol also. However, clinical studies have shown sustained improvement in asthma symptoms and lung function. Concurrent use of inhaled glucocorticoid with salmeterol is advocated for patients with persistent asthma.

Long-acting β_2 agonists are superior to short-acting ones in COPD.

Formoterol is another long-acting selective β_2 agonist which has a faster onset of action within 10 min. Therefore, it can be used for rapid reversal of bronchoconstriction as well as on a regular morning-evening schedule for round-the-clock bronchodilatation.

METHYLXANTHINES

Theophylline and its compounds have been extensively used in asthma, but are not considered first line drugs any more; used more often in COPD. Theophylline is one of the three naturally occurring methylated xanthine alkaloids *caffeine*, *theophylline* and *theobromine*. The chemical relation between the three is depicted below:



Theophylline—1, 3, Dimethyl Xanthine

Theobromine—3, 7, Dimethyl Xanthine

1, 3, 7, Trimethylxanthine
CAFFEINE

They are consumed as beverages. The sources and average alkaloid contents of the beverages, as they are usually prepared are given below:

1. *Thea sinensis* (Tea leaves)	Caffeine Theophylline	50 mg 1 mg	in an average cup of tea
2. *Coffea arabica* (Coffee seeds)	Caffeine	75 mg	in an average cup of coffee
3. *Theobroma cacao* (Cocoa, chocolate)	Theobromine Caffeine	200 mg 4 mg	in an average cup of cocoa
4. *Cola acuminata* (Guru nuts)	Caffeine	30 mg	in 200 ml bottle of cola drink

Pharmacological actions

1. *CNS* Caffeine and theophylline are CNS stimulants, primarily affect the higher centres. Caffeine produces a sense of wellbeing, alertness, beats boredom, allays fatigue, thinking becomes clearer. It tends to improve performance and increase motor activity. Higher doses cause nervousness, restlessness, panic, insomnia and excitement. Still higher doses produce tremors, delirium and convulsions. Theophylline has greater propensity to produce these adverse effects at higher doses and is definitely more toxic than caffeine.

They also stimulate medullary vagal, respiratory and vasomotor centres. Vomiting at high doses is due both to gastric irritation and CTZ stimulation.

2. *CVS* Methylxanthines directly stimulate the heart and increase force of myocardial contractions. They tend to increase heart rate by direct action, but decrease it by causing vagal stimulation—net effect is variable. Tachycardia is more common with theophylline. Cardiac output and cardiac work are increased. At high doses, cardiac arrhythmias may be produced.

Methylxanthines, especially theophylline, dilate systemic blood vessels, including coronaries, by direct action: peripheral resistance is reduced. However, cranial vessels are constricted, especially by caffeine: this is one of the basis of its use in migraine.

Effect on BP is variable and unpredictable.

3. *Smooth muscles* All smooth muscles are relaxed, most prominent effect is exerted on

bronchi, especially in asthmatics. Theophylline is more potent: slow but sustained dose-related bronchodilatation is produced—vital capacity is increased. Biliary spasm is relieved, but effect on intestines and urinary tract is negligible. Caffeine has minimal actions.

4. *Kidney* They are mild diuretics; act by inhibiting tubular reabsorption of Na^+ and water.

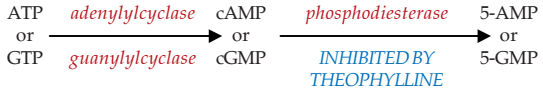
5. *Skeletal muscles* Caffeine enhances contractile power of skeletal muscles. Enhanced diaphragmatic contractility probably contributes to beneficial effects of theophylline in dyspnoea.

6. *Stomach* Methylxanthines stimulate secretion of acid and pepsin in stomach. They are also gastric irritants.

7. *Metabolism* Caffeine and to a smaller extent theophylline increase BMR.

8. *Mast cells and inflammatory cells* Theophylline inhibits the release of histamine and other mediators from mast cells and activated inflammatory cells. This may contribute to its therapeutic effect in bronchial asthma.

Mechanism of action Three distinct cellular actions of methylxanthines have been defined—
(a) Release of Ca^{2+} from sarcoplasmic reticulum, especially in skeletal and cardiac muscle.
(b) Inhibition of phosphodiesterase which degrades cyclic nucleotides intracellularly.



Thus, the concentration of cyclic nucleotides is increased. Bronchodilatation, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells.
(c) Blockade of adenosine receptors: adenosine acts as a local mediator in CNS, CVS and other organs—contracts smooth muscles, especially bronchial; dilates cerebral blood vessels, depresses cardiac pacemaker and inhibits gastric secretion. Methylxanthines produce opposite effects.

Action (c) is exerted at concentrations in the therapeutic range and may be more important. There is some evidence indicating contribution of raised cAMP levels (action 'b') in bronchial smooth muscle to the therapeutic response.

Pharmacokinetics Theophylline is well absorbed orally. It is distributed in all tissues and extensively metabolized in liver by demethylation and oxidation. Only 10% is excreted unchanged in urine. At therapeutic concentrations, the t½ in adults is 7–12 hours. Children eliminate it much faster and elderly more slowly.

Theophylline metabolizing enzymes are saturable, t½ is prolonged with higher doses as kinetics changes from first to zero order: plasma concentrations, therefore, increase disproportionately.

Adverse effects Theophylline has a narrow margin of safety. Adverse effects are primarily referable to g.i.t., CNS and CVS, *viz* dyspepsia, vomiting, nervousness, tremor, delirium, hypotension, arrhythmias and convulsions.

Interactions

1. Agents which induce theophylline metabolism and decrease its plasma level are smoking, phenytoin, rifampicin, phenobarbitone, charcoal broiled meat meal.
2. Drugs which inhibit theophylline metabolism and increase its plasma level are—erythromycin, ciprofloxacin, cimetidine, oral contraceptives, allopurinol; dose should be reduced to 2/3rd.
3. Theophylline enhances the effects of—furosemide, sympathomimetics, digitalis, oral anticoagulants, hypoglycaemics.

Uses

1. *Bronchial asthma and COPD*: Theophylline benefits by causing bronchodilatation as well as presumably by decreasing release of inflammatory mediators, improved mucociliary clearance, stimulation of respiratory drive and by augmenting diaphragmatic contractility. However,

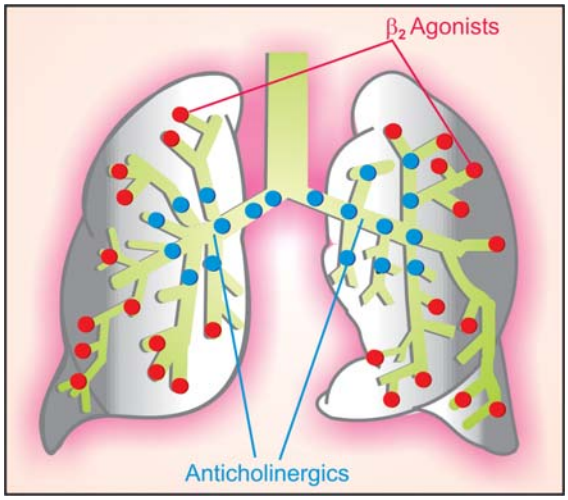


Fig. 19.1: Primary sites of bronchodilator action of inhaled adrenergic β_2 agonists and inhaled anticholinergics. Salbutamol mainly relaxes bronchiolar smooth muscle; Ipratropium blocks bronchoconstriction mainly in the larger airways

because of narrow margin of safety and limited efficacy, its use has declined. Oral theophylline can be used in COPD and in mild-to-moderately severe asthma, as a 3rd line drug supplemented by inhaled β_2 agonists.

Use of intravenous aminophylline (theophylline-ethylenediamine, a water-soluble double salt) in status asthmaticus is outmoded.

2. *Apnoea in premature infant*: Theophylline reduces the frequency and duration of episodes of apnoea that occur in some preterm infants.

ANTICHOLINERGICS (*see* Ch. 5)

Atropinic drugs cause bronchodilatation by blocking cholinergic constrictor tone; act primarily in the larger airways (Fig. 19.1).

Inhaled ipratropium bromide is less efficacious than inhaled sympathomimetics, but can add to their response. Patients of asthmatic bronchitis, COPD and psychogenic asthma respond better to anticholinergics. Inhaled ipratropium/tiotropium are the bronchodilators of choice in COPD. They produce slower response than inhaled sympathomimetics and are better suited for regular prophylactic use than for control of an acute attack. Nebulized ipratropium mixed with salbutamol is employed in refractory asthma.

LEUKOTRIENE ANTAGONISTS

Since it was realized that cystenyl leukotrienes (LT-C_4/D_4) are important mediators of bronchial asthma, efforts were made to develop their antagonists and synthesis inhibitors. Two *cys*LT_1 receptor antagonists *montelukast* and *zafirlukast* have recently become available.

Montelukast and Zafirlukast Both have similar actions and clinical utility. They competitively antagonise *cys*LT_1 receptor mediated bronchoconstriction, increased vascular permeability and recruitment of eosinophils. Bronchodilatation, reduced sputum eosinophil count, suppression of bronchial inflammation and hyperreactivity are noted in asthma patients. Parameters of lung function show variable but definite improvement.

Montelukast and zafirlukast are indicated for prophylactic therapy of mild-to-moderate asthma as alternatives to inhaled glucocorticoids. Though overall efficacy is lower than inhaled steroids, they may obviate need for the latter. In severe asthma, they may permit reduction in steroid dose. However, they are not to be used for terminating asthma episodes.

Both montelukast and zafirlukast are very safe drugs; produce few side effects like headache and rashes. Eosinophilia and neuropathy are infrequent.

They are well absorbed orally. The plasma t½ of montelukast is 3 to 6 hours, while that of zafirlukast is 8 to 12 hours.

MAST CELL STABILIZERS

Sodium cromoglycate (Cromolyn sod.)

It is a synthetic chromone derivative which inhibits degranulation of mast cells by trigger stimuli. Release of mediators of asthma like histamine,

LTs, PAF, interleukins, etc. from mast cells as well as other inflammatory cells is opposed. Long-term treatment decreases the cellular inflammatory response: bronchial hyperreactivity is reduced to variable extents: bronchospasm induced by allergens, irritants, cold air and exercise may be prevented. However, AG:AB reaction is not interfered with. It is also not a bronchodilator and does not antagonise constrictor action of histamine, ACh, LTs, etc. Therefore, it is ineffective if given during an asthmatic attack.

Sod. cromoglycate is not absorbed orally. It is administered as an aerosol through metered dose inhaler.

Uses

1. *Bronchial asthma:* Sod. cromoglycate is used as a long-term prophylactic in patients not adequately controlled by inhaled bronchodilators. Therapeutic benefit is more likely in extrinsic (atopic) and exercise induced asthma. Its popularity has declined because of less complete and less consistent response than inhaled steroids.

2. *Allergic rhinitis:* Cromoglycate is not a nasal decongestant, but regular prophylactic use as a nasal spray produces symptomatic improvement in many patients.

3. *Allergic conjunctivitis:* Regular use as eye drops is beneficial in some chronic cases.

Adverse effects Bronchospasm, throat irritation and cough occurs in some patients, especially with fine powder inhalation. Rarely headache, dizziness, and arthralgia have been reported.

Ketotifen It is an antihistaminic (H_1) with some cromoglycate like action; stimulation of immunogenic and inflammatory cells (mast cells, macrophages, eosinophils, lymphocytes, neutrophils) and mediator release are inhibited. It is not a bronchodilator but produces sedation.

After 6–12 weeks of use, it reduces respiratory symptoms in 50–70% patients of bronchial asthma, but improvement in lung function is marginal. It also produces symptomatic relief in many patients with atopic dermatitis, perennial rhinitis, conjunctivitis, urticaria and food allergy.

CORTICOSTEROIDS

These also are not bronchodilators; benefit by reducing bronchial hyperreactivity, mucosal edema and by suppressing inflammatory response to AG:AB reaction or other trigger stimuli. Their mechanism of action is detailed in Ch. 14.

The realization that asthma is primarily an inflammatory disease which, if not controlled, accentuates with time, and the availability of inhaled steroids that produce few adverse effects has led to early introduction and more extensive use of glucocorticoids in asthma. Corticosteroids afford more complete and sustained symptomatic relief than bronchodilators or cromoglycate, suppress bronchial hyperreactivity, and may influence airway remodeling, retarding disease progression. However, long-term systemic steroid therapy has its own adverse effects which may be worse than asthma itself.

Systemic steroid therapy It is resorted to in asthma under the following two situations:

(i) *Severe chronic asthma:* not controlled by bronchodilators and inhaled steroids, or when there are frequent recurrences of increasing severity. After good control, try shifting the patient onto an inhaled steroid. Few patients require long-term oral steroids—in them dose should be kept at minimum.

(ii) *Status asthmaticus/acute asthma exacerbation:* asthma attack not respnding to intensive bronchodilator therapy: start with high dose of a rapidly acting i.v. glucocorticoid which generally acts in 6–24 hours—shift to oral therapy for 5 to 7 days and then discontinue abruptly or taper rapidly.

Inhaled steroids These have high topical and low systemic activity (due to poor absorption and/or marked first pass metabolism).

Beclomethasone dipropionate, *budesonide* and *fluticasone* have similar properties. Because airway inflammation is present in early mild disease as well, and bronchial remodeling starts developing from the beginning, it has been suggested that inhaled steroids should be the 'step one' for all asthma patients. However, currently inhaled steroids are not considered necessary for patients with mild and episodic asthma. They are indicated when inhaled β_2 agonists are required almost daily or the disease is not only episodic.

Inhaled steroids suppress bronchial inflammation, increase peak expiratory flow rate, reduce need for rescue β_2-agonist inhalations and prevent episodes of acute asthma. However, they have no role during an acute attack or in status asthmaticus. Long-term experience has shown that efficacy of inhaled steroids is maintained and reinstitution of oral steroids is seldom needed. Short courses of oral steroids may be added during periods of exacerbation.

COPD: High dose inhaled steroids are beneficial only in advanced COPD with frequent exacerbations; should not be used in early/mild cases.

Hoarseness of voice, dysphonia, sore throat, asymptomatic or symptomatic oropharyngeal candidiasis are the most common side effects. This can be minimized by use of a spacer, gargling after every dose and prevented as well as treated by topical nystatin.

Choice of treatment

A stepwise guideline to the treatment of asthma as per needs of the patient has been recommended:

1. *Mild episodic asthma* (symptoms less than once daily, normal in between attacks): Inhaled short-acting β_2 agonist at onset of each episode. No regular prophylactic therapy.

2. *Seasonal asthma* Start regular inhaled cromoglycate/low dose inhaled steroid (200–400 µg/day) 3–4 weeks before anticipated seasonal attacks and continue till 3–4 weeks after the season is over. Treat individual episodes with inhaled short-acting β_2 agonist.

3. *Mild chronic asthma with occasional exacerbations* (symptoms once daily or so) Regular inhaled low-dose steroid. Alternatively, inhaled cromoglycate. Episode treatment with inhaled short-acting β_2 agonist.

4. *Moderate asthma with frequent exacerbations* (attacks affect activity, occur > 1 per day or mild baseline symptoms) increasing doses of inhaled steroid (up to 1,600 µg/day) + inhaled long-acting β_2 agonist. Leukotriene antagonists may be tried in patients not accepting inhaled steroids. Episode treatment with inhaled short-acting β_2 agonist.

5. *Severe asthma* (continuous symptoms; frequent exacerbations/hospitalization) Regular inhaled steroid (800–2,000 µg/day) through a large volume spacer device + inhaled long-acting β_2 agonist (salmeterol) twice daily. Rescue treatment with short-acting inhaled β_2 agonist. Additional treatment with one or more of the following may be considered:

Sustained release oral theophylline/inhaled ipratropium bromide.

In patients not adequately controlled or those needing frequent emergency care—institute oral steroid therapy.

6. *Status asthmaticus/Refractory asthma*

(i) Hydrocortisone hemisuccinate 100 mg i.v. *stat* followed by 100 mg/8 hr infusion.

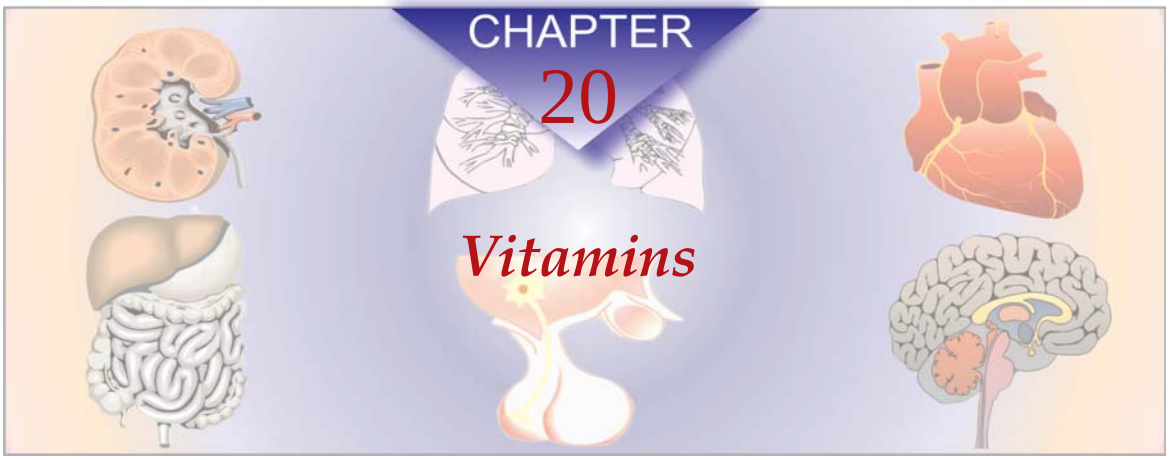
(ii) Nebulized salbutamol + ipratropium bromide intermittent inhalations.

(iii) Intermittent humidified oxygen inhalation.

(iv) Salbutamol/terbutaline 0.4 mg i.m./s.c. may be added since inhaled drug may not reach smaller bronchi due to severe narrowing/plugging.

(v) Treat chest infection with intensive antibiotic therapy.

(vi) Correct dehydration and acidosis with saline + sod. bicarbonate/lactate infusion.



Vitamins are nonenergy producing organic compounds, essential for normal human metabolism, that must be supplied in small quantities in the diet. This definition excludes the inorganic essential trace minerals and essential amino acids and fatty acids which are required in much larger quantities.

The importance of vitamins as drugs is primarily in the prevention and treatment of deficiency diseases. Some vitamins do have other empirical uses in pharmacological doses. Vitamins, as a class, are overpromoted, overprescribed and overused. Myths like 'they energise the body', 'any physical illness is accompanied by vitamin deficiency', 'vitamin intake in normal diet is precariously marginal', 'they are harmless' are rampant.

Vitamins are traditionally divided into two groups:

(a) *Fat soluble* **(A, D, E, K):** These (except vit K) are stored in the body for prolonged periods and are liable to cause cumulative toxicity after regular ingestion of large amounts. Some interact with specific cellular receptors analogous to hormones.

(b) *Water soluble* (B complex, C): These are meagerly stored: excess is excreted with little chance of toxicity. They act as cofactors for specific enzymes of intermediary metabolism.

Vitamin D (Ch. 16), vit K, folic acid and B_{12} (Ch. 17) have already been considered. Some relevant information is tabulated in Table 20.1.

Table 20.1: Chemical forms, stability and daily allowance of vitamins

Vitamin	*Chemical forms*	*Thermostability*	*Daily allowance (adult males)*
	Fat-soluble vitamins		
A	Retinol (A_1) Dehydroretinol (A_2) β-Carotene (provit.)	Stable in absence of air	1000 µg (4,000 IU)
D	Calciferol (D_2) Cholecalciferol (D_3) Calcitriol	Stable	5 µg (200 IU) 1 µg
E	α-Tocopherol	Stable; air & UV light decompose	10 mg
K	Phytonadione (K_1) (Phylloquinone) Menaquinones (K_2) Menadione (K_3) Acetomenaphthone	Stable, decomposed by light	50–100 µg
	Water-soluble vitamins		
B_1	Thiamine	Relatively labile	1.5 mg
B_2	Riboflavin	Relatively stable	1.7 mg
B_3	Nicotinic acid Nicotinamide } Niacin Tryptophan (provit.)	Stable	20 mg
B_6	Pyridoxine Pyridoxal Pyridoxamine	Stable in absence of air	2 mg
	Pantothenic acid	Labile	4–7 mg
	Biotin	Stable	0.1–0.2 mg
	Folic acid Folinic acid	Labile	0.2 mg
B_{12}	Cyanocobalamin Hydroxocobalamin Methylcobalamin	Stable	2 µg
C	Ascorbic acid	Labile in solution	60 mg

FAT-SOLUBLE VITAMINS

VITAMIN A

Vitamin A occurs in nature in several forms, viz. retinol, retinal, dehydroretinal in fish liver oils, egg, milk, butter. The plant pigment β carotene is a provitamin found in carrot, turnip, spinach, etc.

Retinol is absorbed from the intestines by a carrier-mediated transport. Absorption is aided by bile and is normally complete, but not in steatorrhoea, bile deficiency and from protein poor diet. Retinol ester circulates in chylomicrons and is stored in liver cells. Free retinol released by hepatocytes combines with *retinol binding protein* (*RBP* a plasma globulin) and is transported to the target cells. On entering them, it gets bound to the *cellular retinol binding protein* (*CRBP*). Small amount is conjugated with glucuronic acid, excreted in bile, undergoes enterohepatic circulation.

In contrast to retinol, only 30% of dietary β carotene is absorbed. It is split into two molecules of *retinal* in the intestinal wall; only half of this is reduced to retinol and utilized.

Physiological role and actions

(a) *Visual cycle* Retinal generated by reversible oxidation of retinol is a component of the light sensitive pigment *Rhodopsin* which is synthesized by rods during dark adaptation. This pigment gets bleached and split into its components by dim light and in the process generates a nerve impulse. Retinal so released is reutilized. A similar pigment (Iodopsin) is synthesized in the cones—responsible for vision in bright light, colour vision and primary dark adaptation. In vit. A deficiency rods are affected more than cones; irreversible structural changes with permanent night blindness occur if the deprivation is long term.

(b) *Epithelial tissue* Vit A promotes differentiation and maintains structural integrity of epithelia all over the body. It also promotes mucus secretion, inhibits keratinization and improves resistance to infection. It appears to have the ability to retard development of malignancies of epithelial structures. Vit A is also required for bone growth.

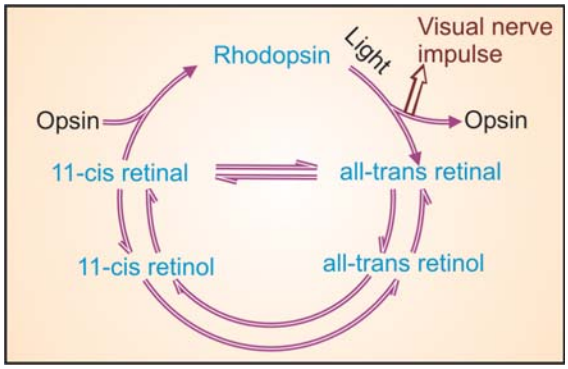


Fig. 20.1: The role of vit A in visual cycle

(c) *Reproduction* Retinol is needed for maintenance of spermatogenesis and foetal development.

(d) *Immunity* Increased susceptibility to infection occurs in vit A deficiency. Physiological amount of vit A appears to be required for proper antibody response, normal lymphocyte proliferation and killer cell function.

Deficiency and use Vit A deficiency is quite prevalent, especially among infants and children in developing countries. Manifestations are:

- Xerosis (dryness) of eye, 'Bitot's spots', keratomalacia (softening of cornea), corneal opacities, night blindness (nyctalopia) progressing to total blindness.
- Dry and rough skin with papules (phrynoderma), hyperkeratinization, atrophy of sweat glands.
- Keratinization of bronchopulmonary epithelium, increased susceptibility to infection.
- Unhealthy gastrointestinal mucosa, diarrhoea.
- Increased tendency to urinary stone formation due to shedding of ureteric epithelial lining.
- Sterility due to faulty spermatogenesis, abortions, foetal malformations.
- Growth retardation, impairment of special senses.

Vit A is used for prophylaxis (3,000–5,000 IU/day) and treatment (50,000–100,000 IU for 1–3

days) of vit A deficiency. Retinoic acid and other retinoids are used for acne, psoriasis.

Hypervitaminosis A Regular ingestion of gross excess of retinol (100,000 IU daily for months) has produced toxicity—nausea, vomiting, itching, erythema, dermatitis, exfoliation, hair loss, bone and joint pains, loss of appetite, irritability, bleeding, increased intracranial tension and chronic liver disease. Excess retinol is also teratogenic in animals and man. Daily intake should not exceed 20,000 IU.

Acute poisoning has been described after consumption of polar bear liver which contains 30,000 IU/g vit A.

Retinoic acid (vit A acid) Retinoic acid has vit A activity in epithelial tissues and promotes growth, but is inactive in eye and reproductive organs. All-trans retinoic acid (Tretinoin) is used topically, while 13–cis retinoic acid (Isotretinoin) is given orally for acne.

Retinoid receptors Retinol and retinoic acid act through *nuclear retinoid receptors* which function in a manner analogous to the steroid receptors: activation results in modulation of protein synthesis. Two distinct families of retinoid receptors, *viz. Retinoic acid receptors (RARs)* and *Retinoid X receptors (RXRs)* have been identified with differing affinities for different retinoids.

VITAMIN E

A number of tocopherols, of which α tocopherol is the most abundant and potent, have vit E activity. Wheat germ oil is the richest source, others are cereals, nuts, spinach and egg yolk.

Vit E is absorbed from intestine through lymph with the help of bile; it circulates in plasma in association with β-lipoprotein, is stored in tissues and excreted slowly in bile and urine as metabolites.

Physiological role and actions Vit E acts as *antioxidant*, protecting unsaturated lipids in cell membranes, coenzyme Q, etc. from free radical oxidation damage and limiting generation of toxic peroxidation products. However, vit E might be having some more specific action or a structural role in biological membranes.

Deficiency Experimental vit E deficiency in animals produces recurrent abortion, degenerative changes in spinal cord, skeletal muscles and heart, and haemolytic anaemia. No clear-cut vit E deficiency syndrome has been described in humans, but vit E deficiency has been implicated in certain neuromuscular diseases in children, neurological defects in hepatobiliary disease and some cases of haemolytic anaemia.

Supplemental doses of vit E have been given prophylactically to patients with hepatobiliary disease, haemolytic anaemia, to premature infants and subjects with G-6-PD deficiency or acanthocytosis.

Large doses (400–600 mg/day) have been reported to afford symptomatic improvement in intermittent claudication, fibrocystic breast disease and nocturnal muscle cramps.

For its antioxidant property, vit E has been promoted for recurrent abortion, sterility, menopausal syndrome, toxaemia of pregnancy, atherosclerosis, ischaemic heart disease, cancer prevention, several skin diseases, prevention of neurodegenerative disorders, and many other conditions, but without convincing evidence of benefit.

Toxicity Even large doses of vit E for long periods have not produced any significant toxicity, but creatinuria and impaired wound healing have been reported; abdominal cramps, loose motions and lethargy have been described as side effects of vit E.

Vit E can interfere with iron therapy.

WATER-SOLUBLE VITAMINS

THE VITAMIN B COMPLEX GROUP

Thiamine (Aneurine, B_1)

Thiamine is a pyrimidine compound present in the outer layers of cereals (rice polishing), pulses, nuts, green vegetables, yeasts, egg and meat.

Physiological amounts are absorbed by active transport. When large doses are given orally, some passive diffusion also occurs. Limited amounts are stored in tissues; excess is rapidly excreted in urine.

Physiological role After conversion in the body to *Thiamine pyrophosphate*, it acts as a coenzyme in carbohydrate metabolism: decarboxylation of ketoacids and hexose monophosphate shunt. Requirement is dependent upon carbohydrate intake. It also appears to play some role in neuromuscular transmission.

Deficiency symptoms The syndrome of thiamine deficiency beriberi is seen in *dry* and *wet* forms:

Dry Beriberi: Neurological symptoms are prominent—polyneuritis with numbness, tingling, hyperesthesia, muscular weakness and atrophy resulting in 'wrist drop', 'foot drop', mental changes, sluggishness, poor memory, loss of appetite and constipation.

Wet Beriberi: Cardiovascular system is primarily affected—palpitation, breathlessness, high output cardiac failure and ECG changes. Protein deficiency is commonly associated and adds to the generalised anasarka due to CHF.

Therapeutic uses

1. Prophylactically (2–10 mg daily) in infants, pregnant women, chronic diarrhoeas, patients on parenteral alimentation.
2. Beriberi—100 mg/day i.m. or i.v.
3. Chronic alcoholics: Most neurological symptoms are due to thiamine deficiency.
4. In neurological and cardiovascular disorders, hyperemesis gravidarum, chronic anorexia and obstinate constipation—symptoms improve dramatically if thiamine deficiency has been causative.

Thiamine is nontoxic.

Riboflavin (B_2)

Riboflavin is a yellow flavone compound found in milk, egg, liver, green leafy vegetables, grains. It is well absorbed by active transport and phosphorylated in the intestine. Riboflavin phosphate (Flavin mononucleotide: FMN) is formed in other tissues as well. Body does not significantly store riboflavin; larger doses are excreted unchanged in urine.

Actions and physiological role Flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) are coenzymes for flavoproteins involved in many oxidation-reduction reactions.

Deficiency symptoms Riboflavin deficiency generally occurs in association with other deficiencies. Characteristic lesions are angular stomatitis; sore and raw tongue, lips, throat, ulcers in mouth; vascularization of cornea. Dry scaly skin, loss of hair; anaemia and neuropathy develop later.

Riboflavin is used only to prevent and treat ariboflavinosis.

Niacin (B_3)

Niacin refers to *Nicotinic acid* as well as *Nicotinamide*—pyridine compounds found in liver, fish, meat, cereal husk, nuts and pulses. The amino acid *tryptophan* (mainly from animal protein) can be regarded as a provitamin, as it is partially converted in the body to nicotinic acid.

Niacin is completely absorbed from gastrointestinal tract. Physiological amounts are metabolized in the body, while large doses are excreted unchanged in urine. Modest amounts are stored in liver.

Physiological role and actions Nicotinic acid is readily converted to its amide which is a component of the coenzyme *Nicotinamide-adenine-dinucleotide* (NAD) and its *phosphate* (NADP) involved in oxidation-reduction reactions. These pyridine nucleotides act as hydrogen acceptors in the electron transport chain in tissue respiration, glycolysis and fat synthesis.

Nicotinic acid (but not nicotinamide) in large doses is a vasodilator, particularly of cutaneous vessels. It also lowers plasma lipids.

Deficiency symptoms Niacin deficiency produces 'Pellagra', cardinal manifestations of which are: *Dermatitis*—sun burn like dermal rash on hands, legs and face, *Diarrhoea*—with enteritis, stomatitis, glossitis, and *Dementia*—with hallucinations preceded by headache, insomnia, poor memory, motor and sensory disturbances.

Anaemia and hypoproteinaemia are common in pellagra. Chronic alcoholics are particularly at risk of developing pellagra.

Therapeutic uses

1. Prophylaxis and treatment of pellagra. Nicotinamide is preferred because it does not cause flushing and other side effects seen with nicotinic acid.
2. Hartnup's disease: in which tryptophan transport is impaired.
3. Nicotinic acid (not nicotinamide) has been used in peripheral vascular disease and as hypolipidaemic drug (Ch. 17).

Adverse effects Nicotinic acid, in pharmacological doses, has many side effects and toxicities (p. 264). Nicotinamide is innocuous.

Pyridoxine (B_6)

Pyridoxine, Pyriodoxal and *Pyridoxamine* are related naturally occurring pyridine compounds that have vit B_6 activity. Dietary sources are—liver, meat, egg, soybean, vegetables and whole grain. All three forms of the vitamin are well absorbed from the intestine. They are oxidized in the body and excreted as pyridoxic acid. Little is stored.

Physiological role and actions Pyridoxine and pyridoxamine are readily oxidized to pyridoxal which is then phosphorylated to *pyridoxal phosphate*—the coenzyme form. Pyridoxal dependent enzymes include transaminases and decarboxylases involved in synthesis and metabolism of amino acids, formation of 5-HT, dopamine, histamine, GABA and aminolevulinic acid (first step in synthesis of haeme). High protein diet increases pyridoxine requirement.

Prolonged intake of large doses of pyridoxine can suppress lactation, give rise to dependence, and has been linked with sensory neuropathy. Otherwise, pyridoxine is free from pharmacological actions and side effects.

Drug interactions

1. Isoniazid reacts with pyridoxal to form a hydrazone, and thus inhibits generation of pyridoxal phosphate. Isoniazid also combines with pyridoxal phosphate to interfere with its coenzyme function. Due to formation of hydrazones, the renal excretion of pyridoxine compounds is increased. Thus, isoniazid therapy produces a pyridoxine deficiency state.
2. Hydralazine, cycloserine and penicillamine also interfere with pyridoxine utilization and action.
3. Pyridoxine, by promoting formation of dopamine from levodopa in peripheral tissues, reduces its availability in the brain, abolishing the therapeutic effect in parkinsonism.

Deficiency symptoms Deficiency of vit B_6 usually occurs in association with that of other B vitamins. Symptoms ascribed to pyridoxine deficiency are—seborrheic dermatitis, glossitis, growth retardation, mental confusion, lowered seizure threshold or convulsions, peripheral neuritis and anaemia.

Therapeutic uses

1. Prophylactically (2–5 mg daily) in alcoholics and patients with deficiency of other B vitamins.
2. To prevent and treat (10–50 mg/day) isoniazid, hydralazine and cycloserine induced neurological disturbances.
3. Pyridoxine responsive anaemia (due to defective haeme synthesis) and homocystinuria are rare genetic disorders that are benefited by large doses of pyridoxine.

VITAMIN C (ASCORBIC ACID)

Ascorbic acid is a 6 carbon organic acid with structural similarity to glucose. It is a potent

reducing agent and *l*-form is biologically active. Citrus fruits (lemons, oranges) and black currants are the richest sources; others are tomato, potato, green chilies, cabbage and other vegetables.

Ascorbic acid is nearly completely absorbed from g.i.t. and widely distributed extra-and intracellularly. Increasing proportions are excreted in urine with higher intakes and body is not able to store more than 2.5 g. It is partly oxidized to active (dehydroascorbic acid) and inactive (oxalic acid) metabolites.

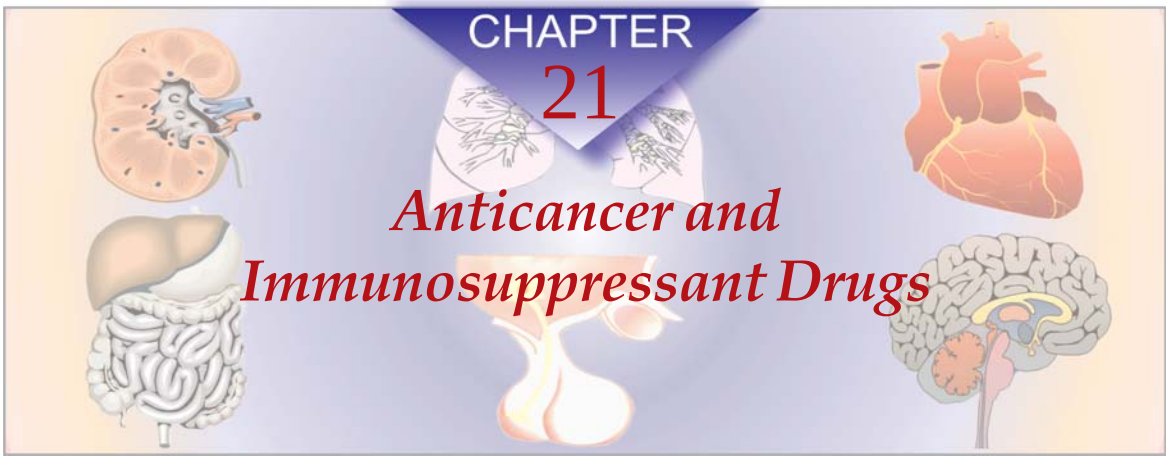
Physiological role and actions Vit C plays a role in many oxidative and other metabolic reactions, e.g. hydroxylation of proline and lysine residues of protocollagen—essential for formation and stabilization of collagen; conversion of folic acid to folinic acid, biosynthesis of adrenal steroids, catecholamines, oxytocin and ADH as well as metabolism of cyclic nucleotides and prostaglandins.

Deficiency symptoms Severe vit C deficiency *Scurvy*, once prevalent among sailors is now seen only in malnourished infants, children, elderly, alcoholics and drug addicts. Symptoms stem primarily from connective tissue defect: increased capillary fragility—swollen and bleeding gums, petechial and subperiosteal haemorrhages, deformed teeth, brittle bones, impaired wound healing, anaemia and growth retardation.

Therapeutic uses

1. Prevention of ascorbic acid deficiency in individuals at risk (*see* above) and in infants: 50–100 mg/ day.
2. Treatment of scurvy—0.5–1.5 g/day.
3. Postoperatively (500 mg daily): though vit C does not enhance normal healing, suboptimal healing can be guarded against.
4. Anaemia: Ascorbic acid enhances iron absorption and is frequently combined with ferrous salts. Anaemia of scurvy is corrected by ascorbic acid.
5. To acidify urine (1 g TDS-QID) in urinary tract infections.
6. Large doses (2–6 g/day) of ascorbic acid have been tried for a variety of purposes (common cold to cancer) with inconsistent results. Severity of common cold symptoms may be somewhat reduced, but not the duration of illness or its incidence.

Adverse effects Ascorbic acid is well tolerated in usual doses. Mega doses given for long periods can cause 'rebound scurvy' on stoppage. The risk of urinary oxalate stones may be increased.



CHAPTER 21

Anticancer and Immunosuppressant Drugs

ANTICANCER DRUGS

The anticancer drugs either kill cancer cells or modify their growth. However, selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy. Cancer chemotherapy is now of established value and a highly specialized field; only the general principles and an outline will be presented here.

In addition to their prominent role in leukaemias and lymphomas, drugs are used in conjunction with surgery, radiotherapy and immunotherapy in the *combined modality approach* for many solid tumours, especially metastatic.

Cancer chemotherapy is employed for:

1. Cure or prolonged remission: as the primary treatment modality.
2. Palliation: alleviation of symptoms and/or prolongation of life.
3. Adjuvant chemotherapy: to mop up any residual malignant cells after surgery or radiotherapy.

CLASSIFICATION

A. Drugs acting directly on cells (Cytotoxic drugs)

1.	*Alkylating agents*	
	Nitrogen mustards	Mechlorethamine Cyclophosphamide, Chlorambucil, Melphalan
	Alkyl sulfonate	Busulfan
	Nitrosoureas	Lomustine (CCNU),
	Triazine	Dacarbazine (DTIC)
2.	*Antimetabolites*	
	Folate antagonist	Methotrexate (Mtx)
	Purine antagonist	6-Mercaptopurine (6-MP), 6-Thioguanine (6-TG), Azathioprine
	Pyrimidine antagonist	5-Fluorouracil (5-FU), Cytarabine
3.	*Vinca alkaloids*	Vincristine (Oncovin), Vinblastine
4.	*Taxanes*	Paclitaxel, Docetaxel
5.	*Epipodophyllotoxin*	Etoposide
6.	*Camptothecin analogues*	Topotecan, Irinotecan
7.	*Antibiotics*	Actinomycin D Doxorubicin Daunorubicin Bleomycins
8.	*Miscellaneous*	Hydroxyurea, Procarbazine, L-Asparaginase, Cisplatin, Carboplatin

B. Drugs altering hormonal milieu

1.	*Glucocorticoids*	Prednisolone and others
2.	*Estrogens*	Ethinylestradiol
3.	*Antiestrogen*	Tamoxifen
4.	*Antiandrogen*	Flutamide

5. *5-α reductase inhibitor* — Finasteride
6. *GnRH analogues* — Naferelin, Goserelin
7. *Progestins* — Hydroxyprogesterone acetate, etc.

General toxicity of cytotoxic drugs

Majority of the cytotoxic drugs have more profound effect on rapidly multiplying cells, because the most important target of action are the nucleic acids and their precursors; rapid nucleic acid synthesis occurs during cell division. Many cancers (especially large solid tumours) have a lower growth fraction (lower percentage of cells are in division) than normal bone marrow, epithelial linings, reticuloendothelial (RE) system and gonads. These tissues are particularly affected in a dose-dependent manner by majority of drugs; though there are differences in susceptibility to individual members.

1. *Bone marrow* Depression of bone marrow results in granulocytopenia, agranulocytosis, thrombocytopenia, aplastic anaemia. This is the most serious toxicity; often limits the dose that can be employed. Infections and bleeding are the usual complications.

2. *Lymphoreticular tissue* Lymphocytopenia and inhibition of lymphocyte function results in suppression of cell mediated as well as humoral immunity.

Because of action (1) and (2) + damage to epithelial surfaces, the host defence mechanisms (specific as well as nonspecific) are broken down → susceptibility to all infections is increased. Of particular importance are the opportunistic infections due to low pathogenicity organisms, e.g. *Candida*, *Pneumocystis carinii* and other fungi, *Herpes zoster*, cytomegalovirus, *Toxoplasma.*

3. *GIT* Stomatitis, diarrhoea, shedding of mucosa, haemorrhages occur due to decrease in the rate of renewal of the mucous lining. Drugs that frequently cause mucositis are—bleomycin, actinomycin D, daunorubicin, doxorubicin, fluorouracil and methotrexate.

Nausea and vomiting are prominent with many cytotoxic drugs. This is due to direct stimulation of CTZ by the drug as well as generation of emetic impulses/mediators from the upper g.i.t. and other areas.

The emetogenic potential of cytotoxic drugs may be graded as:

High	Moderate	Mild
Cisplatin	Carboplatin	Bleomycin
Mustine	Cytarabine	Chlorambucil
Cyclophosphamide	Procarbazine	Busulfan
Actinomycin D	Vinblastine	Fluorouracil
Dacarbazine	Doxorubicin	6-Mercaptopurine
Mithramycin	Daunorubicin	6-Thioguanine
		Hydroxyurea
		Vincristine
		Methotrexate
		Etoposide
		l-Asparaginase

4. *Skin* Alopecia occurs due to damage to the cells in hair follicles. Dermatitis is another complication.

5. *Gonads* Inhibition of gonadal cells causes oligozoospermia and impotence in males; inhibition of ovulation and amenorrhoea are common in females.

6. *Foetus* Practically all cytotoxic drugs given to pregnant women profoundly damage the developing foetus → abortion, foetal death, teratogenesis.

7. *Carcinogenicity* Secondary cancers, especially leukaemias, lymphomas and histocytic tumours appear with greater frequency many years after the use of cytotoxic drugs. This may be due to depression of cell mediated and humoral *blocking factors* against neoplasia.

8. *Hyperuricaemia* This is secondary to massive cell destruction (uric acid is a product of purine metabolism). Gout and urate stones in the urinary tract may develop. Allopurinol is protective by decreasing uric acid synthesis.

In addition to these general toxicities, individual drugs may produce specific adverse effects, e.g. neuropathy by vincristine, cardiomyopathy by doxorubicin, cystitis and alopecia by cyclophosphamide.

Oral complications of cancer chemotherapy

The oral mucosa is particularly susceptible to cytotoxic drugs because of high epithelial cell turnover. Many chemotherapeutic drugs produce oral lesions. Oral mucositis is often an early manifestation of toxicity. The gingival tissue and oral mucosa are regularly subjected to minor trauma during chewing, and breaches are common. Oral microbial flora is large and can be the source of local as well as blood-borne infection. Neutropenia and depression of immunity caused by the drug indirectly increase the chances of oral infections. Thrombocytopenia due to bone marrow depression may cause gingival or mucosal bleeding. Antifibrinolytic drugs like epsilon aminocaproic acid or tranexaemic acid may help check the bleeding. Platelet transfusion is required if the platelet count is very low. Xerostomia (causing rapid progression of dental caries) and angular cheilitis are other problems associated with chemotherapy.

Many of the oral/dental complications of chemotherapy can be minimized by a thorough dental check-up before starting the regimen. Any carious cavities, periodontal lesions, impacted last molars and other potential sources of infection should be appropriately treated. All sharp cusps or dentures should be smoothened to avoid injury. Good oral hygiene should be maintained throughout the course.

Stomatitis and oral ulcers can be treated with chlorhexidine mouthwash. Nystatin or clotrimazole lotion may be used for *Candida* infection. As mucositis progresses, oral lesions become increasingly painful and may interfere with eating. Benzocaine lozenges or lignocaine gel can reduce pain but may interfere with taste and increase the risk of injury to oral mucosa. Opioid analgesics may have to be prescribed. Systemic antibiotics to cover organisms like *Pseudomonas, Klebsiella, E.coli* are often needed in addition to those for gram-positive cocci and anaerobes for chemotherapy related oral infections.

In a patient receiving chemotherapy, any dental procedure should be undertaken only after giving due regard to his/her immune and haemostatic status and in consultation with the patient's physician. Appropriate prophylactic antibiotic to eliminate the risk of infection is important, since infections can easily set in or get disseminated in subjects compromised by the chemotherapy.

NOTES ON DRUGS

Alkylating agents

These compounds produce highly reactive carbonium ion intermediates which transfer alkyl groups to cellular macromolecules by forming covalent bonds. The position 7 of guanine residues in DNA is specially susceptible, but other molecular sites are also involved. This results in cross linking/abnormal base pairing/scission of DNA strand. Cross linking of nucleic acids with proteins can also take place.

Alkylating agents have cytotoxic and radiomimetic (like ionizing radiation) actions. Many are cell cycle non-specific, i.e. act on dividing as well as resting cells. Some have CNS stimulant and cholinergic properties.

Cyclophosphamide is the most commonly used alkylating agent, effective in a wide range of tumours, and has prominent immunosuppressant action. Chloramphenicol increases its toxicity by inhibiting its metabolism. *Chlorambucil* is selective for lymphoid tissue and is used for maintenance therapy in chronic lymphocytic leukaemia and Hodgkin's disease. *Busulfan* is selective for myeloid elements and the drug of choice for chronic myeloid leukaemia. *Melphalan* is very effective in multiple myeloma. *Lomustine* is highly lipid soluble and especially valuable for brain tumours and meningeal leukaemia. The most important indication of *dacarbazine* is

malignant melanoma; also useful in Hodgkin's disease.

Antimetabolites

These are analogues related to normal components of DNA or of coenzymes involved in nucleic acid synthesis. They competitively inhibit utilization of normal substrate or get themselves incorporated forming dysfunctional macromolecules.

1. *Folate antagonist:*

Methotrexate (Mtx) is one of the oldest and highly efficacious antineoplastic drugs; inhibits dihydrofolate reductase (DHFRase)—blocking the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA) which is an essential coenzyme required for one carbon transfer reactions in *de novo* purine synthesis and amino acid interconversions. The inhibition is pseudo-irreversible because Mtx has 50,000 times higher affinity for the enzyme than the normal substrate.

Methotrexate has cell cycle specific action—kills cells in S phase; primarily inhibits DNA synthesis, but also affects RNA and protein synthesis. It exerts major toxicity on bone marrow.

Aspirin and sulfonamides decrease its renal tubular secretion enhancing its toxicity.

The toxicity of Mtx cannot be overcome by folic acid, because it will not be converted to the active coenzyme form. However, *Folinic acid* (N5 formyl THFA, cirtrovorum factor) rapidly reverses the effects. High dose Mtx with 'folinic acid rescue' has been employed in many difficult-to-treat neoplasms. Mtx is used in choriocarcinoma, acute leukaemia, carcinoma of tongue/pharynx/lung, etc. and as immunosuppressant in rheumatoid arthritis, psoriasis, organ transplantation.

2. *Purine antagonists*

Mercaptopurine (6-MP) and *thioguanine (6-TG)* are highly effective antineoplastic drugs. They are converted in the body to corresponding monoribonucleotides which inhibit purine synthesis and utilization of purine nucleotides.

They are specially useful in childhood acute leukaemia, choriocarcinoma and in some solid tumours.

Azathioprine has marked effect on T-lymphocytes, suppresses cell-mediated immunity (CMI) and is used primarily as immunosuppressant in organ transplantation, rheumatoid arthritis, etc.

Azathioprine and 6-MP are metabolized by xanthine oxidase; their metabolism is inhibited by allopurinol; dose has to be reduced to ¼–½ if allopurinol is given concurrently. Thioguanine is not a substrate for xanthine oxidase; its dose need not be reduced if allopurinol is given.

3. *Pyrimidine antagonists*

Fluorouracil (5-FU) is converted in the body to the corresponding nucleotide which blocks the conversion of deoxyuridilic acid to deoxythymidylic acid. Selective failure of DNA synthesis occurs due to non-availability of thymidylate: thymidine can partially reverse its toxicity. Fluorouracil itself gets incorporated into nucleic acids and this may contribute to its toxicity.

It has been particularly used for many solid tumours—breast, colon, urinary bladder, liver, etc. Topical application in cutaneous basal cell carcinoma has yielded gratifying results.

Cytarabine is phosphorylated in the body to corresponding nucleotide which inhibits DNA synthesis by DNA polymerase. It is cell cycle specific and acts primarily during S phase. Its main use is to induce remission in acute leukaemia in children, also in adults. Other uses are—Hodgkin's disease and non-Hodgkin lymphoma.

Vinca alkaloids

These are mitotic inhibitors, bind to microtubular protein—'tubulin', prevent its polymerization and assembly of microtubules, cause disruption of mitotic spindle and interfere with cytoskeletal function. The chromosomes fail to move apart during mitosis: metaphase arrest occurs. They are cell cycle specific and act in the mitotic phase.

Vincristine (oncovin) is very useful for inducing remission in childhood acute leukaemia. Other

indications are lymphosarcoma, Hodgkin's disease, Wilms' tumour, Ewing's sarcoma and carcinoma lung. Prominent adverse effects are peripheral neuropathy and alopecia. Bone marrow depression is minimal.

Vinblastine is primarily employed with other drugs in Hodgkin's disease and testicular carcinoma. Bone marrow depression is more prominent, while neurotoxicity and alopecia are less marked than with vincristine.

Taxanes

Paclitaxel is obtained from bark of the Western yew tree, which exerts cytotoxic action by a novel mechanism. It enhances polymerization of tubulin: a mechanism opposite to that of vinca alkaloids. This results in inhibition of normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic functions.

The indications of paclitaxel are metastatic ovarian and breast carcinoma after failure of first line chemotherapy and relapse cases. It has also shown efficacy in advanced cases of head and neck cancer, small cell lung cancer, esophageal adenocarcinoma, etc.

The major toxicity is reversible myelosuppression and 'stocking and glove' neuropathy. Chest pain, arthralgia, myalgia, mucositis and edema can be troublesome.

Docetaxel is a more potent congener of paclitaxel found effective in breast and ovarian cancer refractory to first line drugs. Small cell cancer lung, pancreatic, gastric and head/neck carcinomas are the other indications. Major toxicity is neutropenia, but neuropathy is less frequent.

Epipodophyllotoxins

Etoposide is a semisynthetic derivative of podophyllotoxin, a plant glycoside. It is not a mitotic inhibitor, but arrests cells in the G_2 phase and causes DNA breaks by affecting DNA topoisomerase II function. It has been primarily used in testicular tumours, lung cancer, Hodgkin's and other lymphomas, carcinoma bladder.

Camptothecin analogues

Topotecan and *Irinotecan* are two semisynthetic analogues of camptothecin, an antitumour principle obtained from a Chinese tree. They act in a manner similar to etoposide, but interact with a different enzyme DNA topoisomerase I.

Topotecan is used in metastatic carcinoma of ovary and small cell lung cancer after primary chemotherapy has failed. The major toxicity is bone marrow depression, especially neutropenia.

Irinotecan is a prodrug which is indicated in metastatic/advanced colorectal carcinoma, cancer lung/cervix/ovary, etc. Dose limiting toxicity is diarrhoea.

Antibiotics

These are products obtained from microorganisms and have prominent antitumour activity. Practically, all of them intercalate between DNA strands and interfere with its template function.

Actinomycin D (Dactinomycin) is highly efficacious in Wilms' tumour and rhabdomyosarcoma and has produced good results in a few other malignancies. Prominent adverse effects are vomiting, stomatitis, diarrhoea, erythema and desquamation of skin, alopecia and bone marrow depression.

Daunorubicin (Rubidomycin) and *Doxorubicin* are antitumour antibiotics with quite similar chemical structures. However, utility of daunorubicin is limited to acute leukaemia while doxorubicin, in addition, is effective in many solid tumours. They are capable of causing breaks in DNA strands by activating topoisomerase II and generating quinone-type free radicals. They have mutagenic and carcinogenic potential.

Both these antibiotics produce cardiotoxicity (arrhythmias, cardiomyopathy—heart failure) as a unique adverse effect. Marrow depression, alopecia, stomatitis are the other toxic effects.

Bleomycin chelates copper or iron, produces superoxide ions and intercalates between DNA strands—causes chain scission and inhibits repair. It is highly effective in testicular tumour and squamous cell carcinoma of skin, oral cavity, head and neck, and esophagus; also useful in Hodgkin's lymphoma.

Mucocutaneous toxicity and pulmonary fibrosis, but little myelosuppression are the special features.

Miscellaneous cytotoxic drugs

Hydroxyurea blocks the conversion of ribonucleotides to deoxyribonucleotides—thus interferes with DNA synthesis; exerts S-phase specific action. Its primary therapeutic value is in chronic myeloid leukaemia, psoriasis, polycythaemia vera and in some solid tumours. Myelosuppression is the major toxicity.

Procarbazine After metabolic activation (it is inactive as such), procarbazine depolymerizes DNA and causes chromosomal damage. It is a component of the popular MOPP regimen for Hodgkin's disease. It is also useful in non-Hodgkin lymphomas and oat cell carcinoma of lung.

Procarbazine is a weak MAO inhibitor, produces some CNS effects and interacts with foods and drugs. Alcohol causes hot flushing and a disulfiram like reaction in patients receiving procarbazine.

L-Asparaginase is selectively toxic to childhood lymphoblastic leukaemia cells, because they are deficient in L-asparagine synthetase and thus dependent on supply of L-asparagine from the medium. However, clinical response to L-asparaginase is short lasting. It can cause liver damage and allergic reactions, but mucositis, bone marrow depression and alopecia do not occur.

Cisplatin is a platinum coordination complex that is hydrolysed intracellularly to produce a highly reactive moiety which causes cross linking of DNA. It can also react with –SH groups in proteins and has radiomimetic property.

Cisplatin is very effective in metastatic testicular and ovarian carcinoma. It has found use in many other solid tumours as well.

Cisplatin is a highly emetic drug. The most important toxicity is renal impairment. Tinnitus, deafness, neuropathy and hyperuricaemia are other problems. Shock like state sometimes occurs during i.v. infusion.

Carboplatin is a less reactive second generation platinum compound that is better tolerated and has a toxicity profile different from cisplatin. Nephrotoxicity, ototoxicity and neurotoxicity are low. Nausea and vomiting is milder. The dose limiting toxicity is thrombocytopenia and less often leucopenia. It is primarily indicated in ovarian carcinoma, and has shown promise in squamous carcinoma of head and neck, small cell lung cancer and seminoma.

Hormones

They are not cytotoxic, but modify the growth of hormone-dependent tumours. All hormones are only palliative.

Glucocorticoids have marked lympholytic action—are primarily used in acute childhood leukaemia and lymphomas. They induce remission rapidly but relapses inevitably occur after variable intervals and gradually the responsiveness is lost. Considerable palliative effects are obtained in Hodgkin's disease and they have a secondary role in some hormone responsive breast cancers.

Corticosteroids are also valuable for the control of complications like hypercalcaemia, haemolysis and bleeding due to thrombocytopenia. Moreover, they afford symptomatic relief by antipyretic and mood elevating action and potentiate the antiemetic action of ondansetron/metoclopramide.

Estrogens produce gratifying results in carcinoma prostate, which is an androgen-dependent tumour. However, relapses eventually occur, as hormone dependence is gradually lost, but life is prolonged. On the same rationality, estrogens have

been used in the palliative treatment of carcinoma of male breast.

Some breast cancers have estrogen receptors in their cells. These respond to estrogens/antiestrogens.

Antiestrogen: Tamoxifen (*see* Ch. 15) is effective in estrogen receptor positive as well as negative breast cancer in both pre-as well as postmenopausal women; response is better in the older age group. It is a first line drug for palliative treatment of carcinoma breast, and after mastectomy.

Antiandrogen Flutamide (*see* p 230) antagonises androgen action on prostate carcinoma and has palliative effect in advanced/metastatic cases. Because it increases androgen levels, combination with orchiectomy or GnRH analogues is required to produce full therapeutic effect.

5-α reductase inhibitor Finasteride (*see* p 230) inhibits conversion of testosterone to dihydrotestosterone in prostate (and other tissues), has palliative effect in advanced carcinoma prostate.

GnRH agonists (*see* p 214) They indirectly inhibit estrogen/androgen secretion by suppressing FSH and LH release from pituitary and have palliative effect in advanced estrogen/androgen dependent carcinoma breast/prostate.

Progestins bring about temporary remission in some cases of advanced, recurrent (after surgery/radiotherapy) and metastatic endometrial carcinoma.

GENERAL PRINCIPLES IN CHEMOTHERAPY OF CANCER

1. In cancer chemotherapy selectivity of drugs for the tumour cells is limited: toxicity is high and measures to enhance selectivity are needed. Immunological defence against malignant cells is minimal or absent.

2. A single clonogenic malignant cell is capable of producing progeny that can kill the host. Survival time is related to the number of cells that escape chemotherapeutic attack.

3. In any cancer, subpopulations of cells differ in their rate of proliferation and susceptibility to cytotoxic drugs. These drugs kill cancer cells by first order kinetics, i.e. a certain fraction of cells present are killed by one treatment.

4. Drug regimens which can effectively palliate large tumour burdens may be curative when applied to minute residual tumour cell population after surgery and/or irradiation. This is the basis of the combined modality approach.

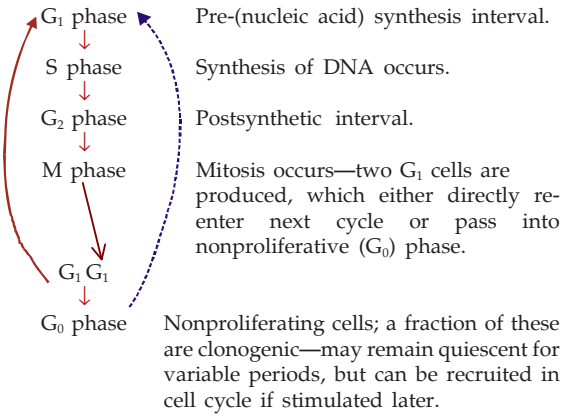
5. Whenever possible, complete remission should be the goal of cancer chemotherapy: drugs are often used at maximum tolerated doses. Intensive regimens used early yield better results.

6. Generally a combination of 2–6 drugs is given in intermittent pulses to achieve *total tumour cell kill*, giving time in between for normal cells to recover.

Synergistic combinations and rational sequences are devised by utilizing:

(a) Drugs which are effective when used alone.
(b) Drugs with different mechanisms of action.
(c) Drugs with differing toxicities.
(d) Empirically by trial and error; optimal schedules are mostly developed by this procedure.
(e) *Kinetic scheduling*: on the basis of cell cycle specificity/nonspecificity of drugs and the phase of cell cycle at which a drug exerts its toxicity.

Proliferating cells enter the cell cycle which consists of:



Cytotoxic drugs are either cell cycle specific or cell cycle nonspecific.

(a) *Cell cycle nonspecific* Kill resting as well as dividing cells, e.g. nitrogen mustard, cyclophosphamide, chlorambucil, carmustine, dacarbazine, 5-FU, L-asparaginase, cisplatin, procarbazine, actinomycin D.

(b) *Cell cycle specific* Kill only actively dividing cells. Their toxicity is generally expressed in S phase. However, these drugs may show considerable phase selectivity.

Growth fraction of solid tumours is often low: it is logical to use cell cycle specific drugs in short courses (pulses) of treatment. This allows noncycling cells (which are generally less susceptible to drugs) to re-enter the cycle between drug courses.

7. Tumours often become resistant to the drug used repeatedly due to selection of less responsive cells.

IMMUNOSUPPRESSANT DRUGS

These are drugs which inhibit cellular/humoral or both immune response and have their major use in organ transplantation and autoimmune diseases. The drugs are:

1. *Specific T-cell inhibitors*
   (Calcineurin inhibitors)
   Cyclosporine, Tacrolimus
2. *Cytotoxic drugs*
   (Antiproliferative drugs)
   Azathioprine, Cyclophosphamide, Methotrexate, Chlorambucil
3. *Glucocorticoids*
   Prednisolone and others
4. *Antibodies*
   Muromonab CD3, Antithymocyte globulin (ATG).

The development of immune response and the sites of action of different immunosuppressants is summarized in Fig. 21.1.

Specific T-cell inhibitors
(Calcineurin inhibitors)

Cyclosporine It is a cyclic polypeptide with 11 amino acids, obtained from a fungus and introduced in 1977 as a highly selective immunosuppressant which has markedly increased the success of organ transplantations. It profoundly and selectively inhibits T lymphocyte proliferation, IL-2 and other cytokine production and response of inducer T cells to IL-1 without any effect on suppressor T-cells.

Cyclosporine enters target cells and binds to a protein called *cyclophilin*. The complex then binds to and inactivates the enzyme *calcineurin* which is involved in transcription of cytokine genes in the antigen activated helper T-cells. As a result, response of the helper T cell to antigenic stimulation fails. T cell proliferation and production of killer lymphocytes is attenuated.

Cyclosporine selectively suppresses cell-mediated immunity, prevents graft rejection and yet leaves the recipient with enough immune activity to combat bacterial infection. Unlike cytotoxic immunosuppressants, it is free of toxic effects on bone marrow and RE system. Humoral immunity remains intact. However, it is nephrotoxic—the major limitation, and impairs liver function. Of particular concern to dentists is that cyclosporine causes gum hyperplasia in about 1/3rd recipients. It can be minimized by good oral hygiene and plaque control. Other adverse effects are sustained rise in BP, precipitation of diabetes, hyperkalaemia, opportunistic infections, hirsutism, tremor and seizures.

Cyclosporine is the most effective drug for prevention and treatment of graft rejection reaction. It is routinely used in renal, bone marrow and other transplantations.

Cyclosporine is a second line drug in autoimmune diseases like severe rheumatoid arthritis, uveitis, dermatomyositis, etc. and in psoriasis.

Drug interactions with a large number of drugs occur. All nephrotoxic drugs like aminoglycosides, vancomycin, amphotericin B and NSAIDs enhance its toxicity. By depressing renal function,

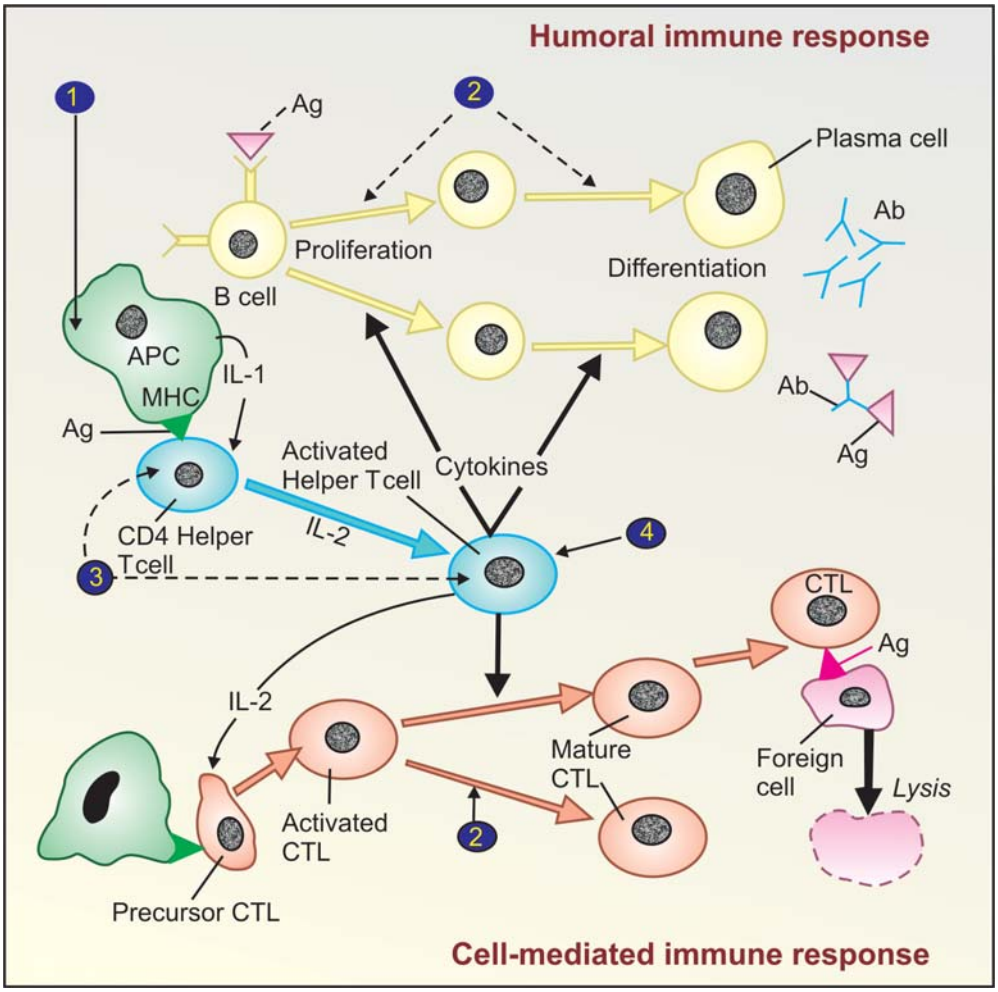


Fig. 21.1: Generation of humoral and cell-mediated immune response and sites of action of immunosuppressant drugs

The antigen (Ag) is processed by macrophages or other antigen presenting cells (APC), coupled with class II major histocompatibility complex (MHC) and presented to the CD4 helper cell which are activated by interleukin-I (IL-1), proliferate and secrete cytokines—these in turn promote proliferation and differentiation of antigen activated B cells into antibody (Ab) secreting plasma cells. Antibodies finally bind and inactivate the antigen.

In cell-mediated immunity—-foreign antigen is processed and presented to CD4 helper T cell which elaborate IL-2 and other cytokines that in turn stimulate proliferation and maturation of precursor cytotoxic lymphocytes (CTL) that have been activated by antigen presented with class I MHC. The mature CTL (Killer cells) recognize cells carrying the antigen and lyse them.

1. Glucocorticoids inhibit MHC expression and IL-1, IL-2, IL-6 production so that helper T-cells are not activated.
2. Cytotoxic drugs block proliferation and differentiation of T and B cells.
3. Cyclosporine and tacrolimus inhibit antigen stimulated activation and proliferation of helper T cells as well as expression of IL-2 and other cytokines by them.
4. Antibodies like muromonab CD3, antithymocyte globulin specifically bind to helper T cells, prevent their response and deplete them

it can reduce excretion of many drugs. Phenytoin, phenobarbitone, rifampin and other enzyme inducers lower its blood levels (transplant rejection may result). On the other hand, CYP3A4 inhibitors erythromycin, ketoconazole and related drugs inhibit its metabolism to cause toxicity. K^+ supplements and K^+ sparing diuretics can produce marked hyperkalaemia in patients on cyclosporine.

Tacrolimus (FK506) It is a newer immunosuppressant chemically different from cyclosporine but having the same mechanism of action and is ~100 times more potent.

Cytotoxic immunosuppressants
(Antiproliferative drugs)

Certain cytotoxic drugs used in cancer chemotherapy exhibit prominent immunosuppressant action, mainly by preventing clonal expansion of T and B lymphocytes.

Azathioprine (*see* p. 300) It is a purine antimetabolite which has more marked immunosuppressant than antitumour action. The basis for this difference is not clear, but may be due to its selective uptake into immune cells and intracellular conversion to the active metabolite 6-mercaptopurine. It selectively affects differentiation and function of T cells and inhibits cytolylic lymphocytes; cell-mediated immunity is primarily depressed.

The most important application of azathioprine is prevention of renal and other graft rejection, but is less effective than cyclosporine; generally combined with it or used in patients developing cyclosporine toxicity. It has also been used in some autoimmune diseases.

Cyclophosphamide This cytotoxic drug has more marked effect on B cells and humoral immunity compared to that on T cells and cell-mediated immunity. It has been particularly utilized in bone marrow transplantation. Low doses are occasionally used for maintenance therapy in pemphigus, systemic lupus erythematosus and idiopathic thrombocytopenic purpura.

Methotrexate This folate antagonist is a potent immunosuppressant which markedly depresses cytokine production and cellular immunity, and has antiinflammatory property. It has been used as a first line drug in many autoimmune diseases like rapidly progressing rheumatoid arthritis, pemphigus, myasthenia gravis, uveitis, chronic active hepatitis. Low dose Mtx maintenance therapy is relatively well tolerated.

Chlorambucil It has relatively weak immunosuppressant action which is sometimes utilized in autoimmune diseases and transplant maintenance regimens.

Glucocorticoids (*see* Ch. 14)

Glucocorticoids have potent immunosuppressant and antiinflammatory action, inhibit several components of the immune response. They particularly inhibit MHC expression and proliferation of T lymphocytes. Accordingly, they have a more marked effect on CMI.

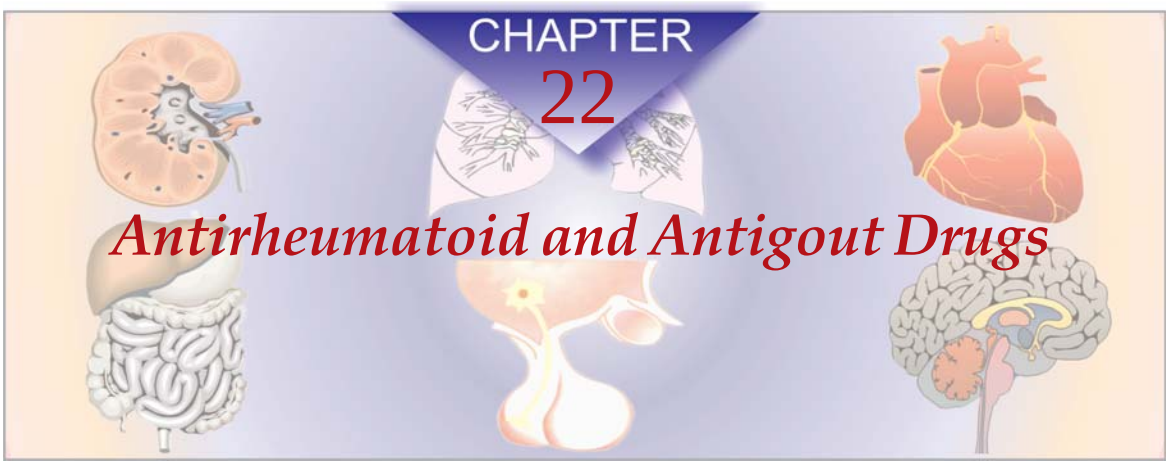
Corticosteroids are widely employed as companion drug to cyclosporine in various organ transplants. They are used in practically all cases of severe autoimmune diseases, especially during exacerbation. Long-term complications are the greatest limitations of steroid use.

Immunosuppressant antibodies

Muromonab CD3 It is a murine monoclonal antibody against the CD3 glycoprotein located near to the T cell receptor on helper T cells. It inhibits participation of T cells in the immune response. T cells rapidly disappear from circulation leading to an immune blocked state.

Muromonab CD3 has been used as induction therapy together with corticosteroids and azathioprine for organ transplantation.

Antithymocyte globulin (ATG) It is a polyclonal antibody purified from horse or rabbit immunized with human thymic lymphocytes which binds to T lymphocytes and depletes them. It is a potent immunosuppressant and has been used primarily to suppress acute allograft rejection episodes. It can also be used in induction regimens.



CHAPTER 22

Antirheumatoid and Antigout Drugs

ANTIRHEUMATOID DRUGS

These are drugs which (except corticosteroids), can suppress the rheumatoid process and bring about a remission, but do not have nonspecific antiinflammatory or analgesic action. They are also referred to as *disease modifying antirheumatic drugs* (DMARDs) or slow acting antirheumatic drugs (SAARDs). The onset of benefit with DMARDs takes a few months of regular treatment and relapses often occur a few months after cessation of therapy.

Rheumatoid arthritis (RA) is an autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage. Immune complexes composed of IgM activate complement and release factors which are chemotactic for neutrophils. These inflammatory cells release lysosomal enzymes which damage cartilage and erode bone, while PGs produced in the process cause vasodilatation and pain. RA is a chronic progressive, crippling disorder with a waxing and waning course. NSAIDs are the first line drugs. They afford symptomatic relief (in pain, swelling, morning stiffness, immobility) but do not arrest the disease process. Though the conventional approach is to induct a DMARD only when NSAIDs have failed to afford adequate relief, or when deformity and bony changes progress rapidly, most rheumatologists now add methotrexate/sulfasalazine to NSAIDs even before the latter have failed, so as to delay/reduce deformity and crippling later on. More than one DMARD may be used concurrently. Corticosteroids are added only as adjuvants to NSAIDs.

A. *Disease modifying antirheumatic drugs (DMARDs)*
   1. Gold
   2. d-Penicillamine
   3. Chloroquine or Hydroxychloroquine
   4. Sulfasalazine
   5. Leflunomide
   6. Immunosuppressants
      Methotrexate, Azathioprine.

B. *Adjuvant drugs:* Corticosteroids.

1. Gold

Gold is considered to be the most effective agent for arresting the rheumatoid process and preventing involvement of additional joints. It reduces chemotaxis, phagocytosis, macrophage and lysosomal activity, monocyte differentiation and inhibits cell-mediated immunity (CMI), but the exact mechanism of action is not known. By an effect on synovial membrane and collagen, it prevents joint destruction; may induce healing of bony erosions. It is effective in psoriatic arthropathy also.

Toxicity of parenteral gold salt (hypotension, dermatitis, kidney and liver damage, bone marrow depression) is high, and it is rarely used now. *Auranofin* is an orally active gold compound, less efficacious and less toxic than parenteral gold; infrequently used.

2. d-Penicillamine

It is a copper chelating agent with a gold-like action in RA, but less efficacious; bony erosions do not heal. It is not favoured now because it does not offer any advantage in terms of toxicity, which is similar to gold. Loss of taste, systemic lupus and myasthenia gravis are the other adverse effects.

3. Chloroquine and hydroxychloroquine (*see* Ch. 33)

These are antimalarial drugs found to induce remission in up to 50% patients of RA. They are less effective and less toxic than gold. Their mechanism of action is not known, however, they have been found to reduce monocyte interleukin I, consequently inhibiting B lymphocytes. Antigen processing may be interfered with.

For rheumatoid arthritis these drugs have to be given for long periods: accumulate in tissues and produce toxicity, most disturbing of which is retinal damage and corneal opacity.

Chloroquine/hydroxychloroquine are employed in milder nonerosive disease in case methotrexate or sulfasalazine cannot be given.

4. Sulfasalazine (*see* Ch. 18)

It is a compound of sulfapyridine and 5-amino salicylic acid (5-ASA); has antiinflammatory activity and is primarily used in ulcerative colitis. In addition, it suppresses the disease in significant number of RA patients. The mechanism of action is not known. Sulfapyridine split off in the colon by bacterial action and absorbed systemically appears to be the active moiety (contrast ulcerative colitis in which 5-ASA acting locally in the colon is the active component). Generation of superoxide radicals and cytokine elaboration by inflammatory cells may be suppressed.

Because of fewer adverse effects, it is a good alternative to methotrexate for milder/early cases.

5. Leflunomide

This recently introduced immunomodulator inhibits proliferation of activated lymphocytes in patients with active RA. Arthritic symptoms are suppressed and radiological progression of disease is retarded. In clinical trials its efficacy has been rated comparable to methotrexate or sulfasalazine and onset of benefit is faster (4 weeks).

Leflunomide is rapidly converted in the body to an active metabolite which inhibits *dihydroorotate dehydrogenase* and pyrimidine synthesis in actively dividing cells, but the precise mechanism of action is not known.

Adverse effects of leflunomide are diarrhoea, headache, nausea, rashes, loss of hair, thrombocytopenia and leukopenia. Leflunomide appears to be a suitable alternative to methotrexate or sulfasalazine in RA.

6. Immunosuppressants (*see* Ch. 21)

Methotrexate (Mtx) This dihydrofolate reductase inhibitor has prominent immunosuppressant and antiinflammatory property. Beneficial effects in RA are probably related to inhibition of cytokine production, chemotaxis and cell-mediated immune reaction. Induction of oral low dose (7.5–15 mg) weekly Mtx regimen has improved acceptability of this drug in RA. Mtx is now the DMARD of choice for most patients.

Nodulosis, oral ulceration and g.i. upset are the major side effects of low-dose Mtx regimen.

Azathioprine This purine antimetabolite immunosuppressant induces remission in a smaller percentage of RA patients, and is used as a second line DMARD.

7. Corticosteroids (*see* Ch 14)

They have potent immunosuppressant and antiinflammatory activity but do not arrest the rheumatoid process or induce remission. They can be inducted almost at any stage in RA, if potent antiinflammatory action is required while continuing the NSAID ± DMARD.

Long-term use of corticosteroids carries serious disadvantages. Therefore, either low doses are used to supplement NSAIDs or high doses

are employed over short periods in cases with severe systemic manifestations.

DRUGS USED IN GOUT

Gout It is a metabolic disorder characterized by hyperuricaemia (normal plasma urate 1–4 mg/dL). Uric acid, a product of purine metabolism, has low water solubility, especially at low pH. When blood levels are high, it precipitates and deposits in joints, kidney and subcutaneous tissue (tophy).

Secondary hyperuricaemia occurs in:

(a) Leukaemias, lymphomas, polycythaemia—especially when treated with chemotherapy or radiation: due to enhanced nucleic acid metabolism and uric acid production.
(b) Drug induced—thiazides, furosemide, pyrazinamide, ethambutol, levodopa, reduce uric acid excretion by kidney.
Drugs used are:

For acute gout

NSAIDs
Colchicine
Corticosteroids

For chronic gout / hyperuricaemia

Uricosurics	*Synthesis inhibitor*
Probenecid	Allopurinol
Sulfinpyrazone	

ACUTE GOUT

Acute gout manifests as sudden onset of severe inflammation in a small joint (commonest is metatarso-phalangeal joint of great toe) due to precipitation of urate crystals in the joint space. The joint becomes red, swollen and extremely painful: requires immediate treatment.

1. NSAIDs

One of the strong antiinflammatory drugs, e.g. *indomethacin, naproxen* or *piroxicam* is given in relatively high and quickly repeated doses. They are quite effective in terminating the attack, but may take 12–24 hours, i.e. response is somewhat slower than with colchicine, but they are generally better tolerated; majority of patients prefer them over colchicine. After the attack is over, they may be continued at lower doses for 3–4 weeks while drugs to control hyperuricaemia take effect.

2. Colchicine

It is an alkaloid from *Colchicum autumnale* which is neither analgesic nor antiinflammatory, but it specifically suppresses gouty inflammation. It does not inhibit the synthesis or promote the excretion of uric acid. Thus, it has no effect on blood uric acid levels.

An acute attack of gout is started by the precipitation of urate crystals in the synovial fluid that start an inflammatory response→ granulocyte migration into the joint. Granulocytes phagocytose urate crystals and release a glycoprotein which aggravates the inflammation.

Colchicine inhibits release of the glycoprotein and the subsequent events. By binding to fibrillar protein tubulin, it inhibits granulocyte migration into the inflamed joint and thus interrupts the vicious cycle. Other actions of colchicine are:

(a) Antimitotic: causes metaphase arrest by binding to microtubules of mitotic spindle.
(b) Increases gut motility through neural mechanisms.

Toxicity is high and dose related.
Nausea, vomiting, watery or bloody diarrhoea and abdominal cramps occur as dose limiting adverse effects. In overdose, colchicine produces kidney damage, CNS depression, intestinal bleeding; death is due to muscular paralysis and respiratory failure.

Use

Colchicine is the fastest acting drug to control an attack of acute gout. However, because of its higher toxicity, most physicians prefer using a NSAID. Small doses of colchicine can abort an attack of acute gout if taken at the first symptom. Maintenance doses of colchicine can be employed

for prophylaxis of acute gout, while blood urate levels are normalized by allopurinol/probenecid.

3. Corticosteroids

Intra-articular injection of a soluble steroid suppresses symptoms of acute gout. Crystalline preparations should not be used. It is indicated in refractory cases and those not tolerating NSAIDs/colchicine.

Systemic steroids are rarely needed. They are very effective and produce as rapid a response as colchicine, but are reserved for cases not responding to or not tolerating NSAIDs.

CHRONIC GOUT

When pain and stiffness persist in a joint between attacks, gout has become chronic. Other cardinal features are hyperuricaemia, tophi (chalk-like stones under the skin) and urate stones in the kidney. Chronic gouty arthritis may cause progressive disability and permanent deformities.

1. Probenecid

It is a highly lipid-soluble organic acid developed in 1951 to inhibit renal tubular secretion of penicillin so that its duration of action could be prolonged. It competitively blocks active transport of organic acids in renal tubules. This transport is bidirectional: net effect depends on whether secretion or reabsorption of the particular organic acid is quantitatively more important, e.g.:
(a) Penicillin is predominantly secreted by the proximal tubules, its reabsorption is minimal. Net effect of probenecid is inhibition of excretion; more sustained blood levels are achieved.
(b) Uric acid is largely reabsorbed by active transport, while less of it is secreted; only 1/10th of filtered load is excreted in urine. Probenecid, therefore, promotes its excretion and reduces its blood level.

Probenecid does not have any other significant pharmacological action; it is neither analgesic nor antiinflammatory.

Interactions

1. In addition to penicillins, it inhibits the urinary excretion of cephalosporins, sulfonamides, methotrexate and indomethacin.
2. It inhibits biliary excretion of rifampicin. Pyrazinamide and ethambutol may interfere with uricosuric action of probenecid.
3. Probenecid inhibits tubular secretion of nitrofurantoin which may not attain antibacterial concentration in urine.
4. Salicylates block uricosuric action of probenecid.

Pharmacokinetics Probenecid is completely absorbed orally; 90% plasma protein bound: partly conjugated in liver and excreted by the kidney; plasma t½ is 8–10 hours.

Adverse effects Probenecid is generally well tolerated.
Dispepsia is the most common side effect. Rashes and other hypersensitivity phenomena are rare. Toxic doses cause convulsions and respiratory failure.

Uses

Probenecid is a second line/adjuvant drug to allopurinol for treating chronic gout and hyperuricaemia. It gradually lowers blood urate level; arthritis, tophi and other lesions may take months to resolve. Colchicine/NSAID cover is advised concurrently during the initial 1–2 months to avoid precipitation of acute gout.

Probenecid is also used to prolong penicillin or ampicillin action by enhancing and sustaining their blood levels, e.g. in gonorrhoea, SABE.

2. Sulfinpyrazone

It is a pyrazolone derivative related to phenylbutazone having uricosuric action, but is neither analgesic nor antiinflammatory. At the usual therapeutic doses, it inhibits tubular reabsorption of uric acid, but smaller doses can decrease urate excretion. It also inhibits platelet aggregation.

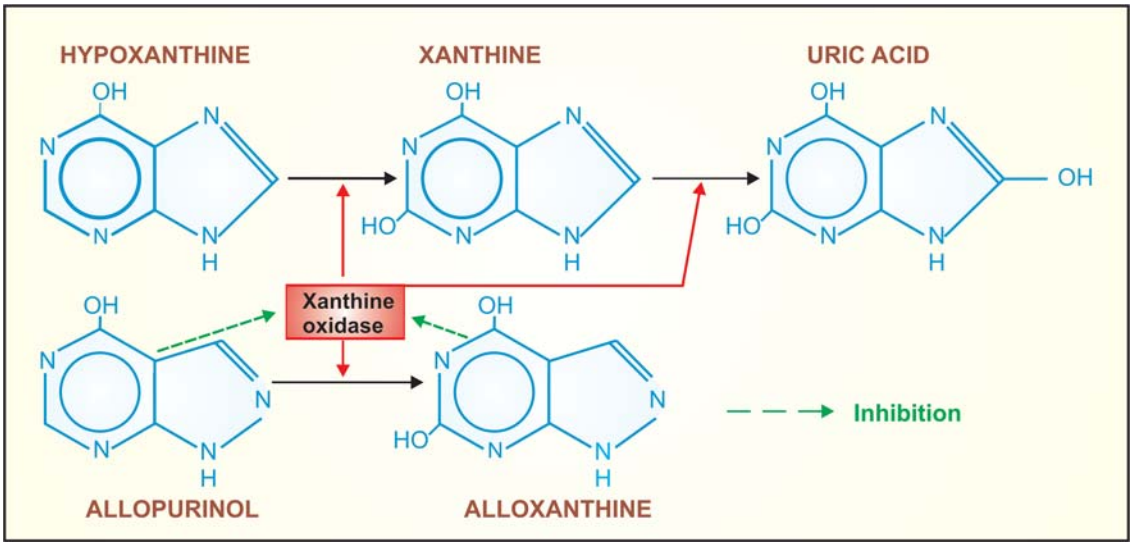


Fig. 22.1: Uric acid synthesis and the action of allopurinol

Sulfinpyrazone is well absorbed orally; 98% plasma protein bound. Excretion is fairly rapid, mainly by active secretion in proximal tubule. Uricosuric action of a single dose lasts for 6–10 hours.

Gastric irritation is the most common side effect—contraindicated in patients with peptic ulcer. Rashes and other hypersensitivity reactions are uncommon. The only indication of sulfinpyrazone is hyperuricaemia and chronic gout as an alternative to probenecid.

3. Allopurinol

This hypoxanthine analogue was synthesized as a purine antimetabolite for cancer chemotherapy. However, it had no antineoplastic activity but was a substrate as well as inhibitor of *xanthine oxidase*, the enzyme responsible for uric acid synthesis (Fig. 22.1).

Allopurinol itself is a short-acting (t½ 2 hr) competitive inhibitor of xanthine oxidase, but its major metabolite *alloxanthine (oxypurine)* is long acting (t½ 24 hr) and noncompetitive inhibitor—primarily responsible for uric acid synthesis inhibition *in vivo*. During allopurinol administration, plasma concentration of uric acid is reduced and that of hypoxanthine and xanthine is somewhat increased. In place of uric acid alone, all 3 oxipurines are excreted in urine. Since xanthine and hypoxanthine are more soluble, have a higher renal clearance than that of uric acid and each has its individual solubility, precipitation and crystallization in tissues and urine does not occur.

Because of raised levels of xanthine and hypoxanthine, some feedback inhibition of *de novo* purine synthesis and reutilization of metabolically derived purine also occurs.

Pharmacokinetics About 80% of orally administered allopurinol is absorbed. It is not bound to plasma proteins; metabolized largely to alloxanthine. During chronic medication, it inhibits its own metabolism and about 1/3rd is excreted unchanged, the rest as alloxanthine.

Interactions

(a) It inhibits the degradation of 6-mercaptopurine and azathioprine: their doses should be reduced to 1/3rd but not that of thioguanine, because it follows a different metabolic path.

(b) Probenecid given with allopurinol has complex interaction; while probenecid shortens t½ of alloxanthine, allopurinol prolongs t½ of probenecid.
(c) It can potentiate warfarin and theophylline by inhibiting their metabolism.
(d) A higher incidence of skin rashes has been reported when ampicillin is given to patients on allopurinol.
(e) Iron therapy is not recommended during allopurinol treatment.

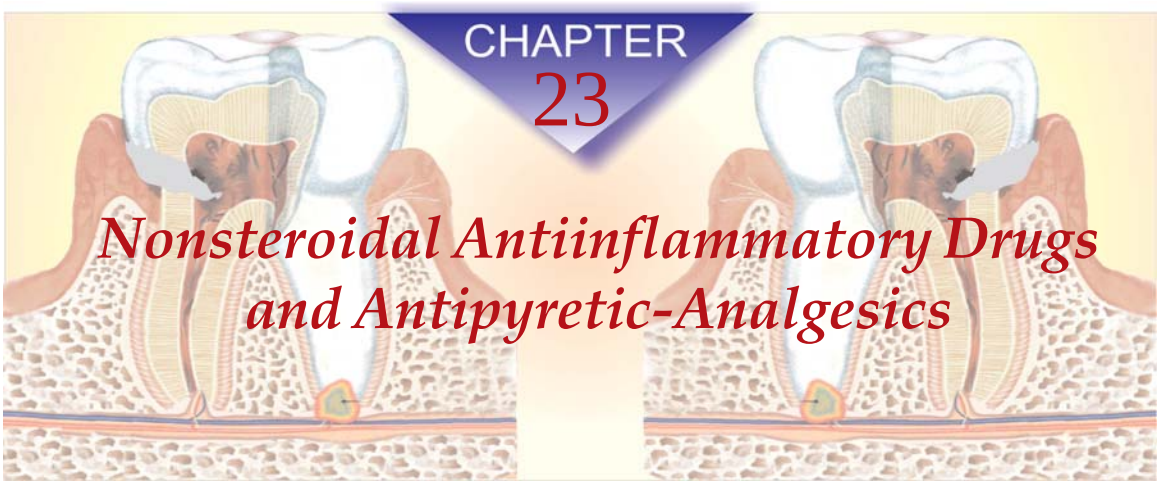
Adverse effects These are uncommon.
Hypersensitivity reaction consisting of rashes, fever, malaise and muscle pain is the most frequent.
Gastric irritation, headache, nausea and dizziness are infrequent; do not need withdrawal.
Liver damage is rare.

Uses Allopurinol is the first choice drug in *chronic gout*. Probenecid can be combined with it when the body load of urate is large. With long-term allopurinol therapy, tophi gradually disappear and nephropathy is halted, even reversed.

Secondary hyperuricaemia due to cancer chemotherapy/radiation/thiazides or other drugs: can be controlled by allopurinol.

Allopurinol has also been used to potentiate 6-mercaptopurine or azathioprine, and as an adjuvant drug in kala-azar.

Drugs Important in Dental Therapeutics



CHAPTER 23

Nonsteroidal Antiinflammatory Drugs and Antipyretic-Analgesics

Pain (algesia) is an ill-defined, unpleasant sensation, usually evoked by an external or internal noxious stimulus. It is a warning signal and primarily protective in nature, but causes discomfort and suffering; may even be unbearable. Dental pain is usually acute in nature and is the most important symptom for which the patient comes to the dentist.

Analgesic is a drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness. Analgesics relieve pain as a symptom without affecting its cause. They are used when the noxious stimulus (evoking pain) cannot be removed, or as an adjuvant to more etiologic approach to pain, such as antibiotic treatment of apical tooth abscess.

Analgesics are divided into two groups, *viz.*

A. Opioid/narcotic/morphine like analgesics.
B. Nonopioid/non-narcotic/antipyretic/aspirin-like analgesics or nonsteroidal antiinflammatory drugs (NSAIDs).

The antipyretic-analgesics and NSAIDs are more commonly employed for dental pain because tissue injury and inflammation due to tooth abscess, caries, tooth extraction, etc. is the primary cause of acute dental pain.

The NSAIDs and antipyretic-analgesics are a class of drugs that have analgesic, antipyretic and antiinflammatory actions in different measures. In contrast to morphine, they do not depress CNS, do not produce physical dependence, have no abuse liability and are particularly effective in inflammatory pain. They act primarily on peripheral pain mechanisms but also in the CNS to raise pain threshold.

CLASSIFICATION

A. *Nonselective COX inhibitors (conventional NSAIDs)*

1. *Salicylates*: Aspirin.
2. *Propionic acid derivatives*: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3. *Anthranilic acid derivative*: Mephenamic acid.
4. *Aryl-acetic acid derivatives*: Diclofenac.
5. *Oxicam derivatives*: Piroxicam, Tenoxicam.
6. *Pyrrolo-pyrrole derivative*: Ketorolac.
7. *Indole derivative*: Indomethacin.
8. *Pyrazolone derivatives*: Phenylbutazone, Oxyphenbutazone.

B. *Preferential COX-2 inhibitors*

Nimesulide, Meloxicam, Nabumetone

C. *Selective COX-2 inhibitors*

Celecoxib, Rofecoxib, Valdecoxib, Etoricoxib

D. *Analgesic- antipyretics with poor antiinflammatory action*

1. *Paraaminophenol derivative*: Paracetamol (Acetaminophen).

2. *Pyrazolone derivatives*: Metamizol (Dipyrone), Propiphenazone.
3. *Benzoxazocine derivative*: Nefopam.

NSAIDs and prostaglandin (PG) synthesis inhibition

In 1971, Vane and coworkers made the landmark observation that aspirin and some NSAIDs blocked prostaglandin (PG) generation. This is now considered to be the major mechanism of action of NSAIDs. Prostaglandins, prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) are produced from arachidonic acid by the enzyme cyclooxygenase (*see* p. 109) which exists in a constitutive (COX-1) and an inducible (COX-2) isoforms; the former serves physiological 'house keeping' functions; while the latter, normally present in minute quantities, is induced by cytokines and other signal molecules at the site of inflammation → generation of PGs locally which mediate many of the inflammatory changes. However, COX-2 is constitutively present at some sites in brain and in juxtaglomerular cells: may serve physiological role at these sites. Most NSAIDs inhibit COX-1 and COX-2 nonselectively, but now some selective COX-2 inhibitors have been produced.

Aspirin inhibits COX irreversibly by acetylating one of its serine residues; return of COX activity depends on synthesis of fresh enzyme.

Beneficial actions due to PG synthesis inhibition

- Analgesia: prevention of pain nerve ending sensitization
- Antipyresis
- Antiinflammatory
- Antithrombotic
- Closure of ductus arteriosus

Other NSAIDs are competitive and reversible inhibitors of COX, return of activity depends on their dissociation from the enzyme which in turn is governed by the pharmacokinetic characteristics of the compound.

Analgesia PGs induce hyperalgesia (*see* p 112) by affecting the transducing property of free nerve endings—stimuli that normally do not elicit pain are able to do so. NSAIDs do not affect the tenderness induced by direct application of PGs, but block the pain sensitizing mechanism induced by bradykinin, TNFα, interleukins (ILs) and other algesic substances. They are, therefore, more effective against inflammation associated pain, including acute dental/postextraction pain.

Antipyresis NSAIDs reduce body temperature in fever, but do not cause hypothermia in normothermic individuals. Fever during infection is produced through the generation of pyrogen, ILs, TNFα, interferons which induce PG production in hypothalamus—raise its temperature set point. NSAIDs block the action of pyrogens but not that of PGE_2 injected into the hypothalamus. The isoform present at this site appears to be COX-2. However, fever can occur through non-PG mediated mechanisms as well; inhibition of COX does not entirely explain the antipyretic action of NSAIDs.

Shared toxicities due to PG synthesis inhibition

- Gastric mucosal damage
- Bleeding: inhibition of platelet function
- Limitation of renal blood flow : Na^+ and water retention
- Delay/prolongation of labour
- Asthma and anaphylactoid reactions in susceptible individuals

Antiinflammatory The most important mechanism of antiinflammatory action of NSAIDs is considered to be inhibition of PG synthesis at the site of injury. The antiinflammatory potency of different compounds roughly corresponds with their potency to inhibit COX. However, nimesulide is a potent antiinflammatory but relatively weak COX inhibitor. PGs are only one of the mediators of inflammation; inhibition of COX does not depress the production of other mediators like LTs, PAF, cytokines, etc. Inflammation is

the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages, and there are many targets for antiinflammatory action.

Activated endothelial cells express adhesion molecules (ECAM-1, ICAM-1) on their surface and play a key role in directing circulating leukocytes to the site of inflammation. Similarly, inflammatory cells express *selectins* and *integrins*. Certain NSAIDs may act by additional mechanisms including inhibition of expression/activity of some of these molecules. Growth factors like GM-CSF, IL-6 and lymphocyte transformation factors may also be affected. Stabilization of leucocyte lysosomal membrane and antagonism of certain actions of kinins may be contributing to NSAID action.

Table 23.1: Features of nonselective COX inhibitors and selective COX-2 inhibitors

Action	*COX-1/COX-2 inhibitors*	*COX-2 inhibitors*
1. Analgesic	+	+
2. Antipyretic	+	+
3. Antiinflammatory	+	+
4. Antiplatelet aggregatory	+	–
5. Gastric mucosal damage	+	–
6. Renal salt/water retention	+	+
7. Delay/prolongation of labour	+	+
8. Ductus arteriosus closure	+	?
9. Aspirin sensitive asthma precipitation	+	?

Dysmenorrhoea Involvement of PGs in dysmenorrhoea has been clearly demonstrated: level of PGs in menstrual flow, endometrial biopsy and that of $PGF_{2\alpha}$ metabolite in circulation are raised in dysmenorrhoeic women. NSAIDs lower uterine PG levels—afford excellent relief in 60–70% and partial relief in the remaining. Ancillary symptoms of headache, muscle ache and nausea are also relieved.

Antiplatelet aggregatory NSAIDs inhibit synthesis of both proaggregatory (TXA_2) and antiaggregatory (PGI_2) prostanoids, but effect on platelet TXA_2 predominates → therapeutic doses of most NSAIDs inhibit platelet aggregation: bleeding time is prolonged. Aspirin is highly active; acetylates platelet COX irreversibly in portal circulation before it is deacetylated by first pass metabolism in liver. Small doses are, therefore, able to exert antithrombotic effect for several days. Risk of postextraction bleeding is enhanced.

Ductus arteriosus closure During foetal circulation, ductus arteriosus is kept patent by local elaboration of PGE_2 and PGI_2. Unknown mechanisms switch off this synthesis at birth and the ductus closes. When this fails to occur, small doses of indomethacin or aspirin bring about closure in majority of cases within a few hours by inhibiting PG production. Administration of NSAIDs in late pregnancy has been found to promote premature closure of ductus in some cases. Dentists should avoid prescribing NSAIDs near term.

Parturition Sudden spurt of PG synthesis by uterus probably triggers labour and facilitates its progression. Accordingly, NSAIDs have the potential to delay and retard labour. However, labour can occur in the absence of PGs.

Gastric mucosal damage Gastric pain, mucosal erosion/ulceration and blood loss are produced by all NSAIDs to varying extents: relative gastric toxicity is a major consideration in the choice of NSAIDs. Inhibition of synthesis of gastroprotective PGs (PGE_2, PGI_2) is clearly involved, though local action inducing back diffusion of H^+ ions in gastric mucosa also plays a role. Deficiency of PGs reduces mucus and HCO_3^- secretion, tends to enhance acid secretion and may promote mucosal ischaemia. Thus, NSAIDs enhance aggressive factors and contain defensive factors in gastric mucosa—are ulcerogenic. Paracetamol, a very weak inhibitor of COX, is practically free of gastric toxicity and selective COX-2 inhibitors are safer. Stable PG analogues (misoprostol) administered concurrently with NSAIDs antagonise their gastric toxicity.

Adverse effects of NSAIDs

Gastrointestinal
Gastric irritation, erosions, peptic ulceration, gastric bleeding/perforation, esophagitis

Renal
Na^+ and water retention, chronic renal failure, interstitial nephritis, papillary necrosis (rare)

Hepatic
Raised transaminases, hepatic failure (rare)

CNS
Headache, mental confusion, behavioural disturbances, seizure precipitation

Haematological
Bleeding, thrombocytopenia, haemolytic anaemia, agranulocytosis

Others
Asthma exacerbation, nasal polyposis, skin rashes, pruritus, angioedema

Renal effects Conditions leading to hypovolaemia, decreased renal perfusion and Na^+ loss induce renal PG synthesis which brings about intrarenal adjustments by promoting vasodilatation, inhibiting tubular Cl^- reabsorption (Na^+ and water accompany) and opposing ADH action.

NSAIDs produce renal effects by at least 3 mechanisms:

- COX-1 dependent impairment of renal blood flow and reduction of g.f.r. → can worsen renal insufficiency.
- Juxtaglomerular COX-2 (probably COX-1 also) dependent Na^+ and water retention.
- Rare ability to cause papillary necrosis on habitual intake.

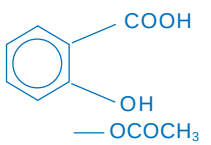
Renal effects of NSAIDs are not marked in normal individuals but become significant in those with CHF, hypovolaemia, hepatic cirrhosis, renal disease and in patients receiving diuretics or antihypertensives: Na^+ retention and edema can occur; diuretic and antihypertensive drug effects are blunted.

Anaphylactoid reactions Aspirin precipitates asthma, angioneurotic swellings, urticaria or rhinitis in certain susceptible individuals. These subjects react similarly to chemically diverse NSAIDs, ruling out immunological basis for the reaction. Inhibition of COX with consequent diversion of arachidonic acid to LTs and other products of lipoxygenase pathway may be involved, but there is no proof.

SALICYLATES

Aspirin

Aspirin is acetylsalicylic acid. It is rapidly converted in the body to salicylic acid which is responsible for most of the actions. Other actions are the result of acetylation of certain macromolecules including COX. Aspirin is one of the oldest analgesic-antiinflammatory drugs and is still widely used.



Salicyclic acid

(Aspirin)

PHARMACOLOGICAL ACTIONS

1. Analgesic, antipyretic, antiinflammatory actions Aspirin is a weaker analgesic than morphine type drugs: aspirin 600 mg ~ codeine 60 mg, but it effectively relieves inflammatory, tissue injury related, connective tissue and integumental pain. It is relatively ineffective in severe visceral and ischaemic pain. The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG-mediated sensitization of nerve endings. A central subcortical action raising threshold to pain perception also contributes, but the morphine-like action on psychic processing or reaction component of the pain is missing. No sedation, subjective effects, tolerance or physical dependence is produced.

Aspirin resets the hypothalamic thermostat and rapidly reduces fever by promoting heat loss (sweating, cutaneous vasodilatation), but does not decrease heat production.

Antiinflammatory action is exerted at high doses (3–5 g/day or 100 mg/kg/ day). Signs of inflammation like pain, tenderness, swelling, vasodilatation and leucocyte infiltration are suppressed. However, progression of the underlying disease in rheumatoid arthritis, rheumatic fever and osteoarthritis, etc. is not affected.

2. Metabolic effects These are significant only at antiinflammatory doses. Cellular metabolism is increased, especially in skeletal muscles, due to uncoupling of oxidative phosphorylation → increased heat production. There is increased utilization of glucose → blood sugar may decrease (especially in diabetics) and liver glycogen is depleted. However, hyperglycaemia is often seen at toxic doses: this is due to central sympathetic stimulation → release of Adr and corticosteroids. Chronic use of large doses cause negative N_2 balance by increased conversion of protein to carbohydrate.

3. Respiration The effects are dose dependent. At antiinflammatory doses, respiration is stimulated by peripheral (increased CO_2 production) and central (increased sensitivity of respiratory centre to CO_2) actions. Hyperventilation is prominent in salicylate poisoning. Further rise in salicylate level causes respiratory depression; death is due to respiratory failure.

4. Acid-base and electrolyte balance Antiinflammatory doses produce significant changes in the acid-base and electrolyte composition of body fluids. Initially, respiratory stimulation predominates and tends to wash out CO_2 despite increased production → respiratory alkalosis, which is compensated by increased renal excretion of HCO_3^- (with accompanying Na^+, K^+ and water). Most adults treated with 4–6 g/day of aspirin stay in a state of *compensated respiratory alkalosis.*

Still higher doses cause respiratory depression with CO_2 retention, while excess CO_2 production continues → *respiratory acidosis*. To this are added dissociated salicylic acid as well as metabolic acids (lactic, pyruvic, acetoacetic) which are produced in excess + metabolically derived sulfuric and phosphoric acid which are retained due to depression of renal function. All these combine to cause *uncompensated metabolic acidosis* since plasma HCO_3^- is already low. Most children manifest this phase during salicylate poisoning; while in adults, it is seen in late stages of poisoning only.

Dehydration occurs in poisoning due to increased water loss in urine (to accompany Na^+, K^+ and HCO_3^-), increased sweating and hyperventilation.

5. CVS Aspirin has no direct effect in therapeutic doses. Larger doses increase cardiac output to meet increased peripheral O_2 demand and cause direct vasodilatation. Toxic doses depress vasomotor centre: BP may fall. Because of increased cardiac work as well as Na^+ and water retention, CHF may be precipitated in patients with low cardiac reserve.

6. GIT Aspirin and released salicylic acid irritate gastric mucosa → cause epigastric distress, nausea and vomiting. It also stimulates CTZ: vomiting has a central component as well at higher doses.

Aspirin (pKa 3.5) remains unionized and diffusible in the acid gastric juice; but on entering the mucosal cell (pH 7.1), it ionizes and becomes indiffusible. This 'ion trapping' in the gastric mucosal cell enhances gastric toxicity. Further, aspirin particle coming in contact with gastric mucosa promotes local back diffusion of acid → focal necrosis of mucosal cells and capillaries → acute ulcers, erosive gastritis, congestion and microscopic haemorrhages. The occult blood loss in stools is increased by even a single tablet of aspirin; averages 5 ml/day at antiinflammatory doses. Haematemesis occurs occasionally: may be an idiosyncratic reaction.

Soluble aspirin tablets containing calcium carbonate + citric acid and other buffered preparations are less liable to cause gastric ulceration.

7. Urate excretion Dose-related effect is seen:
< 2 g/day—urate retention and antagonism of all other uricosuric drugs.
2–5 g/day—variable effects, often no change.
> 5 g/day—increased urate excretion.
Aspirin is not suitable for use in chronic gout.

8. Blood Aspirin, even in small doses, irreversibly inhibits TXA_2 synthesis by platelets. Thus, it interferes with platelet aggregation and bleeding time is prolonged to nearly twice the normal value. This effect lasts for about a week (turnover time of platelets).

Long-term intake of large doses decrease synthesis of clotting factors in liver and predisposes to bleeding; can be prevented by prophylactic vit K therapy.

PHARMACOKINETICS

Aspirin is absorbed from stomach and small intestines. Its poor water solubility is the limiting factor in absorption: microfining the drug-particles and inclusion of an alkali (solubility is more at higher pH) enhances absorption. However, higher pH also favours ionization, thus decreasing the diffusible form.

Aspirin is rapidly deacetylated in the gut wall, liver, plasma and other tissues to release salicylic acid which is the major circulating and active form. It is ~80% bound to plasma proteins and has a volume of distribution ~0.17 L/kg. It slowly enters brain but freely crosses placenta. Both aspirin and salicylic acid are conjugated in liver with glycine → salicyluric acid (major pathway); and with glucuronic acid. Few other minor metabolites are also produced. The metabolites are excreted by glomerular filtration as well as tubular secretion. Normally, only 1/10th is excreted as free salicylic acid, but this can be increased by alkalinization.

The plasma t½ of aspirin as such is 15–20 min, but taken together with that of released salicylic acid, it is 3–5 hours. However, metabolic processes get saturated over the therapeutic range; t½ of antiinflammatory doses may be 8–12 hours, while that during poisoning may be up to 30 hours. Thus, elimination is dose dependent.

ADVERSE EFFECTS

(a) *Side effects* that occur at analgesic dose (0.3–1.5 g/day) are nausea, vomiting, epigastric distress, increased occult blood loss in stools. The most important adverse effect of aspirin is gastric mucosal damage and peptic ulceration.

(b) *Hypersensitivity and idiosyncrasy* Though infrequent, these can be serious. Reactions include rashes, fixed drug eruption, urticaria, rhinorrhoea, angioedema, asthma and anaphylactoid reaction. Profuse gastric bleeding occurs in rare instances.

(c) *Antiinflammatory doses* (3–5 g/day) produce the syndrome called salicylism—dizziness, tinnitus, vertigo, reversible impairment of hearing and vision, excitement and mental confusion, hyperventilation and electrolyte imbalance. The dose has to be titrated to one which is just below that producing these symptoms; tinnitus is a good guide.

Aspirin therapy in children with rheumatoid arthritis has been found to raise serum transaminases, indicating liver damage. An association between salicylate therapy and 'Reye's syndrome', a rare form of hepatic encephalopathy seen in children having viral (varicella, influenza) infection, has been noted. In adults also, long-term therapy with high dose aspirin can cause insidious onset hepatic injury. Salt and water retention occurs in a dose-related manner.

(d) *Acute salicylate poisoning* It is more common in children. Fatal dose in adults is estimated to be 15–30 g, but is considerably lower in children. Serious toxicity is seen at serum salicylate levels > 50 mg/dl. Manifestations are:

Vomiting, dehydration, electrolyte imbalance, acidotic breathing, hyper/hypoglycaemia,

petechial haemorrhages, restlessness, delirium, hallucinations, hyperpyrexia, convulsions, coma and death due to respiratory failure + cardiovascular collapse.

Treatment is symptomatic and supportive. Most important is external cooling and i.v. fluid with Na^+, K^+, HCO_3^- and glucose: according to need determined by repeated monitoring. Gastric lavage to remove unabsorbed drug; forced alkaline diuresis or haemodialysis to remove absorbed drug is indicated in severe cases. Blood transfusion and vit K should be given if bleeding occurs.

Precautions and contraindications

- Aspirin is contraindicated in patients who are sensitive to it and in peptic ulcer, bleeding tendencies, in children suffering from chickenpox or influenza. Due to risk of Reye's syndrome, pediatric formulations of aspirin are prohibited in India and the UK.
- In chronic liver disease: cases of hepatic necrosis have been reported.
- It should be avoided in diabetics, in those with low cardiac reserve or frank CHF and in juvenile rheumatoid arthritis.
- Aspirin should be stopped 1 week before elective surgery, dental extraction. In case this is not possible, adequate haemostasis must be ensured by packing the socket and use of local haemostatics if needed.
- Given during pregnancy, it may be responsible for low birth weight babies. Delayed or prolonged labour, greater postpartum blood loss and premature closure of ductus arteriosus are possible if aspirin is taken at or near term.
- It should be avoided by breastfeeding mothers.
- Avoid high doses in G-6-PD deficient individuals—haemolysis can occur.

Interactions

1. Aspirin displaces warfarin, naproxen, sulfonylureas, phenytoin and methotrexate from binding sites on plasma proteins: toxicity of these drugs may occur. Its antiplatelet action increases the risk of bleeding in patients on oral anticoagulants.
2. It inhibits tubular secretion of uric acid (at analgesic doses) and antagonizes uricosuric action of probenecid. Tubular secretion of methotrexate is also interfered.
3. It blunts diuretic action of furosemide or thiazides and reduces K^+ conserving action of spironolactone. Competition between canrenone (active metabolite of spironolactone) and aspirin for active transport in proximal tubules has been demonstrated.

USES

1. *As analgesic* For headache, toothache, backache, myalgia, joint pain, pulled muscle, neuralgias and dysmenorrhoea; it is effective in low doses (0.3–0.6 g) and analgesic effect is maximal at ~ 1000 mg. Majority of painful dental conditions respond very well to these doses of aspirin repeated 6–8 hourly.

2. *As antipyretic* It is effective in fever of any origin; dose is same as for analgesia. However, paracetamol, being safer, is generally preferred.

3. *Acute rheumatic fever* Aspirin is the first drug to be used in all cases; other drugs are added or substituted only when it fails or in severe cases (corticosteroids act faster). It brings about marked symptomatic relief in 1–3 days, but granulomatous lesions, nodules, cardiac complications, valvular defects, chorea and duration of disease are not altered.

4. *Rheumatoid arthritis* Aspirin in a dose of 3–5 g/day is effective in most cases; produces relief of pain, swelling and morning stiffness. Progress of the disease process is not affected.

Since large doses of aspirin are poorly tolerated for long periods, the newer NSAIDs are preferred by most.

5. *Osteoarthritis* It affords symptomatic relief only; may be used on 'as and when required' basis, but paracetamol is the first choice analgesic for most cases.

Drug interactions with NSAIDs

Pharmacodynamic

Diuretics	:	↓ diuresis
β blocker	:	↓ antihypertensive effect
ACE inhibitors	:	↓ antihypertensive effect
Anticoagulants	:	↑ risk of g.i. bleed
Sulfonylureas	:	↑ risk of hypoglycaemia
Alcohol	:	↑ risk of g.i. bleed
Cyclosporine	:	↑ nephrotoxicity
Corticosteroids	:	↑ risk of g.i. bleed

Pharmacokinetic

Oral anticoagulants Sulfonylureas Phenytoin Valproate	Metabolism inhibited; Competition for plasma protein binding
Digoxin Lithium Aminoglycosides Methotrexate	↓ Renal excretion of interacting drug

6. *Postmyocardial infarction and poststroke patients* By inhibiting platelet aggregation, aspirin lowers the incidence of reinfarction. Large studies have demonstrated that aspirin 60–100 mg/day reduces the incidence of myocardial infarction (MI): is now routinely prescribed to post-infarct patients; many recommend it for primary prophylaxis as well.

Aspirin reduces 'transient ischaemic attacks' and lowers incidence of stroke in such patients.

7. Other less well established uses of aspirin are:
(a) Pregnancy-induced hypertension and pre-eclampsia.
(b) Patent ductus arteriosus: aspirin can bring about closure and avoid surgery.
(c) Familial colonic polyposis: aspirin and other NSAIDs suppress polyp formation and afford symptomatic relief in this rare disorder.
(d) Prevention of colon cancer: incidence of colon cancer among regular aspirin users is much lower.
(e) To prevent flushing attending nicotinic acid ingestion, which is due to PG release in the skin.

Comorbid conditions aggravated by NSAIDs

- Peptic ulcer
- Hypertension
- Congestive heart failure
- Renal insufficiency
- Haemostatic disorders

ASPIRIN 350 mg tab, COLSPRIN 100, 325, 650 mg tabs, ECOSPRIN 75, 150, 325 mg tabs, DISPRIN 350 mg tab, LOPRIN 75, 162.5 mg tabs.

An injectable preparation has been made available recently; BIOSPIRIN: Lysine acetylsalicylate 900 mg + glycine 100 mg/vial for dissolving in 5 ml water and i.v. injection.

Other salicylates (salicylamide, benorylate, diflunisal) are seldom if ever used.

PROPIONIC ACID DERIVATIVES

Ibuprofen was the first member of this class to be introduced in 1969 as a better tolerated alternative to aspirin. Many others have followed. All have similar pharmacodynamic properties, but differ considerably in potency and to some extent in duration of action (Table 23.2).

The antiinflammatory efficacy is rated somewhat lower than high dose of aspirin. All inhibit PG synthesis, naproxen being the most potent; but their *in vitro* potency for this action does not closely parallel *in vivo* antiinflammatory potency. They inhibit platelet aggregation and prolong bleeding time.

Adverse effects Ibuprofen and all its congeners are better tolerated than aspirin. Side effects are milder and their incidence is lower.
Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects. Gastric erosion and occult blood loss are rare.
CNS side effects include headache, dizziness, blurring of vision, tinnitus and depression.
Rashes, itching and other hypersensitivity phenomena are infrequent. However, these drugs precipitate aspirin-induced asthma.

Table 23.2: Dosage and preparations of propionic acid derivatives

	Drug	Plasma t½	Dosage	Preparations
1.	Ibuprofen	2 hr	400–600 mg TDS	BRUFEN, EMFLAM, IBUSYNTH 200, 400, 600 mg tab, IBUGESIC also 100 mg/5 ml susp.
2.	Naproxen	12–16 hr	250 mg BD–TDS	NAPROSYN, NAXID, ARTAGEN, XENOBID 250 mg tab., NAPROSYN also 500 mg tab.
3.	Ketoprofen	2–3 hr	50-100 mg BD–TDS	KETOFEN 50, 100 mg tab; OSTOFEN 50 mg cap. RHOFENID 100 mg tab, 200 mg SR tab; 100 mg/2 ml amp.
4.	Flurbiprofen	4–6 hr	50 mg BD–QID	ARFLUR 50, 100 mg tab, 200 mg SR tab, FLUROFEN 100 mg tab.

Fluid retention is less marked than that with phenylbutazone.
They are not to be prescribed to pregnant women and should be avoided in peptic ulcer patient.

Pharmacokinetics and interactions All are well absorbed orally, highly bound to plasma proteins (90–99%), but displacement interactions are not clinically significant—dose of oral anticoagulants and oral hypoglycaemics need not be altered. Because they inhibit platelet function, use with anticoagulants should, nevertheless, be avoided. Similar to other NSAIDs, they are likely to decrease diuretic and antihypertensive action of thiazides, furosemide and β blockers.

All propionic acid derivatives enter brain, synovial fluid and cross placenta. They are largely metabolized in liver by hydroxylation and glucuronide conjugation and excreted in urine as well as bile.

Uses

1. Ibuprofen is used as a simple analgesic and antipyretic in the same way as low dose of aspirin.
2. Ibuprofen and its congeners are widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders, especially where pain is more prominent than inflammation.
3. They are indicated in soft tissue injuries, tooth extraction, fractures, vasectomy, postpartum and postoperatively: suppress swelling and inflammation and are very popular in dentistry. Ibuprofen (400 mg) has been found equally or more efficacious than a combination of aspirin (650 mg) + codeine (60 mg) in relieving dental surgery pain.

Choice among different members is difficult; *naproxen* is probably more efficacious and better tolerated in antiinflammatory doses. It is longer acting and has the advantage of twice daily dosing. However, individuals vary in their preference for different members.

ANTHRANILIC ACID DERIVATIVE (FENAMATE)

Mephenamic acid An analgesic, antipyretic and antiinflammatory drug, which inhibits COX as well as antagonises certain actions of PGs. Mephenamic acid exerts peripheral as well as central analgesic action.

Adverse effects Diarrhoea is the most important dose-related side effect. Epigastric distress is complained, but gut bleeding is not significant. Haemolytic anaemia is a rare but serious complication.

Pharmacokinetics Oral absorption is slow but almost complete. It is highly bound to plasma proteins—displacement interactions can occur; partly metabolized and excreted in urine as well as bile. Plasma t½ is 2–4 hours.

Uses Mephenamic acid is indicated primarily as analgesic in muscle, joint and soft tissue pain where strong antiinflammatory action is not

needed. It is quite effective in dysmenorrhoea. It may be useful in some cases of rheumatoid and osteoarthritis but has no distinct advantage.

Dose: 250–500 mg TDS; MEDOL 250, 500 mg cap; MEFTAL, 250, 500 mg tab, 100 mg/5 ml susp. PONSTAN 125, 250, 500 mg tab, 50 mg/ml syrup.

ARYL-ACETIC ACID DERIVATIVE

Diclofenac sodium An analgesic-antipyretic-antiinflammatory drug, similar in efficacy to naproxen. It inhibits PG synthesis and has short-lasting antiplatelet action. Neutrophil chemotaxis and superoxide production at the inflammatory site are reduced.

It is well absorbed orally, 99% protein bound, metabolized and excreted both in urine and bile. The plasma t½ is ~2 hours. Because of good tissue penetrability, concentration in joints and other sites of inflammation is maintained for longer period extending the therapeutic effect.

Adverse effects of diclofenac are generally mild: epigastric pain, nausea, headache, dizziness, rashes. Gastric ulceration and bleeding are less common. Reversible elevation of serum aminotransferases can occur; kidney damage is rare.

Diclofenac is among the most extensively used NSAID; employed in rheumatoid and osteoarthritis, toothache, bursitis, ankylosing spondylitis, dysmenorrhoea, post-traumatic and postoperative inflammatory conditions—affords quick relief of pain and wound edema.

Dose: 50 mg TDS, then BD oral, 75 mg deep i.m. VOVERAN, DICLONAC, MOVONAC 50 mg enteric coated tab, 100 mg S.R. tab, 25 mg/ml in 3 ml amp. for i.m. inj. DICLOMAX 25, 50 mg tab, 75 mg/3ml inj.

Diclofenac potassium: VOLTAFLAM 25, 50 mg tab, ULTRA-K 50 mg tab; VOVERAN 1% topical gel.

OXICAM DERIVATIVES

Piroxicam It is a long-acting NSAID with potent antiinflammatory and good analgesic-antipyretic actions. It is a reversible inhibitor of COX; lowers PG concentration in synovial fluid and inhibits platelet aggregation—prolonging bleeding time. In addition, it decreases the production of IgM rheumatoid factor and reduces leucocyte chemotaxis. Thus, it can inhibit inflammation in diverse ways.

Pharmacokinetics Piroxicam is rapidly and completely absorbed: 99% plasma protein bound; largely metabolized in liver by hydroxylation and glucuronide conjugation; excreted in urine and bile; enterohepatic cycling occurs. Plasma t½ is long—nearly 2 days. Steady-state concentrations are achieved in a week. Single daily administration is sufficient.

Adverse effects Common side effects are heart burn, nausea and anorexia, but it is better tolerated and less ulcerogenic than indomethacin or phenylbutazone; causes less faecal blood loss than aspirin. Rashes and pruritus are seen in < 1% patients. Edema and reversible azotaemia have been observed.

Uses Piroxicam is suitable for use as short-term analgesic as well as long-term antiinflammatory drug in rheumatoid and osteoarthritis, ankylosing spondylitis, acute gout, musculoskeletal injuries and in dentistry.

Dose: 20 mg BD for two days followed by 20 mg OD: DOLONEX, PIROX 10, 20 mg cap, 20 mg dispersible tab, 20 mg/ml inj in 1 and 2 ml amps; PIRICAM 10, 20 mg cap.

Tenoxicam A congener of piroxicam with similar properties and uses.

TOBITIL 20 mg tab; dose 20 mg OD.

PYRROLO-PYRROLE DERIVATIVE

Ketorolac A novel NSAID with potent analgesic and modest antiinflammatory activity. In postoperative pain it has equalled the efficacy of morphine, but does not interact with opioid receptors and is free of opioid side effects. Like other NSAIDs, it inhibits PG synthesis and relieves pain by a peripheral mechanism. In short-lasting pain, it has compared favourably with aspirin.

Ketorolac is rapidly absorbed after oral and i.m. administration. It is highly plasma protein bound and 60% excreted unchanged in urine. Major metabolic pathway is glucuronidation; plasma t½ is 5–7 hours.

Adverse effects Nausea, abdominal pain, dyspepsia, ulceration, loose stools, drowsiness, headache, dizziness, nervousness, pruritus, pain at injection site, rise in serum transaminase and fluid retention have been noted.

Use Ketorolac is frequently used in postoperative, dental and acute musculoskeletal pain: 15–30 mg i.m. or i.v. is comparable to 10–12 mg morphine, and can be repeated every 4–6 hours (max. 90 mg/day). It can also be used for renal colic, migraine and pain due to bony metastasis.

Orally it is used in a dose of 10–20 mg 6 hourly for short-term management of moderate pain. In postoperative dental pain ketorolac has been rated superior to aspirin 650 mg, paracetamol 600 mg and equivalent to ibuprofen 400 mg. Continuous use for more than 5 days is not recommended.

KETOROL, ZOROVON, KETANOV, TOROLAC 10 mg tab, 30 mg in 1 ml amp.

INDOLE DERIVATIVE

Indomethacin It is a potent antiinflammatory drug with prompt antipyretic action. Indomethacin relieves only inflammatory or tissue injury related pain. It is a highly potent inhibitor of PG synthesis and suppresses neutrophil motility. In toxic doses it uncouples oxidative phosphorylation (like aspirin).

Pharmacokinetics Indomethacin is well absorbed orally, rectal absorption is slow but dependable. It is 90% bound to plasma proteins, partly metabolized in liver to inactive products and excreted by kidney. Plasma t½ is 2–5 hours.

Adverse effects A high incidence (up to 50%) of gastrointestinal and CNS side effects is produced.

Gastric irritation, nausea, anorexia, gastric bleeding and diarrhoea are prominent.

Frontal headache (very common), dizziness, ataxia, mental confusion, hallucination, depression and psychosis can occur.

Leukopenia, rashes and other hypersensitivity reactions are also reported.

Increased risk of bleeding due to decreased platelet aggregability.

It is contraindicated in machinery operators, drivers, psychiatric patients, epileptics, kidney disease, pregnant women and in children.

Dose: 25–50 mg BD-QID. Those not tolerating the drug orally may be given nightly suppository.

IDICIN, INDOCAP 25 mg cap, 75 mg SR cap, ARTICID 25, 50 mg cap, INDOFLAM 25, 75 mg caps, 1% eye drop. RECTICIN 50 mg suppository.

Uses Because of prominent adverse effects, indomethacin is used as a reserve drug in conditions requiring potent antiinflammatory action like ankylosing spondylitis, acute exacerbations of destructive arthropathies, psoriatic arthritis and acute gout that are not responding to better tolerated NSAIDs.

Malignancy associated fever refractory to other antipyretics may respond to indomethacin. It has been the most common drug used for medical closure of patent ductus arteriosus. Bartter's syndrome responds dramatically, as it does to other PG synthesis inhibitors.

PYRAZOLONES

Antipyrine (phenazone) and amidopyrine (aminopyrine) were introduced in 1884 as antipyretic and analgesic. Their use was associated with high incidence of agranulocytosis: are banned in many countries, including India. *Phenylbutazone* was introduced in 1949 and soon its active metabolite *oxyphenbutazone* was also marketed. These two are potent antiinflammatory drugs, inhibit COX, but have slow onset, weak analgesic and antipyretic action. Their gastric toxicity is high; edema due to Na^+ and water retention is frequent and CNS side effects, hypersensitivity reactions, hypothyroidism are reported. They are banned in many countries and rarely used in others due to residual risk of bone marrow depression and other toxicity. Two other pyrazolones available in India—*metamizol* and *propiphenazone* are primarily used as analgesic and antipyretic.

Metamizol (Dipyrone) In contrast to phenylbutazone, this derivative of amidopyrine is a potent and promptly acting analgesic and antipyretic but poor antiinflammatory and not uricosuric. It can be given orally, i.m. as well as i.v, but gastric irritation, pain at injection site occurs. Occasionally, i.v. injection produces precipitous fall in BP.

Few cases of agranulocytosis were reported and metamizol was banned in the USA and some European countries. However, it has been extensively used in India and other European countries. Adverse reaction data collected over four decades shows that risk of serious toxicity with this drug is lower than with aspirin or many other NSAIDs. However, its fixed dose combination with antispasmodics is banned in India.

Dose: 0.5–1.5 g oral/i.m./i.v.; ANALGIN 0.5 g tab; NOVALGIN, BARALGAN 0.5 g tab, 0.5 g/ml in 2 ml and 5 ml amps; ULTRAGIN 0.5 g/ml inj in 2 ml amp and 30 ml vial.

Propiphenazone Another pyrazolone, similar in properties to metamizol; claimed to be better tolerated. Agranulocytosis has not been reported.

Dose: 300–600 mg TDS; marketed only in combination in several 'over-the-counter', preparations—in SARIDON, ANAFEBRIN: propiphenazone 150 mg + paracetamol 250 mg tab.

DART: propiphenazone 150 mg + paracetamol 300 mg + caffeine 50 mg tab.

PREFERENTIAL COX-2 INHIBITORS

Nimesulide This newer NSAID is a relatively weak inhibitor of PG synthesis and there is some evidence to indicate relative COX-2 selectivity. Antiinflammatory action may be exerted by other mechanisms as well, e.g. reduced generation of superoxide by neutrophils, inhibition of PAF synthesis and TNFα release, free radical scavanging, inhibition of metalloproteinase activity in cartilage. The analgesic, antipyretic and antiinflammatory activity of nimesulide has been rated comparable to other NSAIDs. It has been used primarily for short-lasting painful inflammatory conditions like sports injuries, sinusitis and other ear-nose-throat disorders, dental surgery, bursitis, low backache, dysmenorrhoea, postoperative pain, osteoarthritis and for fever.

Nimesulide is almost completely absorbed orally, 99% plasma protein bound, extensively metabolized and excreted mainly in urine with a t½ of 2–5 hours.

Adverse effects of nimesulide are gastrointestinal (epigastralgia, heart burn, nausea, loose motions), dermatological (rash, pruritus) and central (somnolence, dizziness). Gastric tolerability of nimesulide is better, but an Italian study has shown that ulcer complications are as prevalent as with other NSAIDs. There is also no proof that renal complications are missing: haematuria is reported in few children. Recently, several instances of fulminant hepatic failure have been associated with nimesulide and it has been withdrawn in Spain, Finland and Turky; use in children is banned in Portugal and Israel. Considering that it has not been marketed in the UK, USA, Australia and Canada, the overall safety of this drug, especially in children, has been questioned. However, most asthmatics and those who develop bronchospasm or intolerance to aspirin do not cross react with nimesulide. Its specific usefulness appears to be only in such patients.

Dose: 100 mg BD; NIMULID, NIMEGESIC, NIMODOL 100 mg tab, 50 mg/5 ml susp.

Meloxicam This newer congener of piroxicam has a COX-2 : COX-1 selectivity ratio of about 10. Since measurable inhibition of platelet TXA_2 production (a COX-1 function) occurs at therapeutic doses of meloxicam, it has been labelled 'preferential COX-2 inhibitor'. Efficacy of meloxicam in osteo- and rheumatoid arthritis is comparable to piroxicam. In short-term studies, gastric changes with the lower dose (7.5 mg/day) were found to be similar to placebo, but at the higher dose (15 mg/day) they were intermediate between placebo and piroxicam. Gastric side effects of meloxicam are milder, but ulcer complications (bleeding, perforation) have been reported on long-term use. Thus, there is no convincing evidence that meloxicam is safer than other NSAIDs.

Dose: 7.5-15 mg OD; MELFLAM, MEL-OD, MUVIK, M-CAM 7.5 mg, 15 mg tabs.

Nabumetone It is a recently developed prodrug—generates an active metabolite (6-MNA) which is a relatively more potent COX-2 than

COX-1 inhibitor. It possesses analgesic, antipyretic and antiinflammatory activities; effective in the treatment of rheumatoid and osteoarthritis as well as soft tissue injury. Nabumetone has caused a lower incidence of gastric erosions, ulcers and bleeding, probably because the active COX inhibitor is produced in tissues after absorption. However, confirmatory evidence of its superiority is lacking.

NABUFLAM 500 mg tab; 1 tab OD.

SELECTIVE COX-2 INHIBITORS

Because of the theoretical advantage of inhibiting COX-2 without affecting COX-1 function, some highly selective COX-2 inhibitors have been introduced over the past decade. The selective COX-2 inhibitors cause little gastric mucosal damage; occurrence of peptic ulcer and ulcer bleeds is clearly lower than other NSAIDs. They do not depress TXA_2 production by platelets (COX-1 dependent); do not inhibit platelet aggregation or prolong bleeding time, but may reduce PGI_2 production by vascular endothelium.

Celecoxib The COX-2 selectivity of celecoxib is 6–375-fold measured in different tests. It exerts antiinflammatory, analgesic and antipyretic actions with low ulcerogenic potential. Comparative trials in rheumatoid arthritis have found it to be as effective as naproxen or diclofenac, without affecting COX-1 activity in gastroduodenal mucosa even at maximal therapeutic dose. Platelet aggregation in response to collagen exposure remained intact in celecoxib recipients and serum TXB_2 levels were not reduced. Though tolerability of celecoxib is better than older NSAIDs, still abdominal pain, dyspepsia and mild diarrhoea are the common side effects.

Celecoxib is slowly absorbed, 97% plasma protein bound and metabolized primarily by CYP2C9 with a mean t½ of 11 hours. It is approved for use in osteo-and rheumatoid arthritis in a dose of 100–200 mg BD.

CELACT, REVIBRA, COLCIBRA 100,200 mg caps

Assessment of selective COX-2 inhibitors

Though antiinflammatory efficacy of selective COX-2 inhibitors appears to be similar to other NSAIDs and their superior gastric profile is now established, certain concerns have been raised:

- COX-1 isoenzyme may also have a role in inflammation: selective COX-2 inhibitors may not have as broad range of efficacy as nonselective COX inhibitors.
- Ulcer injury and *H. pylori* induce COX-2 in gastric mucosa—which may contribute to gastroprotective PG synthesis; its inhibition may also be injurious.
- Juxtaglomerular COX-2 is constitutive, inhibition of which can cause salt and water retention; pedal edema, precipitation of CHF and rise in BP have been noted with both celecoxib and rofecoxib.
- COX-2 inhibitors reduce whole body PGI_2 production without affecting platelet TXA_2 synthesis. This may exert prothrombotic influence and enhance cardiovascular risk. The 'vioxx (rofecoxib) gastrointestinal outcomes research' (VIGOR) study in over 8000 patients has lent support to this hypothesis. Patients receiving rofecoxib had a higher incidence of myocardial infarction than those receiving naproxen. However, this may be because prophylactic use of aspirin was not allowed to the study subjects. Another study 'celecoxib long-term arthritis safety study' (CLASS) in which use of aspirin was permitted has not found any increase in cardiovascular events in patients on celecoxib than those on ibuprofen or diclofenac. The recently concluded APPROVe (Adenomatous polyp prevention on VIOXX) trial among subjects with a history of colorectal adenomas has demostrated increased risk for heart attack and stroke beginning after 18 months of treatment with rofecoxib compared to those taking placebo. On the basis of this 3-year study data, the manufacturer of rofecoxib has withdrawn it globally. If increase in cardiovascular events risk is due to selective COX-2 inhibition (causing deficiency of cardioprotective PGI_2), other similar drugs like celecoxib, valdecoxib, etoricoxib may be equally unsafe.

Rofecoxib This highly selective COX-2 inhibitor introduced in 1999 had become very popular for osteo- and rhematoid arthritis as well as for dental, postoperative and acute musculoskeletal pain, but has been withdrawn worldwide by its manufacturer in September 2004 because of higher incidence of myocardial infarction and stroke compared to placebo observed in one study after its long-term (>18 months) use. It has been banned by Govt. of India.

Valdecoxib Another selective COX-2 inhibitor having similar efficacy and tolerability profile as earlier selective COX-2 inhibitors. The plasma t½ is 8–11 hours. In osteoarthritis and rheumatoid arthritis it is recommended in a dose of 10 mg once daily; while for primary dysmenorrhoea, dental or postoperative pain, up to 20 mg twice daily may be used. Few cases of severe skin reaction such as Stevens-Johnson syndrome have been reported.

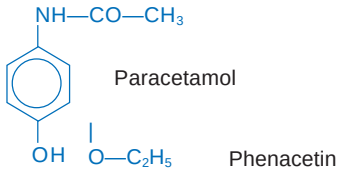
VORTH, VALUS 10 mg tab.

Etoricoxib Yet another new highly selective COX-2 inhibitor suitable for once-a-day treatment of osteo/rheumatoid/acute gouty arthritis, dysmenorrhoea, acute dental surgery pain and similar conditions, without affecting platelet function or damaging gastric mucosa. In one study it has been shown not to increase thrombotic cardiovascular events compared to diclofenac.

Dose: 60–120 mg OD; ETODY 60, 90, 120 mg tabs NUCOXIA 120 mg tab.

PARA-AMINO PHENOL DERIVATIVES

Phenacetin introduced in 1887 was extensively used as analgesic-antipyretic but is now banned because it was implicated in analgesic abuse nephropathy.



Paracetamol (*acetaminophen*) the deethylated active metabolite of phenacetin, was also introduced in the last century but has come into common use only since 1950.

Actions The central analgesic action of paracetamol is like aspirin, i.e. it raises pain threshold, but has weak peripheral antiinflammatory component. Analgesic action of aspirin and paracetamol is additive. Paracetamol is a good and promptly acting antipyretic.

Paracetamol has negligible antiinflammatory action. It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on COX in brain. One explanation offered for the discrepancy between its analgesic-antipyretic and antiinflammatory actions is its poor ability to inhibit COX in the presence of peroxides which are generated at sites of inflammation but are not present in brain.

In contrast to aspirin, paracetamol does not stimulate respiration or affect acid-base balance; does not increase cellular metabolism. It has no effect on CVS. Gastric irritation is insignificant—mucosal erosion and bleeding occur rarely only in overdose. It does not affect platelet function or clotting factors and is not uricosuric.

Pharmacokinetics Paracetamol is well absorbed orally, only about 1/3rd is protein bound in plasma and distribution in the body is quite uniform. It is conjugated with glucuronic acid and sulfate and is excreted rapidly in urine. Plasma t½ is 2–3 hours. Effects after an oral dose last for 3–5 hours.

Adverse effects In isolated antipyretic doses paracetamol is safe and well tolerated. Nausea and rashes occur occasionally, leukopenia is rare.

Analgesic nephropathy occurs after years of heavy ingestion of analgesics; such individuals probably have some personality defect. Pathological lesions are papillary necrosis, tubular atrophy followed by renal fibrosis. Urine concentrating ability is lost and the kidneys shrink. Because phenacetin was commonly abused, it was primarily implicated and went into disrepute, though other analgesics are also liable to produce similar effects.

Acute paracetamol poisoning It occurs specially in small children who have low hepatic glucuronide conjugating ability. If a large dose (> 150 mg/kg or > 10 g in an adult) is taken, serious toxicity can occur. Fatality is common with > 250 mg/kg.

Early manifestations are just nausea, vomiting, abdominal pain and liver tenderness with no impairment of consciousness. After 12–18 hours centrilobular hepatic necrosis occurs

which may be accompanied by renal tubular necrosis and hypoglycaemia that may progress to coma. Jaundice starts after 2 days. Further course depends on the dose taken. Fulminating hepatic failure and death are likely if the plasma levels are high. If the levels are lower —recovery with supportive treatment is the rule.

Mechanism of toxicity N-acetyl-p-benzoquinoneimine (NABQI) is a highly reactive arylating minor metabolite of paracetamol which is detoxified by conjugation with glutathione. When a very large dose of paracetamol is taken, glucuronidation capacity is saturated, more of minor metabolite is formed—hepatic glutathione is depleted and this metabolite binds covalently to proteins in liver cells (and renal tubules) causing necrosis. Toxicity thus shows a threshold effect manifesting only when glutathione is depleted to a critical point.

In chronic alcoholics even 5–6 g/day taken for a few days can result in hepatotoxicity because alcoholism induces CYP2E1 that metabolises paracetamol to NABQI.

Treatment If the patient is brought early, vomiting should be induced or gastric lavage done. Activated charcoal is given to prevent further absorption. Other supportive measures, as needed, should be taken.

N-acetylcysteine infused i.v. or given orally is the specific antidote. It replenishes hepatic glutathione and prevents binding of the toxic metabolite to other cellular constituents.

Ingestion-treatment interval is critical; earlier the better. It is practically ineffective if started 12–16 hours after paracetamol ingestion.

Uses Paracetamol is one of the most commonly used 'over-the-counter' analgesic for headache, musculoskeletal pain, toothache, dysmenorrhoea, etc. where antiinflammatory action is not required. It is relatively ineffective when inflammation is prominent. It is one of the best drugs to be used as antipyretic.

Dose to dose it is equally efficacious as aspirin for noninflammatory conditions. Clinical studies have found paracetamol and aspirin to be equieffective in relieving pain after the extraction of third molars. However, paracetamol is much safer than aspirin in terms of gastric irritation, ulceration and bleeding (can be given to ulcer patients). Because it does not prolong bleeding time, risk of tooth extraction haemorrhage is not accentuated. Paracetamol can be used in all age groups (infants to elderly), pregnant/lactating women, in presence of other disease states and in patients in whom aspirin is contraindicated. It does not have significant drug interactions. Thus, it may be preferred over aspirin for most minor conditions.

Dose: 0.5–1 g TDS; infants 50 mg; children 1–3 years 80–160 mg, 4–8 years 240–320 mg, 9–12 years 300–600 mg. CROCIN 0.5, 1.0 g tabs; METACIN, PARACIN 500 mg tab, 125 mg/5 ml syrup, 150 mg/ml paed. drops, ULTRAGIN, PYRIGESIC, CALPOL 500 mg tab, 125 mg/5ml syrup, NEOMOL, FEVASTIN, FEBRINIL 300 mg/2 ml inj. CROCIN PAIN RELIEF: Paracetamol 650 mg + Caffeine 50 mg tab.

BENZOXAZOCINE DERIVATIVE

Nefopam It is a nonopioid analgesic which does not inhibit PG synthesis. In traumatic, dental and postoperative pain, it acts rapidly. Favourable results have been obtained in short-lasting musculoskeletal pain not responding to other nonopioid analgesics.

Nefopam produces anticholinergic (dry mouth, urinary retention, blurred vision) and sympathomimetic (tachycardia, nervousness) side effects, and nausea is often dose limiting. It is contraindicated in epileptics.

Dose: 30–60 mg TDS oral, 20 mg i.m. 6 hourly. NEFOMAX 30 mg tab, 20 mg in 1 ml amp.

Analgesic/NSAIDs in dentistry

The antipyretic-analgesics/NSAIDs are the mainstay for management of acute dental pain. There is ample evidence of their efficacy in most types of pain encountered in dentistry. The cause and nature of pain (mild, moderate or severe; acute or chronic; ratio of pain: inflammation) along with consideration of risk factors in the patient govern

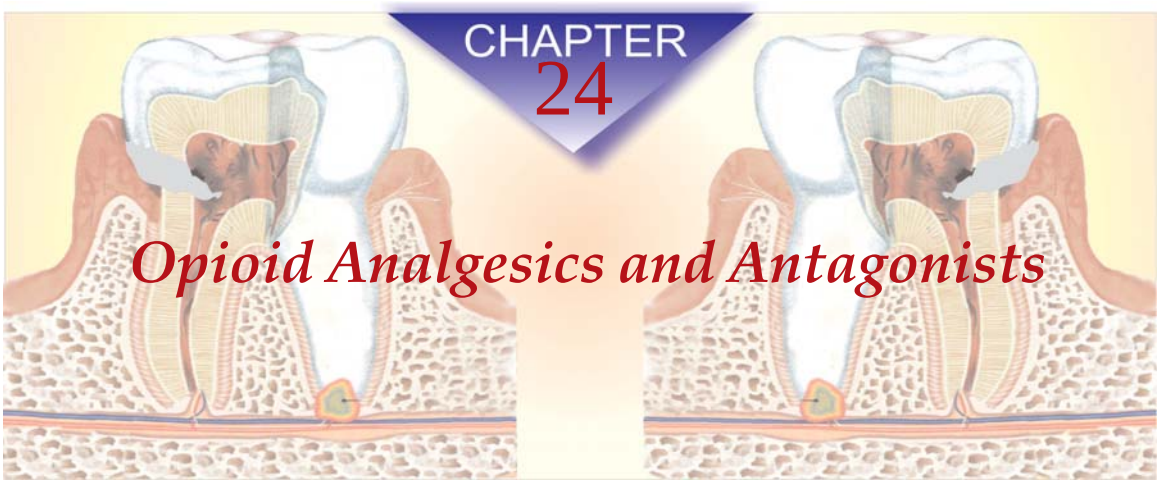
selection of the analgesic. Also to be considered are the past experience of the patient, acceptability and individual preference. Though NSAIDs have a common spectrum of adverse effects, they differ quantitatively among themselves in producing various side effects. Moreover, patients differ in their analgesic response to different NSAIDs. If one NSAID is unsatisfactory in a patient, it does not mean that other NSAIDs will also be unsatisfactory. Some subjects 'feel better' on a particular drug, but not on a closely related one. Thus, no single drug is superior to all others for every patient. It is in this context that availability of such a wide range of NSAIDs may be welcome. Some guidelines are:

1. Mild-to-moderate pain with little inflammation: paracetamol or low-dose ibuprofen.
2. Postextraction or similar acute but short-lasting pain: ketorolac, a propionic acid derivative, diclofenac, nimesulide or aspirin.
3. Gastric intolerance to conventional NSAIDs or predisposed patients: a selective COX-2 inhibitor or paracetamol.
4. Patients with history of asthma or anaphylactoid reaction to aspirin/other NSAIDs: nimesulide.
5. Paediatric patients: only paracetamol, aspirin, ibuprofen and naproxen have been adequately evaluated in children — should be preferred in them. Due to risk of Reye's syndrome, aspirin should be avoided unless viral infection can be ruled out.
6. Pregnancy: paracetamol is the safest; low-dose aspirin is probably the second best.
7. Hypertensive, diabetic, ischaemic heart disease, epileptic and other patients receiving long-term regular medication: possibility of drug interaction with NSAIDs should be considered and the physician consulted.

Analgesic combinations

Combination of aspirin and paracetamol is additive (not supra-additive) and a ceiling analgesic effect is obtained when the total amount of aspirin + paracetamol is ~ 1000 mg. The same is true of combinations of paracetamol with other NSAIDs like ibuprofen, diclofenac, etc. There is no convincing evidence that such combinations are superior to single agents either in efficacy or in safety. If at all used, such combinations should be limited to short periods.

Combination of codeine (an opioid analgesic) with aspirin or paracetamol is also additive, but in this case combination provides additional analgesia beyond the ceiling effect of aspirin/paracetamol. The mechanisms of pain relief by these two classes of drugs are different. Such combination can be considered rational for providing greater analgesia. Adequate clinical data supports use of such combination for pain refractory to single agent.



CHAPTER 24

Opioid Analgesics and Antagonists

OPIOID ANALGESICS

Opium The dark brown, resinous material obtained from poppy (*Papaver somniferum*) capsule is called 'Opium'. It contains two types of alkaloids.

Phenanthrene derivatives
Morphine (10% in opium)
Codeine (0.5% in opium)
Thebaine (0.2% in opium), (Nonanalgesic)

Benzoisoquinoline derivatives
Papaverine (1%), Noscapine (6%) } Nonanalgesic

Opium has been known from the earliest times. Galen (2nd century AD) introduced tincture of opium. Serturner, a pharmacist, isolated the active principle of opium in 1806 and named it *'morphine'* after the Greek god of dreams *Morpheus.* In the last century a large number of semisynthetic and synthetic compounds have been developed with morphine-like, antagonistic and mixed agonistic-antagonistic properties.

MORPHINE

Morphine is the principal alkaloid in opium and still widely used, therefore, described as prototype.

PHARMACOLOGICAL ACTIONS

1. CNS Morphine has site specific depressant and stimulant actions in the CNS. The depressant effects are:

(a) *Analgesia* Morphine is a strong analgesic. Though dull, poorly localized visceral pain is relieved better than sharply defined somatic pain; higher doses can mitigate even severe pain—degree of analgesia increasing with dose. Nociceptive pain arising from stimulation of peripheral pain receptors is relieved better than neuretic pain (such as trigeminal neuralgia) due to inflammation or damage of neural structures. The associated reactions to intense pain (apprehension, fear, autonomic effects) are also depressed. Suppression of pain perception is selective, without affecting other sensations or producing proportionate generalized CNS depression (contrast general anaesthetics).

Perception of pain and its emotional or suffering component are both altered so that pain is no longer as unpleasant or distressing, i.e. the patient tolerates pain better. The analgesic action of morphine has spinal and supraspinal components. Intrathecal injection has been shown to cause segmental analgesia without affecting other modalities. It acts in the substantia gelatinosa of dorsal horn to inhibit release of

excitatory transmitters from primary afferents carrying pain impulses. The action appears to be exerted through interneurones which are involved in the 'gating' of pain impulses. Release of substance P from primary pain afferents in the spinal cord and its postsynaptic action on dorsal horn neurones is inhibited by morphine. Action at supraspinal sites in medulla, midbrain, limbic and cortical areas may alter processing and interpretation of pain impulses as well as send inhibitory impulses through descending pathways to the spinal cord. Several aminergic and other neuronal systems appear to be involved in the action of morphine and simultaneous action at spinal and supraspinal sites greatly amplifies the analgesic action.

(b) *Sedation* which is different from that produced by hypnotics is seen. Drowsiness and indifference to surroundings as well as to own body occurs without motor incoordination, ataxia or apparent excitement (contrast alcohol). Higher doses progressively produce sleep and coma. It has no anticonvulsant action, rather, fits may be precipitated.

(c) *Mood and subjective effects* These are prominent. Morphine has a calming effect; there is loss of apprehension, feeling of detachment, lack of initiative, limbs feel heavy and body warm, mental clouding and inability to concentrate occurs. In the absence of pain or apprehension, these are generally appreciated as unpleasant by normal people. However, patients in pain or anxiety and especially addicts, perceive it as pleasurable: refer it as 'high'. Rapid i.v. injection by addicts gives them a 'kick' or 'rush' which is intensely pleasurable—akin to orgasm. Thus, one has to learn to perceive the *euphoric* effect of morphine.

(d) *Respiratory centre* Morphine depresses respiratory centre in a dose-dependent manner; rate and tidal volume are both decreased: death in poisoning is due to respiratory failure. Neurogenic, hypercapnoeic and later hypoxic drives to respiratory centre are suppressed in succession. In addition, there is indifference to breathing: apnoeic patient may breath if commanded.

(e) *Cough centre* It is depressed; more sensitive to morphine than respiratory centre.

(f) *Temperature regulating centre* It is depressed; hypothermia occurs in cold surroundings.

(g) *Vasomotor centre* It is depressed at higher doses and contributes to the fall in BP.

Morphine stimulates:

(a) *CTZ* Nausea and vomiting occur as side effects, especially if stomach is full and the patient stands or moves about. Thus, morphine appears to sensitize the CTZ to vestibular and other impulses. Larger doses depress vomiting centre directly: emetics should not be tried in morphine poisoning.

(b) *Edinger Westphal nucleus* of III nerve is stimulated producing miosis. This is a central action; no miosis occurs on topical application of morphine to the eye.

(c) *Vagal centre* It is stimulated—can cause bradycardia.

(d) *Certain cortical areas and hippocampal cells* are stimulated. Excitation is seen in an occasional individual. Muscular rigidity and immobility is consistently manifested at high doses: resembles catalepsy seen in rats and mice. Convulsions may occur in morphine poisoning. The proconvulsant action has been ascribed to inhibition of GABA release by hippocampal interneurones. Species like the cat, lion, horse, sheep and cow are uniformly excited and show hyperthermia.

2. Neuro-endocrine Acting on the hypothalamus, morphine can reduce FSH, LH and ACTH release, but increase prolactin and GH release. However, effect on sex hormone levels are clinically insignificant, except in some chronic abusers, who may suffer from infertility. It enhances ADH release and can reduce urine volume. Morphine also causes central sympathetic stimulation resulting in mild hyperglycaemia.

3. CVS Morphine causes vasodilatation due to:
(a) histamine release.
(b) depression of vasomotor centre.
(c) direct action decreasing tone of blood vessels.
There is a shift of blood from pulmonary to systemic circuit due to greater vasodilatation in the latter. Therapeutic doses cause little change in BP of recumbent normovolaemic patient. Postural hypotension and fainting can occur due to impairment of vascular reflexes. Morphine has little direct effect on heart; rate may increase (reflexly due to fall in BP) or decrease (stimulation of vagal centre). Cardiac work is consistently reduced due to decrease in peripheral resistance. Intracranial tension tends to rise as a consequence of CO_2 retention leading to cerebral vasodilatation.

4. GIT Constipation is a prominent feature of morphine action. Several factors contribute:
(a) Action directly on intestines and in CNS increases tone and segmentation but decreases propulsive movements. Tone of duodenum and colon may be increased to the level of spasm.
(b) Spasm of pyloric, ileocaecal and anal sphincters.
(c) Decrease in all gastrointestinal secretions.
(d) Central action causing inattention to defecation reflex.
No tolerance develops to this action: addicts remain chronically constipated.

5. Other smooth muscles

(a) *Biliary tract* Morphine causes spasm of sphincter of Oddi → intrabiliary pressure is increased → may cause biliary colic.

(b) *Urinary bladder* Tone of both detrusor and sphincter is increased → urinary urgency and difficulty in micturition.

(c) *Bronchi* Morphine releases histamine which can cause bronchoconstriction. This is of no consequence in normal individuals, but can be dangerous in asthmatics.

PHARMACOKINETICS

The oral absorption of morphine is unreliable because of high and variable first pass metabolism; oral bioavailability is 1/6 to 1/4th of parenterally administered drug. About 30% is bound to plasma proteins. Only a small fraction enters brain rather slowly. Morphine freely crosses placenta and can affect the foetus more than the mother. It is primarily metabolized in liver by glucuronide conjugation. Morphine-6-glucuronide is an active metabolite (inherently more potent than morphine) which accumulates during chronic dosing and contributes to analgesia, despite its restricted passage across blood-brain barrier. Plasma t½ of morphine averages 2–3 hours. Effect of a parenteral dose lasts 4–6 hours. Elimination is almost complete in 24 hours and morphine is noncumulative. Small amounts may persist due to enterohepatic circulation.

ADVERSE EFFECTS

Side effects of morphine are sedation, mental clouding, lethargy and other subjective effects which may even be dysphoric in some subjects; vomiting is occasional in recumbent patients; constipation is common. Respiratory depression, blurring of vision, urinary retention (especially in elderly males) are the other side effects. BP may fall, especially in hypovolaemic patient and if he/she walks about.

Urticaria, itch, swelling of lips may occur due to histamine release.

Acute morphine poisoning It is accidental, suicidal or seen in drug abusers. In the non-tolerant adult, 50 mg of morphine i.m. produces serious toxicity. Manifestations are extensions of pharmacological action: stupor or coma, flaccidity, shallow and occasional breathing, cyanosis, pinpoint pupil, fall in BP and shock, convulsions may be seen in few, pulmonary edema occurs at terminal stages, death is due to respiratory failure.

Treatment: consists of respiratory support and maintenance of BP (i.v. fluids, vasoconstrictors).

Gastric lavage should be done with pot. permanganate to remove unabsorbed drug.

Naloxone 0.4–0.8 mg i.v. repeated every 2–3 minutes till respiration picks up, is the specific antidote. It has a short duration of action. Injection should be repeated every 1–4 hours later on, according to response.

Tolerance and dependence High degree of tolerance can be developed to morphine and related opioids if the drug is used repeatedly. It is partly pharmacokinetic (enhanced rate of metabolism) but mainly pharmacodynamic (cellular tolerance). Addicts tolerate morphine in grams: lethal dose is markedly increased. Cross tolerance among opioids is of high degree. Morphine tolerant subjects are partially cross tolerant to other CNS depressants as well.

Morphine produces pronounced psychological and physical dependence, its abuse liability is rated high. Concern about abuse has been a major limitation in the use of morphine, but appropriate medial use of morphine seldom progresses to dependence and abuse.

Withdrawal of morphine is associated with marked drug seeking behaviour. Physical manifestations are—lacrimation, sweating, yawning, anxiety, fear, restlessness, gooseflesh, mydriasis, tremor, insomnia, abdominal colic, diarrhoea, dehydration, rise in BP, palpitation and rapid weight loss. Delirium and convulsions are seen only occasionally.

Treatment: consists of withdrawal of morphine and substitution with oral methadone (long acting, orally effective) followed by gradual withdrawal of methadone. However, relapse rate among postaddicts is high. Long-term methadone maintenance and other techniques using agonist-antagonistic drugs are also employed.

PRECAUTIONS AND CONTRAINDICATIONS

Morphine is a drug of emergency, but due care has to be taken in its use.

1. Infants and the elderly are more susceptible to the respiratory depressant action of morphine.
2. It is dangerous in patients with respiratory insufficiency (emphysema, pulmonary fibrosis, cor pulmonale), sudden deaths have occurred.
3. Bronchial asthma: Morphine can precipitate an attack by its histamine releasing action.
4. Head injury: morphine is contraindicated in patients with head injury. Reasons are—

(a) By retaining CO_2, it increases intracranial tension which will add to that caused by head injury itself.

(b) Even therapeutic doses can cause marked respiratory depression in these patients.

(c) Vomiting, miosis and altered mentation produced by morphine interfere with assessment of progress in head injury cases.

5. Hypotensive states and hypovolaemia exaggerate fall in BP due to morphine.
6. Undiagnosed acute abdominal pain: morphine can aggravate certain conditions, e.g. diverticulitis, biliary colic, pancreatitis. Inflamed appendix may rupture.
7. Elderly male: chances of urinary retention are high.
8. Hypothyroidism, liver and kidney disease patients are more sensitive to morphine.
9. Unstable personalities: are liable to continue with its use and become addicted.

Interactions

Phenothiazines, tricyclic antidepressants, MAO inhibitors, amphetamine and neostigmine potentiate morphine and other opioids, either by retarding its metabolism or by a pharmacodynamic interaction at the level of central neurotransmitters.

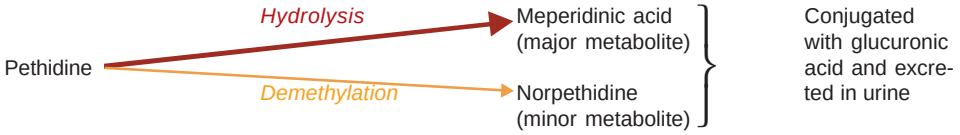
Morphine retards absorption of many orally administered drugs by delaying gastric emptying.

Dose 10–50 mg oral, 10–15 mg i.m. or s.c. or 2–6 mg i.v.; 2–3 mg epidural/intrathecal; children 0.1–0.2 mg/kg.

MORPHINE SULPHATE 10 mg/ml inj; MORCONTIN 10, 30, 60, 100 mg continuous release tabs; 30–100 mg BD; RILIMORF 10,20 mg tabs, 60 mg SR tab.

CLASSIFICATION OF OPIOIDS

1. *Natural opium alkaloids:* Morphine, Codeine



2. *Semisynthetic opiates*: Diacetylmorphine (Heroin), Pholcodeine.

3. *Synthetic opioids:* Pethidine (Meperidine), Fentanyl, Methadone, Dextropropoxyphene, Tramadol.

1. Codeine It is methyl-morphine, occurs naturally in opium, and is partly converted in the body to morphine. It is less potent than morphine (1/10th as analgesic), also less efficacious: the degree of analgesia is comparable to aspirin (60 mg codeine ~ 600 mg aspirin); can relieve mild-to-moderate pain only.

However, it is more selective cough suppressant (only 1/3rd as potent as morphine); subanalgesic doses (10–30 mg) suppress cough. Codeine has very low affinity for opioid receptors. The analgesic action has been ascribed to morphine generated by its demethylation.

Codeine has good activity by oral route (oral: parenteral ratio 1:2). A single oral dose acts for 4–6 hours. Constipation is a prominent side effect, but others are mild. It has been used to control diarrhoea. The abuse liability of codeine is low. Though codeine phosphate is water soluble and can be injected, parenteral preparation is not available.

2. Pholcodeine It has codeine like properties and has been used mainly as antitussive; claimed to be less constipating.

3. Heroin (Diamorphine, Diacetylmorphine) It is about 3 times more potent than morphine; more lipid soluble: enters brain more rapidly but duration of action is similar. It is considered to be more euphorient (especially on i.v. injection) and highly addicting. However, it has no outstanding therapeutic advantage over morphine and has been banned in most countries except the UK.

* *See* Lee F and Cundiff D; *Arch* Intern. Med. **158**, (1998), 2399.

4. Pethidine (Meperidine)

Pethidine was synthesized as an atropine substitute in 1939, and has some actions like it. Though chemically unrelated to morphine, it interacts with opioid receptors (primarily μ) and its actions are blocked by naloxone. Important differences in comparison to morphine are:

1. Dose to dose 1/10th in analgesic potency; however, analgesic efficacy approaches near to morphine and is more than codeine.
2. After i.m. injection, the onset of action is more rapid but duration is shorter (3–4 hours).
3. It does not effectively suppress cough.
4. Spasmodic action on smooth muscles is less marked—miosis, constipation and urinary retention are less prominent.

Pethidine is believed to induce less biliary spasm than morphine; traditionally preferred in cholecystitis/biliary colic. However, there is no objective evidence to support this belief. One study* in patients undergoing cholecystectomy found pethidine to raise common bile duct pressure 14% more than equianalgesic dose of morphine.

5. It is equally sedative and euphoriant, has similar abuse potential. The degree of respiratory depression seen at equianalgesic doses is equivalent to morphine.
6. It causes less histamine release and is safer in asthmatics.
7. It has local anaesthetic action: corneal anaesthesia is seen after systemic doses.
8. It is well absorbed, oral: parenteral activity ratio is high (1/3–1/2). Pethidine is nearly completely metabolized in liver. The plasma t½ of pethidine is 2–3 hours. Acidification of urine increases excretion of unchanged pethidine.

Side effects These are similar to morphine except those mentioned above. Some atropinic effects (dry mouth, blurred vision, tachycardia) may be noted in addition.

Overdose of pethidine produces many excitatory effects—tremors, mydriasis, hyperreflexia, delirium, myoclonus and convulsions. This is due to accumulation of *norpethidine* which has excitant effects. Renal failure patients given repeated doses of pethidine may also experience similar effects.

Nonselective MAO inhibitors interfere with hydrolysis but not with demethylation of pethidine—norpethidine is produced in excess and excitement occurs.

Use Pethidine is primarily used as an analgesic (substitute of morphine) and in preanaesthetic medication, but not for cough or diarrhoea. Potential adverse effects due to accumulation of norpethidine limit its utility in patients who require repeated dosing.

Dose: 50–100 mg i.m., s.c. (may cause irritation, local fibrosis on repeated injection), occasionally given orally or i.v.

PETHIDINE HCL 100 mg/2 ml inj; 50, 100 mg tab.

5. Fentanyl A pethidine congener, 80–100 times more potent than morphine, both in analgesia and respiratory depression. In analgesic doses it produces few cardiovascular effects; has little propensity to release histamine. Because of high lipid solubility, it enters brain rapidly and produces peak analgesia in 5 min after i.v. injection. The duration of action is short: starts wearing off after 30–40 min due to redistribution, while elimination t½ is ~4 hr. In the injectable form it is almost exclusively used in anaesthesia (*see* p. 122). Transdermal fentanyl has become available for use in cancer or other types of chronic pain for patients requiring opioid analgesia.

DUROGESIC transdermal patch delivering 25 µg/hr, 50 µg/hr or 75 µg per hour; the patch is changed every 2 to 3 days.

6. Methadone A synthetic opioid, chemically dissimilar but pharmacologically very similar to morphine—has analgesic, respiratory depressant, emetic, antitussive, constipating and biliary actions similar to morphine.

The most important feature of methadone is high oral: parenteral activity ratio (1 : 2) and its firm binding to tissue proteins. In single doses it is only slightly more potent than morphine and has comparable duration of action (4–6 hours on i.m. injection), but it cumulates in tissues on repeated administration—duration of action is progressively lengthened due to gradual release from these sites; plasma t½ on chronic use is 24–36 hours. Plasma protein binding is 90% and it is metabolized in liver, primarily by demethylation and cyclization—metabolites are excreted in urine. Rifampin and phenytoin can cause withdrawal symptoms to appear in methadone-dependent subjects by inducing its metabolism.

Because of slow and persistent nature of action, sedative and subjective effects are less intense. It is probably incapable of giving a 'kick'. The abuse potential is rated somewhat lower than morphine. Tolerance develops more slowly. Withdrawal syndrome is of gradual onset, taking 1–2 days after discontinuation, is prolonged and less severe.

Methadone has been used primarily as substitution therapy of opioid dependence: 1 mg of oral methadone can be substituted for 4 mg of morphine, 2 mg of heroin and 20 mg of pethidine. Another technique is *methadone maintenance* therapy in opioid addicts—sufficient dose of methadone is given orally to produce high degree of tolerance so that pleasurable effects of i.v. doses of morphine or heroin are not perceived and the subject gives up the habit.

It can also be used as an analgesic for the same conditions as morphine; dose 2.5–10 mg oral or i.m. but not s.c.

PHYSEPTONE 10 mg inj, 2 mg/5 ml linctus.

7. Dextropropoxyphene It is similar in analgesic action and in side effects to codeine, except that it is poor antitussive and probably less constipating. It is nearly ½ as potent as codeine and has a lower oral: parenteral activity ratio. Marketed only in combination with paracetamol for relief of mild-to-moderate pain, the contribution of dextropropoxyphene to the analgesic effect is questionable. The demethylated metabolite of dextropropoxyphene is cardiotoxic.

Its overdose can produce rapid onset respiratory depression, delirium and convulsions. However, the abuse potential of dextropropoxyphene is negligible because of low potency and unpleasant side effects at higher doses.

PARVODEX 60 mg cap: PARVON, PROXYVON, WALAGESIC: dextropropoxyphene 65 mg + paracetamol 400 mg cap; WYGESIC, SUDHINOL 65 mg + paracetamol 650 mg cap.

8. Tramadol This centrally acting analgesic relieves pain by opioid as well as additional mechanisms. Its affinity for μ opioid receptor is modest while that for κ and δ is weak. Unlike other opioids, it inhibits reuptake of NA and 5-HT, and thus activates monoaminergic spinal inhibition of pain. Its analgesic action is only partially reversed by opioid antagonist naloxone.

Injected i.v. 100 mg tramadol is equianalgesic to 10 mg i.m. morphine; oral bioavailability is good (oral: parenteral dose ratio 1.2 : 1). The t½ is 3–5 hours and effects last for 4–6 hrs. Tramadol causes less respiratory depression, sedation, constipation, urinary retention and rise in intrabiliary pressure than morphine. It is well tolerated; side effects are dizziness, nausea, sleepiness, dry mouth and sweating. Haemodynamic effects are minimal—safer in patients with compromised cardiovascular function.

Tramadol is indicated for mild-to-medium intensity short-lasting pain due to diagnostic procedures, injury, surgery, dentistry, etc. as well as for chronic pain including cancer pain, but is not effective in severe pain. Little tendency to dose escalation is seen and abuse potential is low.

Dose: 50–100 oral/i.m./slow i.v. infusion (children 1–2 mg/kg) 4–6 hourly.

CONTRAMAL, DOMADOL, TRAMAZAC 50 mg cap, 100 mg SR tab; 50 mg/ml inj in 1 and 2 ml amps.

USES (of morphine and its congeners)

1. *As analgesic* Opioid analgesics are indicated in severe pain of any type. However, they only provide symptomatic relief without affecting the cause.

Morphine or one of its parenteral congeners is indicated, especially in traumatic, visceral, ischaemic (myocardial infarction), postoperative, burn, cancer pain and the like. It should be given promptly in myocardial infarction to allay apprehension and reflex sympathetic stimulation. Patient controlled analgesia is an attractive technique of postoperative pain control in which the patient himself regulates the rate of i.v. fentanyl infusion according to intensity of pain felt. Opioids, especially pethidine, have been extensively used for obstetric analgesia.

Adequate use of morphine (even i.v.) is indicated in an emergency. It may prevent neurogenic shock and other autonomic effects of excruciating pain. Neuropathic pain responds less predictably to opioid analgesics.

Transdermal fentanyl is a suitable option for chronic cancer and other terminal illness pain.

For milder pain, e.g. toothache, headache, neuralgias, etc., aspirin-like analgesics are preferred. When they are not effective alone, codeine may be added. The combination enhances the ceiling analgesia. For more severe and longer lasting pain, it has been advised to combine a NSAID with the opioid.

2. *Preanaesthetic medication* Morphine and pethidine are used in selected patients.

3. *Balanced anaesthesia and surgical analgesia* Fentanyl, morphine or pethidine are an important component of anaesthetic techniques (*see* p. 122).

4. *Relief of anxiety and apprehension* Specially in myocardial infarction, internal bleeding (haematemesis, threatened abortion, etc.) morphine or pethidine have been employed.

5. *Acute left ventricular failure (cardiac asthma)* Morphine (i.v.) affords dramatic relief by:

(a) Reducing preload on heart due to vasodilatation and peripheral pooling of blood.

(b) Tending to shift blood from pulmonary to systemic circuit; relieves pulmonary congestion and edema.

(c) Allays air hunger by depressing respiratory centre.

Table 24.1: Actions ascribed to different types of opioid receptors

μ (mu)	*κ (kappa)*	*δ (delta)*
Analgesia	Analgesia (spinal κ_1)	Analgesia (Spinal + Affective
(supraspinal μ_1 + spinal μ_2)	(Supraspinal-κ_3)	component of supraspinal)
Respiratory depression (μ_2)	Respiratory depression (lower ceiling)	Respiratory depression
Sedation	Dysphoria, hallucinations	Affective behaviour
Euphoria	Miosis (lower ceiling)	Reinforcing actions
Miosis	Sedation	Reduced g.i. motility
Reduced g.i. motility (μ_2)	Physical dependence (nalorphine type)	
Physical dependence (morphine type)		

(d) Cuts down sympathetic stimulation by calming the patient, reduces cardiac work.

6. *Cough* Codeine or its substitutes are widely used for suppressing dry, irritating cough (*see* Ch. 19).

7. *Diarrhoea* The constipating action of codeine has been used to check diarrhoea and to increase the consistency of stools in colostomy. Synthetic opioids exclusively used as antidiarrhoeals are diphenoxylate and loperamide (*see* Ch. 18).

OPIOID RECEPTORS

Morphine and other opioids exert their actions by interacting with specific receptors present on neurones in the CNS and in peripheral tissues. Chemical modification of morphine structure has yielded a number of compounds which have a complex pattern of morphine-like and other agonistic and antagonistic actions that cannot be explained on the basis of a single opioid receptor. Radioligand binding studies have divided the opioid receptors into three types (μ, κ, δ); which have been cloned. Each has a specific pharmacological profile and pattern of anatomical distribution in brain, spinal cord and peripheral tissues. Subtypes of μ and κ receptor have been identified. The proposed functional role of the 3 types of opioid receptors is listed in Table 24.1.

Opioid ligands can interact with different opioid receptors as agonists, partial agonists or competitive antagonists. The overall pattern of effect of a particular agent depends not only on the nature of its interaction with different opioid receptors but also on its relative affinity for these, e.g. morphine is an agonist on μ, κ and δ receptors,

Table 24.2: Nature of interaction of opioid ligands with the three major types of opioid receptors, and equivalent analgesic doses

Ligand	*μ (mu)*	*κ (kappa)*	*δ (delta)*	*Analgesic* dose (mg)*
1. Morphine	Ago. (St)	Ago. (W)	Ago. (W)	10
2. Nalorphine	Anta. (St)	Ago. (M)	(?)	—
3. Pentazocine	P.Ago., Anta. (W)	Ago. (M)	—	30–60
4. Buprenorphine	P.Ago	Anta. (M)	—	0.3–0.4
5. Butorphanol	P.Ago	Ago. (St)	—	1–3
6. Naloxone	Anta. (St)	Anta. (M)	Anta. (W)	—
7. Met/Leu Enkephalin	Ago. (M)	—	Ago. (St)	—
8. β-Endorphin	Ago. (St)	—	Ago. (St)	—
9. Dynorphin A, B	Ago. (W)	Ago. (St)	Ago. (W)	—

* Equivalent single parenteral analgesic dose.
P. Ago—Partial agonist: have lower efficacy, though affinity (potency) may be high.
St—Strong action; M—Moderate action; W—Weak action (low affinity).

but its affinity for μ receptors is much higher than that for the other two. The effects, therefore, are primarily the result of μ receptor activation.

The nature and intensity of action of complex action opioids and antagonists are summarized in Table 24.2.

μ receptor The μ receptor is characterized by its high affinity for morphine. It is the major receptor mediating actions of morphine and its congeners. Endogenous ligands for μ receptor—peptides called *Endomorphins 1 and 2*—have only recently been found in mammalian brain—produce biological effects ascribed to this receptor. High density of μ receptors has been detected in periaqueductal grey, thalamus, nucleus tractus solitarious, nucleus ambiguus and area postrema.

κ receptor This receptor is defined by its high affinity for ketocyclazocine and dynorphin A; the latter is considered to be its endogenous ligand. *Norbinaltorphimine* is a selective κ antagonist. Analgesia caused by κ agonists is primarily spinal, but lower ceiling supraspinal analgesia is also produced.

δ receptor This receptor has high affinity for Leu/Met enkephalins which are its endogenous ligands. The δ mediated analgesia is again mainly spinal (δ receptors are present in dorsal horn of spinal cord), but the affective component of supraspinal analgesia appears to involve δ receptors because these receptors are present in limbic areas—also responsible for dependence and reinforcing actions. Myenteric plexus neurones express high density of δ receptors—mediate reduced g.i. motility.

Opioid receptor transducer mechanisms All 3 types of opioid receptors (μ, κ, δ) have been cloned; all are G-protein coupled receptors situated mostly on prejunctional neurones. They generally exercise inhibitory modulation by decreasing release of the junctional transmitter (Fig. 24.1). As such, various monoaminergic (NA, DA, 5-HT), GABA, glutamate (NMDA) pathways are intricately involved in opioid actions.

Opioid receptor activation reduces intracellular cAMP formation and opens K^+ channels (mainly through μ and δ receptors) or suppresses

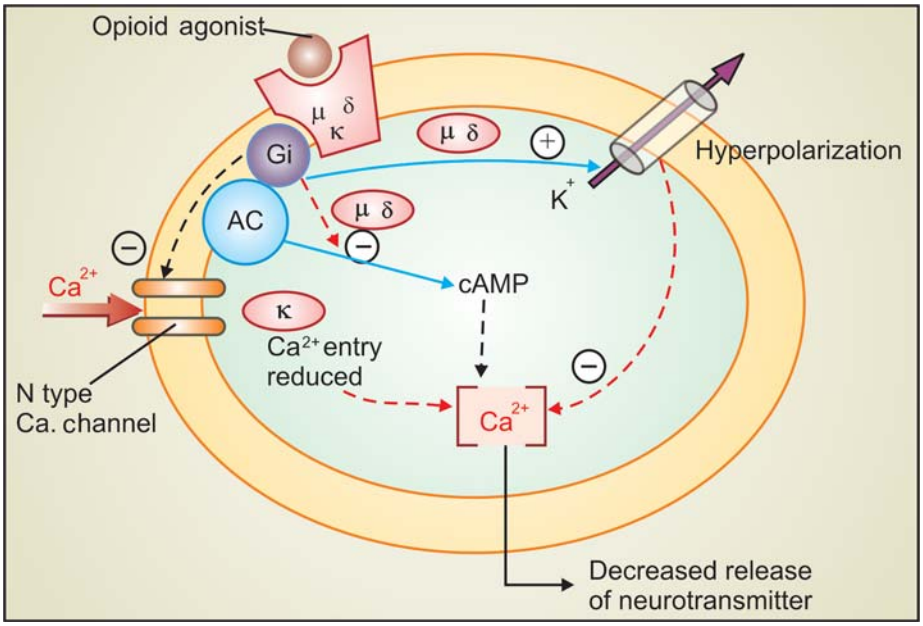


Fig. 24.1: Opioid receptor transducer mechanisms
AC-Adenylyl cyclase; Gi-coupling protein; cAMP-Cyclic AMP

voltage gated N type Ca^{2+} channels (mainly κ receptor). These actions result in neuronal hyperpolarization and reduced availability of intracellular Ca^{2+} → decreased neurotransmitter release by CNS and myenteric neurones.

COMPLEX ACTION OPIOIDS AND OPIOID ANTAGONISTS

1. *Agonist-antagonists (κ analgesics)*
   Nalorphine, Pentazocine, Butorphanol
2. *Partial/weak μ agonist*
   Buprenorphine
3. *Pure antagonists*
   Naloxone, Naltrexone

Clinically, the agonist-antagonist (agonist at one opioid receptor, antagonist at another) and partial/weak agonist (low intrinsic activity) opioids are analgesics of comparable efficacy to low doses of morphine, but with a limited dose range. They cause low ceiling respiratory depression and have lower abuse potential. However, in only few situations they have proven to be advantageous over the full μ agonists.

1. Nalorphine It is a κ agonist and μ antagonist; has analgesic action, but not used clinically because of dysphoric and psychotomimetic effects. Naloxone has replaced it as a morphine antidote.

2. Pentazocine It is the first agonist-antagonist to be used as an analgesic. It has weak antagonistic and more marked agonistic actions. The profile of action is similar to morphine; important differences are:

(a) Analgesia caused by pentazocine is primarily spinal ($κ_1$) and has a different character than that caused by morphine. Parenterally 30 mg pentazocine = 10 mg morphine; but ceiling effect and is lower, i.e. at higher doses proportionate increase in analgesia does not occur.
(b) Sedation and respiratory depression is 1/3 to 1/2 of morphine at lower doses, and has a lower ceiling, does not increase much beyond 60 mg dose.
(c) Tachycardia and rise in BP are produced due to sympathetic stimulation. This increases cardiac work; better avoided in coronary ischaemia and myocardial infarction.
(d) Biliary spasm and constipation are less severe.
(e) Vomiting is less frequent. Other side effects are sweating and lightheadedness.
(f) Subjective effects are pleasurable (morphine like) at lower doses: recognised by post-addicts as an opiate. However, as dose is increased, these become unpleasant (nalorphine like at > 60 mg i.m.) and psychotomimetic effects (κ, σ mediated) appear.

Tolerance, psychological and physical dependence to pentazocine develops on repeated use. Withdrawal syndrome has features of both morphine and nalorphine abstinence, but is milder in intensity. 'Drug seeking' occurs. Abuse liability is rated lower than morphine.

Injected in morphine dependent subjects, it precipitates withdrawal. Antagonistic action is 1/5th as potent as nalorphine: not enough to be useful in morphine poisoning.

Pharmacokinetics and use Pentazocine is effective orally, though considerable first pass metabolism occurs; oral: parenteral ratio is 1 : 3. It is oxidized and glucuronide conjugated in liver and excreted in urine. Plasma t½ is 3–4 hours, duration of action of a single dose is 4–6 hours.
Oral dose: 50–100 mg, efficacy like codeine.
Parenteral dose: 30–60 mg i.m., s.c., may cause local fibrosis on repeated injection due to irritant property.
FORTWIN 25 mg tab., 30 mg/ml inj., PENTAWIN, SUSEVIN 30 mg/ml inj.

Pentazocine is indicated for postoperative and moderately severe pain in burns, trauma, fracture, cancer, etc. Though abuse liability is low, frequent side effects and potential for dysphoric/psychotomimetic effect limits its utility.

3. Butorphanol It is a κ analgesic, similar to but more potent than pentazocine (butorphanol 2 mg = pentazocine 30 mg). Sedation, nausea, cardiac stimulation and other side effects are similar to pentazocine, but subjective effects are less dysphoric and less psychotomimetic (it is a weaker σ agonist at higher doses). BP is not increased.

The abuse potential of butorphanol is low. The most outstanding feature is that butorphanol can neither substitute for nor antagonize morphine. This shows its very weak interaction with μ receptors.

It has been used in a dose of 1–4 mg i.m. or i.v. for postoperative and other short-lasting painful conditions, but should be avoided in patients with cardiac ischaemia.

BUTRUM 1 mg/ml, 2 mg/ml inj.

4. Buprenorphine It is a synthetic thebaine congener, highly lipid-soluble μ analgesic that is 25 times more potent than morphine. It has a slower onset and longer duration of action. After a single dose, analgesia lasts for 6–8 hours; but with repeated use, duration of action increases to ~24 hours.

Sedation, vomiting, miosis, subjective and cardiovascular effects are similar to morphine, but constipation is less marked. Postural hypotension is prominent. Respiratory depression (and analgesia) exhibit ceiling effect. It substitutes for morphine at low levels of dependence but precipitates withdrawal in highly dependent subjects, reflecting its partial agonistic action at μ receptors. Antagonistic action on κ receptor has also been described.

Lower degree of tolerance and physical as well as psychological dependence develops with buprenorphine on chronic use. Its withdrawal syndrome resembles that of morphine but is delayed for several days, is milder and longer lasting. 'Drug seeking' is present. Abuse liability is rated lower than morphine.

Even naloxone (at high dose) only partially reverses buprenorphine effects and does not precipitate its withdrawal; probably because of more tight binding of buprenorphine to opioid receptors.

Buprenorphine has good efficacy by sublingual route, is highly plasma protein bound and remains in tissues for several days; t½ is 40 hours. It is mostly excreted unchanged in bile and finds its way out of the body in faeces.

Dose: 0.3–0.6 mg i.m., s.c. or slow i.v., also sublingual 0.2–0.4 mg 6–8 hourly.

NORPHIN, TIDIGESIC 0.3 mg/ml inj. 1 and 2 ml amps. 0.2 mg sublingual tab; BUPRIGESIC, PENTOREL 0.3 mg/ml inj in 1, 2 ml amp.

Use: Buprenorphine is indicated for long-lasting painful conditions requiring an opioid analgesic, e.g. cancer pain. It has also been recommended for premedication, postoperative pain and in myocardial infarction, but seldom used for dental pain.

PURE OPIOID ANTAGONISTS

1. Naloxone It is N-alylnor-oxymorphone and a competitive antagonist for all types of opioid receptors. However, it blocks μ receptors at much lower doses than those needed to block κ or δ receptors. It is devoid of any kind of agonistic activity even at high doses (20 times μ blocking dose). No subjective or autonomic effects are produced in individuals who have not received an opioid. No physical/psychological dependence or abstinence syndrome has been observed.

Injected intravenously (0.4–0.8 mg) it promptly antagonizes all actions of morphine: analgesia is gone, respiration is not only normalized but even stimulated—probably due to sudden sensitization of respiratory centre to retained CO_2, or it is a manifestation of acute withdrawal, pupils dilate. However, sedation is less completely reversed.

At 4–10 mg dose, it also antagonizes the agonistic actions of nalorphine, pentazocine, etc.

Actions of buprenorphine are prevented but not effectively reversed by naloxone, because it fails to displace buprenorphine that has already bound to the opioid receptors.

Naloxone 0.4 mg i.v. precipitates morphine withdrawal in dependent subjects: the syndrome lasts for 2–3 hours.

It blocks *placebo*, *acupuncture* and *stress*-induced analgesia: showing involvement of endogenous opioid peptides in these.

Naloxone is inactive orally because of high first pass metabolism in liver. Injected i.v. it acts in 2–3 min. The primary pathway of metabolism is glucuronidation. Plasma t½ is 1 hour in adults and 3 hours in newborns.

NARCOTAN 0.4 mg in 1 ml (adult) and 0.04 mg in 2 ml (infant) amps; NALOX, NEX 0.4 mg inj.

Use Naloxone is the drug of choice for morphine poisoning (0.4–0.8 mg i.v. every 2–3 min: max 10 mg) and for reversing neonatal asphyxia due to opioid use during labour. It is also used to treat overdose with other opioids and agonist-antagonists (except buprenorphine).

2. Naltrexone It is chemically related to naloxone and is another pure opioid antagonist devoid of subjective and other agonistic effects. Naltrexone differs from naloxone in being orally active, more potent and having a long duration of action (1–2 days) which makes it suitable for 'opioid blockade' therapy of postaddicts: 50 mg/day is given orally so that if the subject takes his/her usual shot of the opioid, no subjective effects are produced and the craving subsides. Alcohol craving is also reduced by naltrexone; it is being used to prevent relapse of heavy drinking. Side effects are nausea and headache; high doses can cause hepatotoxicity.

NALTIMA 50 mg tab.

ENDOGENOUS OPIOID PEPTIDES

In the mid 1970s, with herculean efforts, a number of peptides having morphine-like actions were isolated from mammalian brain, pituitary, spinal cord and g.i.t. These are active in very small amounts, their actions are blocked by naloxone, and they bind with high affinity to the opioid receptors. There are 3 distinct families of opioid peptides. Each is derived from a specific large precursor polypeptide.

1. Endorphins β-endorphin (β-END) having 31 amino acids is the most important of the endorphins. It is derived from Pro-opio-melanocortin (POMC) which also gives rise to γ-MSH, ACTH and two lipotropins. β-END is primarily μ agonist but also has δ action.

2. Enkephalins Methionine-enkephalin (met-ENK) and leucine-enkephalin (leu-ENK) are the most important. Both are pentapeptides. The large precursor peptide *proenkephalin* has 4 met-ENK and 1 leu-ENK residues. The two ENKs have a slightly different spectrum of activity; while met-ENK has equal affinity for μ and δ sites, leu-ENK prefers δ receptors.

3. Dynorphins Dynorphin A and B (DYN-A, DYN-B) are 8–17 amino acid peptides derived from *prodynorphin* which contains 3 leu-ENK residues also. DYNs are more potent on κ receptors, but also activate μ and δ receptors.

Distribution of the 3 families of peptides is summarized below:

1.	POMC (limited distribution)	– Arcuate nucleus which sends projections to limbic areas and medulla. – Anterior pituitary (modulates hormone release). – Pancreatic islets (modulates insulin, glucagon release)
2.	Proenkephalin (wide distribution)	– Pain areas in spinal cord, trigeminal nucleus, periaqueductal grey matter – Affective areas in limbic system, locus coeruleus and cortex. – Medulla (autonomic functions). – Median eminence of hypothalamus (neuro-endocrine control). – Adrenal medulla, gastric and intestinal glands.
3.	Prodynorphin	– Wide distribution roughly parallel to proenkephalin, but in distinct neurones of the same area.

The opioid peptides constitute an endogenous opioid system which normally modulates pain perception, mood, hedonic (pleasure related) and motor behaviour, emesis, pituitary hormone release and g.i.t. motility, etc.

β-END injected directly into brain is 20–40 times more potent analgesic than morphine. Its primary localization in hypothalamus and pituitary and its long t½ ascribes it a *neurohormone* function which modulates the release of other hormones. It decreases LH, FSH release and increases GH and prolactin release. Naloxone has opposite effects on the levels of these hormones—suggesting that the system is tonically active.

The wide distribution of ENKs and DYNs and their short t½ suggests function as *neuromodulator* or *neurotransmitter*. They appear to regulate pain

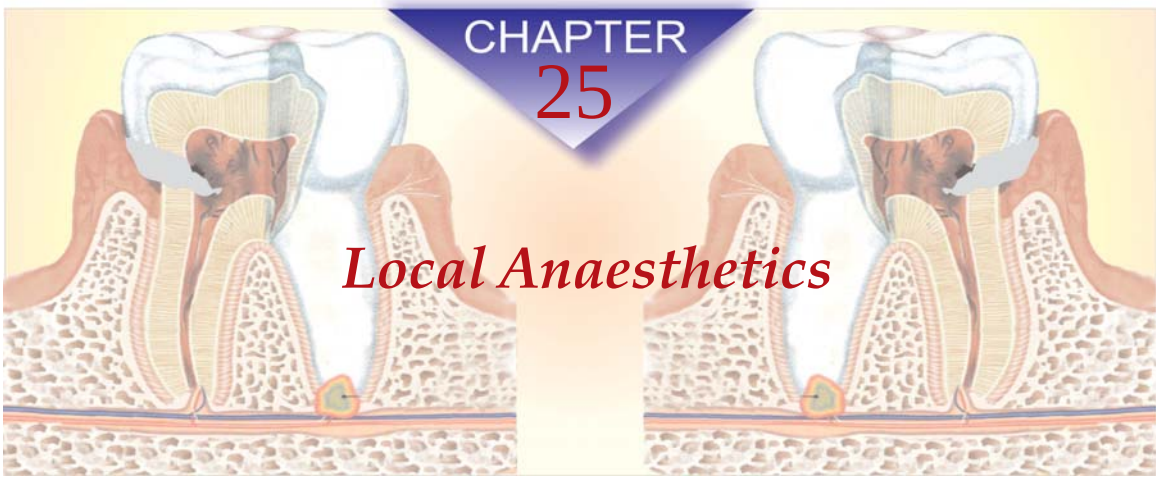
responsiveness at spinal and supraspinal levels. Naloxone blocks placebo, acupuncture and stress-induced analgesias, suggesting the involvement of opioid peptides in these responses. Opioid peptides also appear to participate in regulation of affective behaviour and autonomic function.

Morphine and other opioids act as exogenous agonists on some of the receptors for these peptides. This has given an explanation for the existence of specific receptors in the body for exogenous substances like morphine.

Opioids in dental pain

Dental pain is mostly either due to or associated with inflammation. As such, the antiinflammatory analgesics or NSAIDs are more effective and more suitable than opioid analgesics. The latter are primarily employed as additional drugs with aspirin, paracetamol, ibuprofen or the like to boost their analgesic effect. When an opioid has to be given, an oral drug like codeine is most suited, because dental patients are mostly ambulatory and suffer from dull, continuous, short-lasting pain. Oral pentazocine or tramadol are the alternatives. Risk of producing dependence is negligible with such use. Efficacy of dextropropoxyphene in enhancing analgesic action of NSAIDs is doubtful. Role of injected opioids like morphine, pethidine or fentanyl in dentistry is limited to occasional intraoperative or perioperative use to supplement the local anaesthetic and allay apprehension.

Clearly, the place of analgesics in dental pain is secondary to treatment of the cause of pain by appropriate local (antiseptics, cavity filling, root canal therapy, etc.) and systemic (antibiotics) measures. Short-term use of opioids, as is made in dentistry, has no significant drug interactions or require modification of other concurrent medication.



CHAPTER 25

Local Anaesthetics

Local anaesthetics (LAs) are drugs which upon topical application or local injection cause reversible loss of sensory perception, especially of pain, in a restricted area of the body. They block generation and conduction of nerve impulse at all parts of the neurone where they come in contact, without causing any structural damage. Thus, not only sensory but also motor impulses are interrupted when a LA is applied to a mixed nerve, resulting in muscular paralysis and loss of autonomic control as well.

Local anaesthetics are employed routinely by dentists; so much so that current practice of dentistry is inconceivable without local anaesthesia. Important differences between general and local anaesthesia are tabulated in Table 25.1.

Table 25.1: Comparative features of general and local anaesthesia

	General anaesthesia	*Local anaesthesia*
1. Site of action	CNS	Peripheral nerves
2. Area of body involved	Whole body	Restricted area
3. Consciousness	Lost	Unaltered
4. Care of vital functions	Essential	Usually not needed
5. Physiological trespass	High	Low
6. Poor health patient	Risky	Safer
7. Use in non-cooperative patient	Possible	Not possible
8. Major surgery	Preferred	Cannot be used
9. Minor surgery	Not preferred	Preferred

CLASSIFICATION

Injectable

Low potency, short duration
- Procaine

Intermediate potency and duration
- Lignocaine (Lidocaine)
- Prilocaine

High potency, long duration
- Tetracaine (Amethocaine)
- Bupivacaine
- Ropivacaine
- Dibucaine (Cinchocaine)

Surface Anaesthetic

Soluble
- Cocaine
- Lignocaine
- Tetracaine
- Benoxinate

Insoluble
- Benzocaine
- Butylaminobenzoate (Butamben)

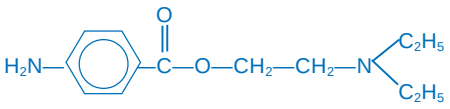
Mepivacaine, Etidocaine, Articaine, Dyclonine are other local anaesthetics occasionally used in some countries.

Some other drugs, e.g. propranolol, chlorpromazine, H_1 antihistaminics, quinine have significant LA activity, but are not used for this purpose because of local irritancy or other prominent systemic activity. Local anaesthesia can be produced by cooling as well, e.g. application of ice, CO_2 snow, ethylchloride spray.

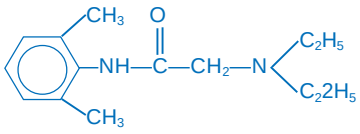
CHEMISTRY

The clinically useful LAs are weak bases with amphiphilic property. A hydrophilic secondary

or tertiary amine on one side and a lipophilic aromatic residue on the other are joined by an alkyl chain through an ester or amide linkage.



PROCAINE



LIGNOCAINE

Ester linked LAs Cocaine, procaine, chloroprocaine, tetracaine, benzocaine.

Amide linked LAs Lignocaine, bupivacaine, dibucaine, prilocaine, ropivacaine.

Features of amide LAs
(compared to ester LAs)

- Produce more intense and longer lasting anaesthesia
- Bind to α_1 acid glycoprotein in plasma
- Not hydrolysed by plasma esterases
- Rarely cause hypersensitivity reactions; no cross sensitivity with ester LAs

Because of their short duration, less intense analgesia and higher risk of hypersensitivity, the ester linked LAs are rarely used for infiltration or nerve block, but are still used on mucous membranes.

MECHANISM OF ACTION

The LAs block nerve conduction by decreasing the entry of Na^+ ions during upstroke of action potential (AP). As the concentration of the LA is increased, the rate of rise of AP and maximum depolarization decreases (Fig. 25.1) causing slowing of conduction. Finally, local depolarization fails to reach the threshold potential and conduction block ensues.

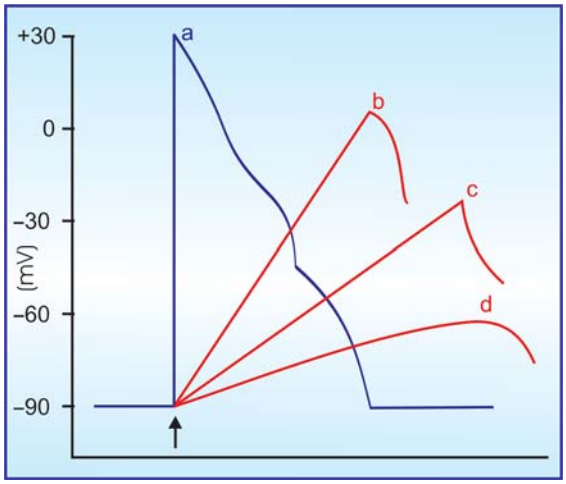


Fig. 25.1: Effect of progressively increasing concentrations (b, c, d) of a local anaesthetic on the generation of an action potential in a nerve fibre, (a) Untreated nerve fibre

The LAs interact with a receptor situated within the voltage sensitive Na^+ channel and raise the threshold of channel opening: Na^+ permeability fails to increase in response to an impulse or stimulus. The details are explained in Fig. 25.2. At physiological pH, the LA molecule is partly ionized. The equilibrium between the unionized base form (B) and the ionized cationic form (BH^+) depends on the pKa of the LA.

The predominant active species (cationic form of LA) is able to approach its receptor only when the channel is open at the inner face and it binds more avidly to the inactive state of the channel. Thus, a resting nerve is rather resistant to blockade, and blockade develops rapidly when the nerve is stimulated repeatedly. Degree of blockade is frequency dependent: greater blockade at higher frequency of stimulation. Moreover, exposure to higher concentration of Ca^{2+} reduces inactivation of Na^+ channels and lessens the degree of block. Blockade of conduction by LA is not due to hyperpolarization; in fact, resting membrane potential is unaltered because K^+ channels are blocked only at higher concentrations of LA.

The onset time of blockade is related primarily to the pKa of the LA. Those with lower pKa

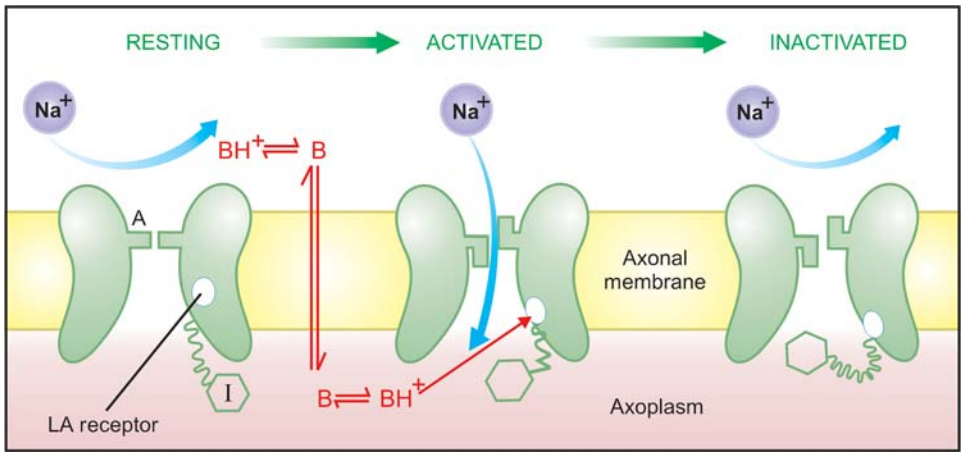


Fig. 25.2: A model of the axonal Na^+channel depicting the site and mechanism of action of local anaesthetics.

The Na^+ channel has an activation gate (A) near its extracellular mouth and an inactivation gate (I) at the intracellular mouth. In the resting state the activation gate is closed. Threshold depolarization of the membrane opens the activation gate allowing Na^+ ions to flow in along the concentration gradient. Within a few msec, the inactivation gate closes and ion flow ceases. The channel recovers to the resting state in a time-dependent manner.

The local anaesthetic (LA) receptor is located within the channel in its intracellular half. The LA traverses the membrane in its lipophilic from (B), reionizes in the axoplasm and approaches the LA receptor through the intracellular mouth of the channel. It is the cationic form (BH^+) of the LA which primarily binds to the receptor. The receptor has higher affinity or is more accessible to the LA in the activated state compared to resting state. Binding of LA to its receptor stabilizes the channel in the inactive state and thus reduces the probability of channel opening.

The neuronal Na^+ channel has been found to be a 300 KDa glycoprotein composed of a large (α) and two small (β_1, β_2) subunits. The α subunit encloses the Na^+ selective pore within its 4 homologous domains (I to IV), each domain has 6 membrane spanning helical segments (S1 to S6) connected alternately by intracellular and extracellular loops. The wall of the pore is formed by all four S5-S6 segments, while the short nonhelical loops connecting S5-S6 on the extracellular surface fold into the pore and serve as the activation gate. Voltage sensors located in the S4 segments move vertically on depolarization and open the activation gate by allosteric conformational change. A few msec later, the short intracellular loop connecting domains III and IV folds into the inner mouth of the pore inactivating the channel. The LA receptor is located in S6 segment of domain IV. Channel activation either transforms the LA receptor to a higher affinity conformation or exposes it on the wall of the pore, and this persists during the subsequent inactivation phase.

(7.6–7.8), e.g. lignocaine, mepivacaine are fast acting, because 30–40% LA is in the undissociated base form at pH 7.4 and it is this form which penetrates the axon. Procaine, tetracaine, bupivacaine have higher pKa (8.1–8.9), only 15% or less is unionized at pH 7.4; these are slow acting. Chloroprocaine is an exception, having rapid onset despite high pKa (9.1).

LOCAL ACTIONS

The clinically used LAs have no/minimal local irritant action and block sensory nerve endings, nerve trunks, neuromuscular junction, ganglionic synapse and receptors (non-selectively), i.e. structures which function through increased Na^+ permeability. They also reduce release of acetylcholine from motor nerve endings. Injected around a mixed nerve they cause anaesthesia of skin and paralysis of voluntary muscle supplied by that nerve.

Sensory and motor fibres are inherently equally sensitive. The sensitivity is determined by diameter of the fibres as well as by fibre type. In general smaller fibres are more sensitive than

larger fibres and nonmyelinated fibres are blocked more easily than myelinated fibres. Fibres differ in the critical length of the axon that must be exposed to the LA for effective blockade. Smaller fibres tend to have shorter critical lengths because in them voltage changes propagate passively for shorter distances. Also, more slender axons have shorter internodal distances and LAs enter the axon at the nodes of Ranvier only. The density of Na^+ channel is much higher at these nodes. Moreover, frequency dependence of blockade makes smaller sensory fibres more vulnerable since they generate high frequency longer lasting action potentials than the motor fibres.

Autonomic fibres are generally more susceptible than somatic fibres. Among the somatic afferents order of blockade is : pain—temperature sense—touch—deep pressure sense. Since pain is generally carried by smaller diameter fibres than those carrying other sensations or motor impulses, pain is the first modality to be affected by LAs. Applied to the tongue, bitter taste is lost first followed by sweet and sour, and salty taste last of all.

In general, fibres that are more susceptible to L A are the first to be blocked and the last to recover. Also, location of the fibre within a nerve trunk determines the latency, duration and often the depth of local anaesthesia. Nerve sheaths restrict diffusion of the LA into the nerve trunk so that fibres in the outer layers are blocked earlier than the inner or core fibres. As a result, the more proximal areas supplied by a nerve are affected earlier because axons supplying them are located more peripherally in the nerve than those supplying distal areas. The differential arrangement of various types of sensory and motor fibres in a mixed nerve may partly account for the differential blockade.

The LA often fails to afford adequate pain control in inflamed tissues (like infected tooth). The likely reasons are:

a. Inflammation lowers pH of the tissue—greater fraction of the LA is in the ionized form hindering diffusion into the axolemma.
b. Blood flow to the inflamed area is increased — the LA is removed more rapidly from the site.
c. Effectiveness of Adr injected with the LA is reduced at the inflamed site.
d. Inflammatory products may oppose LA action.

Addition of a vasoconstrictor, e.g. adrenaline (1:50,000 to 1:200,000):

(i) prolongs duration of action of LAs by decreasing their rate of removal from the local site into the circulation.
(ii) enhances the intensity of nerve block.
(iii) reduces systemic toxicity of LAs: rate of absorption is reduced and metabolism keeps the plasma concentration lower.
(iv) makes the injection more painful.
(v) provides a more bloodless field for surgery.
(vi) increases the chances of subsequent local tissue edema and necrosis as well as delays wound healing by reducing oxygen supply and enhancing oxygen consumption in the affected area.
(vii) may raise BP, increase heart rate and promote arrhythmia in susceptible individuals.

SYSTEMIC ACTIONS

Any LA injected or applied locally is ultimately absorbed and can produce systemic effects depending on the concentration attained in the plasma and tissues.

C.N.S.

All LAs are capable of producing a sequence of stimulation followed by depression. *Cocaine* is a powerful CNS stimulant causing in sequence euphoria—excitement—mental confusion—restlessness—tremor and twitching of muscles—convulsions—unconsciousness—respiratory depression—death, in a dose-dependent manner.

Procaine and other synthetic LAs are much less potent in this regard. At safe clinical doses, they produce little apparent CNS effects. Higher dose or accidental i.v. injection produces CNS stimulation followed by depression.

Lignocaine, on the contrary, can initially cause drowsiness and lethargy, but higher doses produce excitation followed by depression like others.

The basic action of all LAs is neuronal inhibition; the apparent stimulation seen initially is due to inhibition of inhibitory neurones. At high doses, all neurones are inhibited and flattening of waves in EEG is seen.

CVS

Heart LAs are cardiac depressants, but no significant effects are observed at conventional doses. At high doses or on inadvertent i.v. injection, they decrease automaticity, excitability, contractility, conductivity and increase refractory period (RP). They have a quinidine-like antiarrhythmic action. *Procaine* is not used as antiarrhythmic because of short duration of action and propensity to cause CNS effects, but its amide derivative *procainamide* is a classical antiarrhythmic. At high plasma concentrations, electrophysiological properties of heart may be markedly altered, QTc interval is prolonged and LAs can themselves induce cardiac arrhythmias. *Bupivacaine* is relatively more cardiotoxic and has produced ventricular tachycardia or fibrillation. *Lignocaine* has little effect on contractility and conductivity; it abbreviates RP and is used as an antiarrhythmic (*see* Ch. 12).

Blood vessels LAs tend to produce fall in BP. This is primarily due to sympathetic blockade, but high concentrations, as attained locally at the site of injection, do cause direct relaxation of arteriolar smooth muscle. Bupivacaine is more vasodilatory than lignocaine, while prilocaine is the least vasodilatory. Toxic doses of LAs produce cardiovascular collapse. *Cocaine* has sympathomimetic property; causes local vasoconstriction, marked rise in BP and tachycardia.

Procaine and related drugs have weak anticholinergic, antihistaminic, ganglion blocking, neuromuscular blocking and smooth muscle relaxant properties, but these are clinically insignificant.

PHARMACOKINETICS

Soluble surface anaesthetics are rapidly absorbed from mucous membranes and abraded areas, but absorption from intact skin is poor. Procaine does not significantly penetrate mucous membranes. Rate of absorption depends on the blood flow to the area of application or injection; faster absorption occurring from more vascular tissues. Thus, intra-oral injection results in quicker and higher blood levels than s.c. injection, and entry into blood after injection into an alveolar bone (maxilla) is very rapid.

Procaine is negligibly bound to plasma proteins, but amide LAs are bound to plasma α_1 acid glycoprotein. LAs are rapidly but briefly bound to tissues, especially nerves, at the site of injection. Ester linked LAs (procaine, etc.) are rapidly hydrolysed by plasma pseudocholinesterase and the remaining by esterases in the liver. Amide linked LAs (lignocaine, etc.) are degraded only in the liver microsomes by dealkylation and hydrolysis. Metabolism of lignocaine is hepatic blood flow dependent. The maximal safe dose of LAs is lower in patients with hepatic disease and in the elderly who have decreased liver function.

After oral ingestion, both procaine and lignocaine have high first pass metabolism in the liver. Thus, they are not active orally for antiarrhythmic purposes.

ADVERSE EFFECTS

Systemic toxicity on rapid i.v. injection is related to the intrinsic anaesthetic potency of the LA. However, toxicity after topical application or regional injection is influenced by relative rates of absorption and metabolism; those rapidly absorbed but slowly metabolized are more toxic.

1. CNS effects are light-headedness, dizziness, auditory and visual disturbances, mental confusion, disorientation, shivering, twitchings, involuntary movements, finally convulsions and respiratory arrest. This can be prevented and treated by diazepam.

2. Cardiovascular toxicity of LAs is manifested as bradycardia, hypotension, cardiac arrhythmias and vascular collapse.
3. Injection of LAs may be painful, but local tissue toxicity of LAs is low. However, wound healing may be sometimes delayed. Addition of vasoconstrictors enhances the local tissue damage; rarely localized mucosal sloughing and necrosis result. Vasoconstrictors should not be added for ring block of hands, feet, fingers, toes, penis and in pinna. Bupivacaine has the highest local tissue irritancy.
4. Hypersensitivity reactions like rashes, angioedema, dermatitis, contact sensitivity, asthma and rarely anaphylaxis occur. These are more common with ester type LAs, but rare with lignocaine or its congeners. Cross reactivity is frequent among ester compounds, but not with amide linked LAs.

Precautions and interactions

1. Before injecting the LA, aspirate lightly to avoid intravascular injection.
2. Inject the LA slowly and take care not to exceed the maximum safe dose, especially in children.
3. Propranolol (probably other β blockers also) may reduce metabolism of lignocaine and other amide LAs by reducing hepatic blood flow.
4. Vasoconstrictor (adrenaline) containing LA should be avoided for patients with ischaemic heart disease, cardiac arrhythmia, thyrotoxicosis, uncontrolled hypertension, and those receiving β blockers (rise in BP due to unopposed α action) or tricyclic antidepressants (uptake blockade of Adr).

INDIVIDUAL COMPOUNDS

Important properties of local anaesthetics are compared in Table 25.2.

Cocaine It is a natural alkaloid from leaves of *Erythroxylon coca*, a south American plant growing on the foothills of the Andes. The natives of Peru and Bolivia habitually chew these leaves. Cocaine is a good surface anaesthetic and is rapidly absorbed from buccal mucous membrane. It was first used for ocular anaesthesia in 1884. Cocaine should never be injected; it is a protoplasmic poison and causes tissue necrosis. Cocaine produces prominent CNS stimulation with marked effect on mood and behaviour. It induces a sense of wellbeing, delays fatigue and increases power of endurance. In susceptible individuals it produces a state referred to as 'high' leading to strong psychological but little physical dependence. Cocaine is unique among drugs of abuse in not producing significant tolerance on repeated use; sometimes reverse tolerance is seen (behavioural effects are experienced at lower doses).

Cocaine also stimulates vagal centre—bradycardia; vasomotor centre—rise in BP; vomiting centre—nausea and vomiting; temperature regulating centre—pyrexia (also due to increased heat production as a result of enhanced muscular activity).

In the periphery, it blocks uptake of NA and Adr into adrenergic nerve endings, resulting in higher concentration of the transmitter around the receptors—sympathomimetic effect, potentiation of directly acting sympathomimetics and suppression of indirectly acting sympathomimetics. Local vasoconstriction, tachycardia, rise in BP and mydriasis are the reflection of its sympathomimetic action.

Table 25.2: Comparative properties of important local anaesthetics

	Potency			*Concn. used (%)*	*Safe max dose* (for inj.)*		*Onset*	*Metabolism in*		*Duration of nerve block*
	surface	*injection*	*toxic*		*Total mg*	*(mg/kg)*		*plasma*	*liver*	*(min)*
Cocaine	1	1	1	–	not injected		fast	–	+	–
Procaine	1/10	1	1/6	1–2%	400	6	slow	+	+	30–60
Lignocaine	1	2	1/6	0.5–2%	300	4.5	fast	–	+	60–120
Tetracaine	4	10	2	0.25–0.5%	80	1.3	slow	+	+	180–480
Bupivacaine	–	10	2	0.25–0.5%	90	1.4	interm.	–	+	180–360
Dibucaine	6	15	3	0.25–0.5%	50	–	slow	–	+	180–600

* Without adrenaline; addition of adrenaline may increase safe limit by upto 50%

The only indication for cocaine is in ocular anaesthesia. However, it causes constriction of conjunctival vessels, clouding and rarely sloughing of cornea (due to drying and local tissue toxicity). Its use, therefore, is not warranted.

Procaine It is the first synthetic local anaesthetic introduced in 1905. Its popularity declined after the introduction of lignocaine: practically not used now. It is not a surface anaesthetic. Paraaminobenzoic acid (PABA) is released on hydrolysis of procaine which can antagonise the antibacterial action of sulfonamides given to treat infections.

Procaine forms poorly soluble salt with benzyl penicillin; *procaine penicillin* injected i.m. acts for 24 hours due to slow absorption from the site of injection.

Lignocaine (Lidocaine) Introduced in 1948, it is currently the most widely used LA. It is a versatile LA, good both for surface application as well as injection and is available in a variety of forms. Injected around a nerve, it blocks conduction within 3 min, whereas procaine may take 15 min; also anaesthesia is more intense and longer lasting. It is used for surface application, infiltration, nerve block, epidural and spinal anaesthesia. Cross sensitivity with ester LAs is not seen. In contrast to other LAs, early central effects of lignocaine are drowsiness, mental clouding, altered taste and tinnitus. Overdose causes muscle twitching, convulsions, cardiac arrhythmias, fall in BP, coma and respiratory arrest like other LAs. Lignocaine is a popular antiarrhythmic (*see* Ch. 12).

XYLOCAINE, GESICAIN 4% topical solution, 2% jelly, 2% viscous, 5% ointment, 1% and 2% injection (with or without adrenaline), 5% heavy (for spinal anaesthesia); 100 mg/ml spray (10 mg per puff).

For dental anaesthesia: 2 ml cartridge or prefilled syringe containing lignocaine 2% with or without adrenaline 1:80000. The solution in cartridge is preservative free (some patients are allergic to the preservative).

Prilocaine It is similar to lignocaine but does not cause vasodilatation at the site of infiltration and has lower CNS toxicity due to larger volume of distribution. One of its metabolites has potential to cause methaemoglobinaemia.

Eutectic lignocaine/prilocaine This is a unique preparation which can anaesthetise intact skin after surface application. Eutectic mixture refers to lowering of melting point of two solids when they are mixed. This happens when lignocaine and prilocaine are mixed in equal proportion at 25°C. The resulting oily liquid is emulsified into water to form a cream that is applied under occlusive dressing for 1 hr before i.v. cannulation, split skin graft harvesting and other superficial procedures. Anaesthesia up to a depth of 5 mm lasts for 1–2 hr after removal. It has been used as an alternative to lignocaine infiltration.

PRILOX 5% cream.

In dentistry, it has been tried for obtunding pain of intrapalatal injection.

Tetracaine (Amethocaine) A highly lipid-soluble PABA ester, more potent and more toxic due to slow hydrolysis by plasma pseudocholinesterase. It is both surface and conduction block anaesthetic, but its use is restricted to topical application to the eye, nose, throat, tracheobronchial tree and rarely for spinal or caudal anaesthesia of long duration. Though it is slow acting, absorption from tracheobronchial spray is very fast and blood concentrations approach those attained after i.v. injection. Because of rapid mucosal absorption and high systemic toxicity, its use for surface anaesthesia in the mouth is restricted.

ANETHANE powder for solution, 1% ointment.

Bupivacaine A potent and long-acting amide linked LA: used for infiltration, nerve block, epidural and spinal anaesthesia of long duration. A 0.25–0.5% solution injected epidurally produces adequate analgesia without significant motor blockade. As a result, it has become very popular in obstetrics (mother can actively cooperate in vaginal delivery) and for postoperative pain relief by continuous epidural infusion. It has high lipid solubility; distributes more in tissues than in blood after spinal/epidural injection—less likely to reach the foetus (when used during labour) to produce neonatal depression. Bupivacaine is more prone to prolong QTc interval and induce ventricular tachycardia or cardiac depression.

MARCAIN 0.5%, 1% (hyperbaric for spinal anaesthesia).
SENSORCAINE 0.25%, 0.5% inj, 0.5% heavy inj.

Ropivacaine A newer bupivacaine congener, equally long acting but less cardiotoxic. It blocks A δ and C fibres more completely (involved in pain transmission) than A β fibres which control motor function. Though equieffective concentrations of ropivacaine are higher than those of bupivacaine, a greater degree of separation between sensory and motor block has been obtained with ropivacaine when the drugs are injected epidurally. Continuous epidural ropivacaine is being used for relief of postoperative and labour pain. It can also be employed for nerve blocks.

Dibucaine (Cinchocaine) It is the most potent, most toxic and longest acting LA. It is used as a surface anaesthetic on less delicate mucous membranes (anal canal) and occasionally for spinal anaesthesia of long duration.

NUPERCAINE 0.5% inj., NUPERCAINAL 1% ointment, in OTOGESIC 1% ear drops.

Benoxinate It is a good surface anaesthetic for the eye; has little irritancy. A 0.4% solution rapidly produces corneal anaesthesia sufficient for tonometry without causing mydriasis or corneal damage.

BENDZON 0.4% eyedrops.

Benzocaine and Butylaminobenzoate (Butamben) Because of very low aqueous solubility, these LAs are not significantly absorbed from mucous membranes or abraded skin. They produce long-lasting anaesthesia without systemic toxicity. They are used as lozenges for stomatitis, sore throat; as dusting powder/ointment on wounds/ulcerated surfaces and as suppository for anorectal lesions. Both are PABA derivative—can antagonise sulfonamides locally.

PROCTOSEDYL-M: Butylaminobenzoate 1% oint with framycetin and hydrocortisone acetate: for piles.
PROCTOQUINOL 5% ointment of benzocaine.

USES AND TECHNIQUES OF LOCAL ANAESTHESIA

1. Surface anaesthesia It is produced by topical application of surface anaesthetics to mucous membranes and abraded skin. Only the superficial layer is anaesthetised. Onset and duration depends on the site, the drug, its concentration and form, e.g. lignocaine sprayed in mouth or throat acts in 2–5 min and produces anaesthesia for 30–45 min. Addition of Adr does not affect duration of topical anaesthesia. Absorption of soluble LAs from mucous membranes is rapid; blood concentrations of lignocaine and tetracaine sprayed in throat/tracheobronchial tree approach those attained on i.v. injection—toxicity can occur. Except for eutectic lignocaine/prilocaine, no other LA is capable of anaesthetizing intact skin. Surface anaesthesia is extensively used in the eye for tonometry and surgery; pharynx and larynx for intubation, endoscopies, tonsillectomy; urethra for catheterization/dilatation and anal canal for fissure, piles, etc. Topical LA is occasionally applied in the mouth for stomatitis/ulcers, and in nose/ear for painful lesions.

2. Infiltration anaesthesia Dilute solution of LA is infiltrated under the skin in the area of operation—blocks sensory nerve endings. Onset of action is almost immediate and duration is shorter than that after nerve block, e.g. lignocaine 30–60 min, bupivacaine 120–180 min. Infiltration is used for minor operations, e.g. incisions, excisions, hydrocele, herniorrhaphy, etc. when the area to be anaesthetized is small. Relatively larger amount of LA is required compared to the area anaesthetised, but motor function is not affected.

3. Conduction block The LA is injected around nerve trunks so that the area distal to injection is anaesthetised and paralysed.

(a) *Field block* It is produced by injecting the LA subcutaneously in a manner that all nerves coming to a particular field are blocked—as is done for dental procedures, herniorrhaphy, appendicectomy, scalp stitching, operations on forearms and legs, etc. Larger area can be anaesthetised with lesser drug compared to infiltration. The same concentration of LA as for infiltration is used for field block.

(b) *Nerve block* It is produced by injection of the LA around the appropriate nerve trunks or plexuses. The area of resulting anaesthesia is

larger compared to the amount of drug used. Muscles supplied by injected nerve/plexus are paralysed. The latency of anaesthesia depends on the drug and the area to be covered by diffusion, e.g. lignocaine anaesthetises intercostal nerves within 3 min, but brachial plexus block may take 15 min. For plexus block a 'flooding' technique is used and larger volumes are needed. Nerve block lasts longer than field block or infiltration anaesthesia. Frequently performed nerve blocks are—lingual, intercostal, ulnar, sciatic, femoral, brachial plexus, trigeminal, facial, phrenic, etc.—used for tooth extraction, operations on eye, limbs, abdominal wall, fracture setting, trauma to ribs, neuralgias, persistent hiccup, etc.

4. Spinal anaesthesia The LA is injected in the subarachnoid space between L2–3 or L3–4, i.e. below the lower end of spinal cord. The primary site of action is the nerve root in the cauda equina rather than the spinal cord. Lower abdomen and hind limbs are anaesthetised and paralysed. The level of anaesthesia depends on volume and speed of injection, specific gravity of drug solution and posture of the patient. The drug solution could be hyperbaric (in 10% glucose) or isobaric with CSF.

Nerve roots rapidly take up and retain the LA. Since autonomic preganglionic fibres are more sensitive and somatic motor fibres less sensitive than somatic sensory fibres, the level of sympathetic block is about 2 segments higher and the level of motor paralysis about 2 segments lower than the level of cutaneous analgesia.

The duration of spinal anaesthesia depends on the drug used and its concentration. Addition of 0.2–0.4 mg of adrenaline to the LA prolongs spinal anaesthesia by about 1/3rd.

Spinal anaesthesia is used for operations on the lower limbs, pelvis, lower abdomen, prostatectomy, fracture setting, obstetric procedures, caesarean section, etc.

Possible complications of spinal anaesthesia are fall in BP, respiratory paralysis, headache nausea/vomiting, cauda equina syndrome (loss of control over bladder and bowel sphincter) and rarely meningitis.

5. Epidural anaesthesia The spinal dural space is filled with semiliquid fat through which nerve roots travel. The LA injected in this space—acts primarily on nerve roots (in the epidural as well as subarachnoid spaces to which it diffuses) and small amount permeates through intervertebral foramina to produce multiple paravertebral blocks. Epidural injection can be made in the thoracic, lumbar or sacral region according to the area of desired anaesthesia.

Lignocaine and bupivacaine are popular drugs for epidural anaesthesia. Duration of anaesthesia is longer with bupivacaine and action of both the drugs is prolonged by addition of adrenaline. Cardiovascular complications are similar to that after spinal anaesthesia, but headache and neurological complications are less because intrathecal space is not entered. Zone of differential sympathetic blockade is not evident after epidural injection but motor paralysis is 4–5 segments caudal. Continuous epidural anaesthesia can be instituted by inserting a catheter and making repeated injections.

Local anaesthesia in dentistry

In the practice of dentistry LAs are mainly used by nerve block (for branches of lingual nerve) or by infiltration/regional block techniques to carry out various restorative/operative procedures. Less commonly, they are applied topically to painful oral ulcers and other superficial lesions.

The total amount of LA injected for dental anaesthesia is generally much smaller (e.g. 20 – 80 mg of lignocaine) than that used for other purposes like brachial plexus block, multiple nerve blocks or epidural anaesthesia. As such, systemic toxicity of dental anaesthesia is usually not a major concern. Reports of serious adverse effects are rare. Many side effects that have been described (like palpitation, pallor, sweating, uneasiness, giddiness, fainting, nausea, tremor) in fact have their origin in the apprehension of the patient to the injection given in the mouth. However, because the volume of LA needed for dental anaesthesia in children is only marginally

less than that in adults, a higher per kg dose is injected and the safety margin is reduced. It is, therefore, desirable to use vasoconstrictor containing LA in children, though the longer duration of resulting soft tissue anaesthesia is apprehended to cause more postoperative biting injuries.

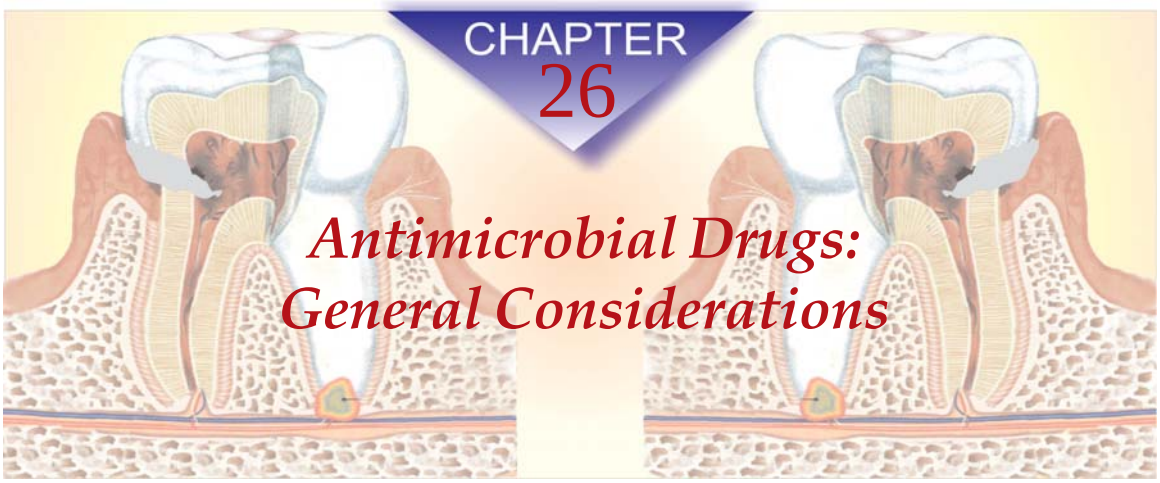
Because of greater vascularity in the upper jaw, soft tissue anaesthesia after maxillary infiltration of the LA is shorter lasting than the same drug injected into the lower jaw. This difference in duration of action is more marked for plain LA solutions than for those containing vasoconstrictor. After nerve block, the duration of dental pulp anaesthesia is generally 1/5th to 1/3rd that of soft tissue anaesthesia. The plain solution may be preferred when a shorter duration of soft tissue anaesthesia without complete pulpal anaesthesia is required, when operative haemorrhage is not a concern, and when vasoconstrictor is contraindicated. Plain LA has been considered appropriate for short maxillary arch procedures.

Lignocaine (2%) with adrenaline (1:80,000) is the standard LA preparation used in dental practice. It produces good soft tissue as well as pulpal anaesthesia and reduces postextraction bleeding. After injection, pulpal anaesthesia is obtained in 2–3 min and lasts for 40–60 min, whereas soft tissues remain anaesthetised for 2–3 hours. However, complete pain relief may not be achieved in few patients with very sensitive teeth or marked inflammation. In comparison, plain lignocaine (2%) provides soft tissue anaesthesia for 45–90 min, while pulpal anaesthesia is brief (10–20 min) and unreliable. Moreover, haemorrhage control is poor due to vasodilatory action of lignocaine. After intraoral injection, systemic absorption of lignocaine is relatively rapid due to high lipid solubility.

Topically, lignocaine may be applied on painful oral ulcers and prior to intraoral injection of the LA in apprehensive patients. The 10% spray formulation produces widespread oral mucosal anaesthesia which may be utilized before taking impressions or dental X-ray in fussy patients.

Bupivacaine (0.5%) with adrenaline (1:200,000) is less frequently used in dentistry. Because of very high lipid solubility, it is largely taken up by peridontal soft tissues and penetration into bone is poorer. The onset of pulpal anaesthesia is slower, may take > 5 min to start, is less intense and relatively short-lasting (<2 hr), while soft tissues may remain anaesthetized for up to 8 hours. Long-lasting oral surgery or procedures, which require extended postoperative pain control such as removal of impacted third molars are the indications for use of bupivacaine.

Ropivacaine is occasionally used in dentistry, and there is no specific indication for it.



CHAPTER 26

Antimicrobial Drugs: General Considerations

Antimicrobial drugs are the greatest contribution of the 20th century to therapeutics. Their advent changed the outlook of the physician about the power drugs can have on diseases. They are one of the few curative drugs. As a class, they are one of the most frequently used as well as misused drugs. Apart from analgesics, they are the commonest drugs that dentists routinely prescribe themselves.

Drugs in this class differ from all others in that they are designed to inhibit/kill the infecting organism and to have no/minimal effect on the recipient. This type of therapy is generally called *chemotherapy* which has come to mean 'treatment of systemic infections with specific drugs that selectively suppress the infecting microorganism without significantly affecting the host.' The basis of selective microbial toxicity is the action of the drug on a component of the microbe (e.g. bacterial cell wall) or metabolic process (e.g. folate synthesis) that is not found in the host, or a high affinity for certain microbial biomolecules. Due to analogy between the malignant cell and the pathogenic microbes, treatment of neoplastic diseases with drugs is also called chemotherapy.

Antibiotics These are substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations. This definition excludes other natural substances which also inhibit microorganisms but are produced by higher forms (e.g. antibodies) or even those produced by microbes but are needed in high concentrations (ethanol, lactic acid, H_2O_2).

Initially, the term 'chemotherapeutic agent' was restricted to synthetic compounds, but now since many antibiotics and their analogues have been synthesized, this criterion has become irrelevant; both synthetic and microbiologically produced drugs need to be included together. However, it would be more meaningful to use the term *antimicrobial agent* (AMA) to designate synthetic as well as naturally obtained drugs that attenuate microorganisms.

The *history* of chemotherapy may be divided into 3 phases.

(a) The period of empirical use: of 'mouldy curd' by Chinese on boils, chaulmoogra oil by the Hindus in leprosy, chenopodium by Aztecs for intestinal worms, mercury by Paracelsus (16th century AD) for syphilis, cinchona bark (17th century AD) for fevers.

(b) Ehrlich's phase of dyes and organometallic compounds (1890–1935): With the discovery of microbes in the later half of the 19th century and that they are the cause of many diseases: Ehrlich toyed with the idea that if certain dyes could selectively stain microbes, they could also be selectively toxic to these organisms, and tried methylene blue, trypan red, etc. He developed the arsenicals—*atoxyl* for sleeping sickness, *arsphenamine* in 1906 and neoarsphenamine in 1909 for syphilis. He coined the term 'chemotherapy' because he used drugs of known chemical structure (that of most other drugs in use at that time was not known) and showed that selective attenuation of infecting parasite was a practical proposition.

(c) The modern era of chemotherapy was ushered by Domagk in 1935 by demonstrating the therapeutic effect of *Prontosil*, a sulfonamide dye, in pyogenic infection. It was soon realized that the active moiety was paraamino benzene sulfonamide, and the dye part was not essential. Sulfapyridine (M & B 693) was the first sulfonamide to be marketed in 1938.

The phenomenon of *antibiosis* was demonstrated by Pasteur in 1877: growth of anthrax bacilli in urine was inhibited by air-borne bacteria. Fleming (1929) found that a diffusible substance was elaborated by *Penicillium* mould which could destroy *Staphylococcus* on the culture plate. He named this substance *penicillin* but could not purify it. Chain and Florey followed up this observation in 1939 which culminated in the clinical use of penicillin in 1941. Because of the great potential of this discovery in treating war wounds, commercial manufacture of penicillin soon started.

In the 1940s, Waksman and his colleagues undertook a systematic search of Actinomycetes as source of antibiotics and discovered *streptomycin* in 1944. This group of soil microbes proved to be a treasure-house of antibiotics and soon tetracyclines, chloramphenicol, erythromycin and many others followed. All three groups of scientists Domagk, Fleming-Chain-Florey and Waksman received the Nobel Prize for their discoveries.

In the past 40 years emphasis has shifted from searching new antibiotic producing organisms to developing semisynthetic derivatives of older antibiotics with more desirable properties or differing spectrum of activity. Few novel synthetic AMAs (e.g. fluoroquinolones, oxazolidinones) have also been produced.

CLASSIFICATION

Antimicrobial drugs can be classified in many ways:

A. Chemical structure

1. *Sulfonamides and related drugs*: Sulfadiazine and others, Sulfones—Dapsone (DDS), Paraaminosalicylic acid (PAS).
2. *Diaminopyrimidines:* Trimethoprim, Pyrimethamine.
3. *Quinolones:* Nalidixic acid, Norfloxacin, Ciprofloxacin, etc.
4. *β-lactam antibiotics:* Penicillins, Cephalosporins, Monobactams, Carbapenems.
5. *Tetracyclines:* Oxytetracycline, Doxycycline, etc.
6. *Nitrobenzene derivative:* Chloramphenicol.
7. *Aminoglycosides:* Streptomycin, Gentamicin, Neomycin, etc.
8. *Macrolide antibiotics:* Erythromycin, Roxithromycin, Azithromycin, etc.
9. *Polypeptide antibiotics:* Polymyxin-B, Colistin, Bacitracin, Tyrothricin.
10. *Glycopeptides:* Vancomycin, Teicoplanin
11. *Oxazolidinone:* Linezolid.
12. *Nitrofuran derivatives:* Nitrofurantoin, Furazolidone.
13. *Nitroimidazoles:* Metronidazole, Tinidazole.
14. *Nicotinic acid derivatives:* Isoniazid, Pyrazinamide, Ethionamide.
15. *Polyene antibiotics:* Nystatin, Amphotericin-B, Hamycin.
16. *Azole derivatives:* Miconazole, Clotrimazole, Ketoconazole, Fluconazole.
17. *Others:* Rifampin, Lincomycin, Clindamycin, Spectinomycin, Sod. fusidate, Cycloserine, Viomycin, Ethambutol, Thiacetazone, Clofazimine, Griseofulvin.

B. Mechanism of action

1. *Inhibit cell wall synthesis*: Penicillins, Cephalosporins, Cycloserine, Vancomycin, Bacitracin.
2. *Cause leakage from cell membranes*: Polypeptides—Polymyxins, Colistin, Bacitracin. Polyenes—Amphotericin B, Nystatin, Hamycin.
3. *Inhibit protein synthesis:* Tetracyclines, Chloramphenicol, Erythromycin, Clindamycin, Linezolid.
4. *Cause misreading of m-RNA code and affect permeability:* Aminoglycosides—Streptomycin, Gentamicin, etc.
5. *Inhibit DNA gyrase:* Fluoroquinolones—Ciprofloxacin.
6. *Interfere with DNA function:* Rifampin, Metronidazole.
7. *Interfere with DNA synthesis:* Acyclovir, Zidovudine.
8. *Interfere with intermediary metabolism:* Sulfonamides, Sulfones, PAS, Trimethoprim, Pyrimethamine, Ethambutol.

C. Type of organisms against which primarily active

1. *Antibacterial:* Penicillins, Aminoglycosides, Erythromycin, etc.
2. *Antifungal*: Griseofulvin, Amphotericin B, Ketoconazole, etc.
3. *Antiviral:* Acyclovir, Amantadine, Zidovudine, etc.
4. *Antiprotozoal:* Chloroquine, Pyrimethamine, Metronidazole, Diloxanide, etc.
5. *Anthelmintic:* Mebendazole, Pyrantel, Niclosamide, Diethyl carbamazine, etc.

D. Spectrum of activity

Narrow spectrum	*Broad spectrum*
Penicillin G	Tetracyclines
Streptomycin	Chloramphenicol
Erythromycin	

The initial distinction between narrow and broad-spectrum antibiotics is no longer clearcut. Drugs with all ranges of intermediate band width, e.g. extended spectrum penicillins, newer cephalosporins, aminoglycosides, fluoroquinolones are now available. However, the terms 'narrow spectrum' and 'broad spectrum' are still applied.

E. Type of action

Primarily bacteriostatic

Sulfonamides	Erythromycin
Tetracyclines	Ethambutol
Chloramphenicol	Clindamycin

Primarily bactericidal

Penicillins	Cephalosporins
Aminoglycosides	Vancomycin
Polypeptides	Ciprofloxacin
Rifampin	Metronidazole
Cotrimoxazole	

Some primarily static drugs may become cidal at higher concentrations (as attained in the urinary tract), e.g. sulfonamides, erythromycin, nitrofurantoin. On the other hand, some cidal drugs, e.g. cotrimoxazole, streptomycin may only be static under certain circumstances.

F. Antibiotics are obtained from:

Fungi

Penicillin	Griseofulvin
Cephalosporin	

Bacteria

Polymyxin B	Tyrothricin
Colistin	Aztreonam
Bacitracin	

Actinomycetes

Aminoglycosides	Macrolides
Tetracyclines	Polyenes
Chloramphenicol	

PROBLEMS THAT ARISE WITH THE USE OF AMAs

1. Toxicity

(a) *Local irritancy*: This is experienced at the site of administration. Gastric irritation, pain and abscess formation at the site of i.m. injection, thromboflebitis of the injected vein are the complications. Practically all AMAs, especially erythromycin, tetracyclines, certain cephalosporins and chloramphenicol are irritants.

(b) *Systemic toxicity:* Practically all AMAs produce dose related and predictable organ toxicities. Characteristic toxicities are exhibited by different AMAs.

Some have a *high therapeutic index*—doses up to 100-fold range may be given without apparent damage to host cells. These include penicillins, some cephalosporins and erythromycin.

Others have a *lower therapeutic index*—doses have to be individualized and toxicity watched for, e.g.:

Aminoglycosides	: 8th cranial nerve and kidney toxicity.
Tetracyclines	: liver and kidney damage, antianabolic effect.
Chloramphenicol	: bone marrow depression.

Still others have a *very low therapeutic index*—use is highly restricted to conditions where no suitable alternative is available, e.g. :

Polymyxin B	: neurological and renal toxicity.
Vancomycin	: hearing loss, kidney damage.
Amphotericin B	: kidney, bone marrow and neurological toxicity.

2. Hypersensitivity reactions

Practically all AMAs are capable of causing hypersensitivity reactions. These are unpredictable and unrelated to dose. The whole range of reactions from rashes to anaphylactic shock can be produced. The more commonly involved AMAs are—penicillins, cephalosporins, sulfonamides.

3. Drug resistance

It refers to unresponsiveness of a microorganism to an AMA and is akin to the phenomenon of tolerance seen in higher organisms.

Natural resistance Some microbes have always been resistant to certain AMAs. They lack the metabolic process or the target site which is affected by the particular drug. This is generally a group or species characteristic, e.g. gram-negative bacilli are normally unaffected by penicillin G, or *M. tuberculosis* is insensitive to tetracyclines. This type of resistance does not pose a significant clinical problem.

Acquired resistance It is the development of resistance by an organism (which was sensitive before) due to the use of an AMA over a period of time. This can happen with any microbe and is a major clinical problem. However, development of resistance is dependent on the microorganism as well as the drug. Some bacteria are notorious for rapid acquisition of resistance, e.g. staphylococci, coliforms, tubercle bacilli. Others like *Strep. pyogenes* and spirochetes have not developed significant resistance to penicillin despite its widespread use for > 50 years. Gonococci quickly developed resistance to sulfonamides, but only slowly and low-grade resistance to penicillin. However, in the past 30 years, highly penicillin-resistant gonococci producing penicillinase have appeared.

Resistance may be developed by mutation or gene transfer.

Mutation It is a stable and heritable genetic change that occurs spontaneously and randomly among microorganisms. It is not induced by the AMA. Any sensitive population of a microbe contains a few mutant cells which require higher concentration of the AMA for inhibition. These are selectively preserved and get a chance to proliferate when the sensitive cells are eliminated by the AMA. Thus, in time it would appear that a sensitive strain has been replaced by a resistant one, e.g. when an antitubercular drug is used alone. Mutation and resistance may be:

(i) *Single step:* A single gene mutation may confer high degree of resistance; emerges rapidly, e.g. enterococci to streptomycin, *E. coli* and *Staphylococci* to rifampin.

(ii) *Multistep:* A number of gene modifications are involved; sensitivity decreases gradually in a stepwise manner. Resistance to erythromycin, tetracyclines and chloramphenicol is developed by many organisms in this manner.

Sometimes mutational acquisition of resistance is accompanied by decrease in virulence, e.g. certain rifampin-resistant staphylococci and low-grade penicillin-resistant gonococci have decreased virulence.

Gene transfer (infectious resistance) from one organism to another can occur by:

(i) *Conjugation* Sexual contact through the formation of a bridge or sex pilus is common among gram-negative bacilli of the same or another species. This may involve chromosomal or extrachromosomal (plasmid) DNA. The gene carrying the 'resistance' or 'R' factor is transferred only if another 'resistance transfer factor' (RTF) is also present. Conjugation frequently occurs in the colon where a large variety of gram-negative bacilli come in close contact. Even nonpatho-

genic organisms may transfer R factor to pathogenic organisms, which may become widespread by contamination of food or water. Chloramphenicol resistance of typhoid bacilli, streptomycin resistance of *E. coli*, penicillin resistance of *Haemophilus* and gonococci and many others have been traced to this mechanism. Concomitant acquisition of multidrug resistance has occurred by conjugation. Thus, this is a very important mechanism of resistance acquisition.

(ii) *Transduction* It is the transfer of gene carrying resistance through the agency of a bacteriophage. The R factor is taken up by the phage and delivered to another bacterium which it infects. Certain instances of penicillin, erythromycin and chloramphenicol resistance have been found to be phage mediated.

(iii) *Transformation* A resistant bacterium may release the resistance carrying DNA into the medium and this may be imbibed by another sensitive organism—becoming unresponsive to the drug. This mechanism is probably not clinically significant except isolated instances of pneumococcal resistance to penicillin G due to altered penicillin binding protein, and some other cases.

Resistance once acquired by any of the above mechanisms becomes prevalent due to the *selection pressure* of a widely used AMA, i.e. presence of the AMA provides opportunity for the resistant subpopulation to thrive in preference to the sensitive population.

Resistant organisms can be drug tolerant or drug destroying or drug impermeable.

(a) Drug tolerant There is loss of affinity of the target biomolecule of the microorganism for a particular AMA, e.g. resistant *Staph. aureus* and *E. coli* develop a RNA polymerase that does not bind rifampin, certain penicillin-resistant pneumococcal strains have altered penicillin binding proteins; and trimethoprim resistance results from plasmid-mediated synthesis of a dihydrofolate reductase that has low affinity for trimethoprim. Another mechnism is acquisition of an alternative metabolic pathway, e.g. certain sulfonamide-resistant bacteria switch over to utilizing preformed folic acid in place of synthesizing it from PABA taken up from the medium.

(b) Drug destroying The resistant microbe elaborates an enzyme which inactivates the drug, e.g.
(i) β-lactamases are produced by staphylococci, *Haemophilus*, gonococci, etc. which inactivate penicillin G. The β-lactamases may be present in low quantity but strategically located periplasmically (as in gram-negative bacteria) so that the drug is inactivated soon after entry, or may be elaborated in large quantities (by gram-positive bacteria) to diffuse into the medium and destroy the drug before entry.
(ii) Chloramphenicol acetyl transferase is acquired by resistant *E. coli*, *H. influenzae* and *S.typhi*.
(iii) Some of the aminoglycoside-resistant coliforms produce enzymes which adenylate/acetylate/phosphorylate specific aminoglycoside antibiotics.

(c) Drug impermeable Many hydrophilic antibiotics gain access into the bacterial cell through specific channels formed by proteins called 'porins', or need specific transport mechanisms. These may be lost by the resistant strains, e.g. concentration of some aminoglycosides and tetracyclines in the resistant gram-negative bacterial strains has been found to be much lower than that in their sensitive counterparts when both were exposed to equal concentrations of the drugs. Similarly, the low degree penicillin-resistant gonococci are less permeable to penicillin G; chloroquine-resistant *P. falciparum* accumulates less chloroquine. The bacteria may also acquire plasmid directed inducible energy dependent efflux proteins in their cell membrane which pump out tetracyclines. Active efflux-based resistance has been detected for erythromycin and fluoroquinolones as well.

Cross resistance Acquisition of resistance to one AMA conferring resistance to another AMA, to which the organism has not been exposed, is

called cross resistance. This is more commonly seen between chemically or mechanistically related drugs, e.g. resistance to one sulfonamide means resistance to all others, and resistance to one tetracycline means insensitivity to all others. Such cross resistance is often complete. However, resistance to one aminoglycoside may not extend to another, e.g. gentamicin-resistant strains may respond to amikacin. Sometimes unrelated drugs show partial cross resistance, e.g. between tetracyclines and chloramphenicol, between erythromycin and lincomycin.

Cross resistance may be two-way, e.g. between erythromycin and clindamycin and vice versa or one-way, e.g. development of neomycin resistance by Enterobacteriaceae makes them insensitive to streptomycin, but many streptomycin-resistant organisms remain susceptible to neomycin.

Prevention of drug resistance It is of utmost clinical importance to curb development of drug resistance. Measures are:

(a) No indiscriminate and inadequate or unduly prolonged use of AMAs should be made. This would minimize the selection pressure and resistant strains will get less chance to preferentially propagate. For acute localized infections in otherwise healthy patients, symptom determined shorter courses of AMAs are being advocated now.

(b) Prefer rapidly acting and selective (narrow spectrum) AMAs whenever possible; broad-spectrum drugs should be used only when a specific one cannot be determined or is not suitable.

(c) Use combination of AMAs whenever prolonged therapy is undertaken, e.g. tuberculosis, SABE.

(d) Infection by organisms notorious for developing resistance, e.g. *Staph. aureus, E. coli, M. tuberculosis, Proteus,* etc. must be treated intensively.

4. Superinfection (Suprainfection)

This refers to the appearance of a new infection as a result of antimicrobial therapy.

Use of most AMAs causes some alteration in the normal microbial flora of the body. The normal flora contributes to host defence by elaborating substances called *bacteriocins* which inhibit pathogenic organisms. Further, ordinarily, the pathogen has to compete with the normal flora for nutrients, etc. to establish itself. Lack of competition may allow even a normally nonpathogenic component of the flora, which is not inhibited by the drug (e.g. *Candida*), to predominate and invade. More complete the suppression of body flora, greater are the chances of developing superinfection. Thus, it is commonly associated with the use of broad/extended spectrum antibiotics, such as tetracyclines, chloramphenicol, ampicillin, newer cephalosporins; especially when combinations of these are employed. Tetracyclines are more prone than chloramphenicol and ampicillin is more prone than amoxicillin to cause superinfection diarrhoeas because of incomplete absorption—higher amounts reach the lower bowel and cause greater suppression of colonic bacteria.

Superinfections are more common when host defence is compromised, as in:

- Corticosteroid therapy
- Leukaemias and other malignancies, especially when treated with anticancer drugs (these are also immunosuppressants and decrease WBC count)
- Acquired immunodeficiency syndrome (AIDS)
- Agranulocysis
- Diabetes, disseminated lupus erythematosus.

Sites involved in superinfection are those that normally harbour commensals, i.e. oropharynx: intestinal, respiratory and genitourinary tracts; occasionally skin.

Superinfections are generally more difficult to treat. The organisms frequently involved, manifestations and drugs for treating superinfections are:

(a) *Candida albicans:* monilial diarrhoea, thrush, vulvovaginitis; treat with nystatin or clotrimazole.

(b) Resistant staphylococci: enteritis; treat with cloxacillin or its congeners.

(c) *Clostridium difficile*: pseudomembranous enterocolitis associated with the use of clindamycin, tetracyclines, aminoglycosides, ampicillin, cotrimoxazole; more common after colorectal surgery; the organism produces an enterotoxin which damages gut mucosa forming plaques; metronidazole and vancomycin are the drugs of choice.

(d) *Proteus*: Urinary tract infection, enteritis; treat with a cephalosporin or gentamicin.

(e) *Pseudomonas*: Urinary tract infection, enteritis; treat with carbenicillin, piperacillin or gentamicin.

To minimize superinfections:

(i) Use specific (narrow-spectrum) AMA whenever possible.
(ii) Do not use antimicrobials to treat trivial, self-limiting or untreatable (viral) infections.
(iii) Do not unnecessarily prolong antimicrobial therapy.

5. Nutritional deficiencies

Some of the B complex group of vitamins and vit K synthesized by the intestinal flora is utilized by man. Prolonged use of antimicrobials which alter this flora may result in vitamin deficiencies.

Neomycin causes morphological abnormalities in the intestinal mucosa—steatorrhoea and malabsorption syndrome can occur.

6. Masking of an infection

A short course of an AMA may be sufficient to treat one infection but only briefly suppress another one contacted concurrently. The other infection will be masked initially, only to manifest later in a severe form. Examples are:

(i) Syphilis masked by the use of a single dose of penicillin which is sufficient to cure gonorrhoea.
(ii) Tuberculosis masked by a short course of streptomycin given for trivial respiratory infection.

CHOICE OF AN ANTIMICROBIAL AGENT

After having established the need for using a systemic AMA in a patient by ascertaining that the condition is due to a treatable (mostly bacterial) infection, and that it is not likely to resolve by itself or by the use of local measures (antiseptics, drainage of pus, etc.), one has to choose a suitable drug from the large number available. The choice depends on the peculiarities of the patient, the infecting organism and the drug.

Patient factors

1. *Age* may affect kinetics of many AMAs. Conjugation and excretion of chloramphenicol is inefficient in the newborn: larger doses produce *gray baby syndrome*. Sulfonamides displace bilirubin from protein binding sites—can cause kernicterus in the neonate because their blood-brain barrier is more permeable. The t½ of aminoglycosides is prolonged in the elderly and they are more prone to develop VIII nerve toxicity. Tetracyclines accumulate in the developing teeth and bone —discolour and weaken them— are contraindicated below the age of 6 years.

2. *Renal and hepatic function* Cautious use and modification of the dose of an AMA (with low safety margin) becomes necessary when the organ of its disposal is defective.

Antimicrobials contraindicated or for whom dose modification is required in *renal insufficieny* are:

Dose reduction needed in renal failure

Even in mild failure

Aminoglycosides	Amphotericin B
Cephalosporins	Ethambutol
Vancomycin	

Only in moderate-severe failure

Metronidazole	Carbenicillin
Cotrimoxazole	Fluoroquinolones

Drugs to be avoided

Cephalothin	Nitrofurantoin
Nalidixic acid	Tetracyclines (except doxycycline)

Antimicrobials to be avoided or used at lower dose *in liver disease* are:

Drugs to be avoided

Erythromycin estolate	Tetracyclines
Pyrazinamide	Nalidixic acid

Dose reduction needed

Chloramphenicol	Isoniazid
Metronidazole	Rifampin
Clindamycin	

3. *Local factors* The conditions prevailing at the site of infection greatly affect the action of AMAs.
(a) Presence of pus and secretions decrease the efficacy of most AMAs, especially sulfonamides and aminoglycosides. Antibiotics cannot cure periodontal or periapical abscesses, unless the pus is surgically drained. Drainage of the abscess reduces the population of causative bacteria, suppresses anaerobic bacteria by exposure to oxygen, and improves diffusion of the antibiotic into the abscess cavity.
(b) Presence of necrotic material or foreign body makes eradication of infection practically impossible.
(c) Haematomas foster bacterial growth; tetracyclines, penicillins and cephalosporins get bound to the degraded haemoglobin in the haematoma.
(d) Lowering of pH at site of infection reduces activity of macrolide and aminoglycoside antibiotics.
(e) Anaerobic environment in the centre of an abscess impairs bacterial transport processes which concentrate aminoglycosides in the bacterial cell, rendering them less susceptible.
(f) Penetration barriers may hamper the access of the AMA to the site of infection in subacute bacterial endocarditis (SABE), endophthalmitis, prostatitis, etc.

4. *Drug allergy* History of previous exposure to an AMA should be obtained. If a drug has caused allergic reaction—it has to be avoided in that patient, e.g. erythromycin or clindamycin are the alternative drugs for dental infection in patients allergic to penicillin. β-lactams, sulfonamides, fluoroquinolones and nitrofurantoin frequently cause allergy.

5. *Impaired host defence* Integrity of host defence plays a crucial role in overcoming an infection. Pyogenic infections occur readily in neutropenic patients; while if cell-mediated immunity is impaired (e.g. AIDS), infections by low-grade pathogens and intracellular organisms abound. In an individual with normal host defence, a bacteriostatic AMA may achieve cure; while intensive therapy with cidal drugs is imperative in those with impaired host defence or when the organisms are protected by a barrier—as in SABE. Even then complete eradication of the organism may not occur.

6. *Pregnancy* All AMAs should be avoided in the pregnant because of risk to the foetus. Penicillins, many cephalosporins and erythromycin are safe, while safety data on most others is not available. Therefore, manufacturers label 'contraindicated during pregnancy'. Tetracyclines carry risk of acute yellow atrophy of liver, pancreatitis and kidney damage in the mother. They also cause teeth and bone deformities in the offspring. Aminoglycosides can cause foetal ear damage. Animal studies indicate increased risk to the foetus especially with fluoroquinolones, cotrimoxazole, chloramphenicol, sulfonamides and nitrofurantoin. Though metronidazole has not been found to be teratogenic, its mutagenic potential warrants caution in use during pregnancy.

7. *Genetic factors* Primaquine, nitrofurantoin, sulfonamides, chloramphenicol and fluoroquinolones are likely to produce haemolysis in G-6PD deficient patient.

Organism-related considerations

Each AMA has a specific effect on a limited number of microbes. Successful chemotherapy must be rational and demands a diagnosis. A clinical diagnosis should first be made, at least tentatively, and the likely pathogen guessed.

Ideally, the identity and antimicrobial sensitivity of the infecting bacteria should be determined before instituting systemic antibacterial therapy. However, being time consuming (at least 48 hours) and expensive, this is impractical for

most dental infections which are acute in nature and treatment cannot be delayed. Moreover, it is not always possible to obtain appropriate samples of infected material for bacteriological testing. Nevertheless, a good guess can generally be made from the clinical features and local experience. The causative organisms of common orodental infections like alveolar abscesses, periodontal abscesses, dental pulp infections, chronic periodontitis, acute necrotizing gingivitis, etc. are usually *Bacteroides* and other anaerobes (mostly gram-negative and a few gram-positive) aerobic gram-positive cocci and spirochetes. The anaerobes predominate, especially in abscesses than in cellulitis.

Orodental infections are often mixed bacterial infections. Therefore, the drugs mostly selected are from penicillin/amoxicillin/a first or second generation cephalosporin (particularly cefuroxime or cefaclor which are active on anaerobes), erythromycin, cotrimoxazole, clindamycin, vancomycin, doxycycline, ofloxacin/gatifloxacin and metronidazole/tinidazole. Most dentists initiate empirical therapy with amoxicillin + metronidazole. Further therapy is modified on the basis of clinical response, but hasty and arbitrary changes in antibiotic therapy are not advisable. If possible (especially in serious infections), specimen for bacteriological examination should be collected before initiating empirical therapy, so that in case of failure of the first choice drug, alternative AMA could be selected in the light of bacteriological findings.

In a few situations like oral thrush, the clinical diagnosis itself indicates the infecting organism (*Candida* in this case) and directs the choice of drug (nystatin/clotrimazole).

Bacteriological sensitivity testing This is generally done by disk-agar diffusion method using standardized concentrations of antibiotics based on clinically attained plasma concentrations of these. As such, they serve only as guides and cannot be blindly extrapolated to the clinical situation in every patient and for every organism. Broth cultures with *break-point* concentration (concentration that demarcates between sensitive and resistant bacteria) of antibiotics probably yield more reliable results. Break-point concentrations are based on clinically attainable serum concentrations of the antibiotic.

Minimum inhibitory concentration (MIC), i.e. the lowest concentration of an antibiotic which prevents visible growth of a bacterium determined in microwell culture plates using serial dilutions of the antibiotic is more informative, but not estimated routinely.

Minimum bactericidal concentration (MBC) of the antibiotic is determined by subculturing from tubes with no visible growth. If the organism is killed, no growth will occur; but if it was only inhibited in the parent culture—it will grow on subculturing in antibiotic-free medium. MBC is the concentration of the antibiotic which kills 99.9% of the bacteria. A small difference between MIC and MBC indicates that the antibiotic is primarily bactericidal, while a large difference indicates bacteriostatic action. MBC is not used to guide selection of antibiotics in clinical practice.

Postantibiotic effect (PAE) After a brief exposure if the organism is placed in antibiotic-free medium, it starts multiplying again, but after a lag period which depends on the antibiotic as well as the organism. This lag period in growth resumption is known as 'postantibiotic effect'. A long postantibiotic effect has been noted with fluoroquinolones, aminoglycosides and β-lactam antibiotics.

Drug factors

When any one of a number of AMAs could be used to treat an infection, choice among them is based upon specific properties of these AMAs:

1. *Spectrum of activity:* For definitive therapy, a narrow spectrum drug which selectively affects the concerned organism is preferred, because it is generally more effective than a broad-spectrum AMA and is less likely to disturb the normal microbial flora. However, for empirical therapy, often a broad-spectrum drug has to be used to cover all likely pathogens.
2. *Type of activity:* A bactericidal antibiotic may be preferred over bacteriostatic because it directly reduces the number of bacteria at the site of infection, while bacteriostatic drug only prevents increase in their number. This is specially important while treating patients with impaired host defence, life-threatening infections, infections at less accessible sites (SABE, osteomyelitis) or when carrier state is possible (typhoid). Further, acute infections generally resolve faster with bactericidal than with bacteriostatic drugs, and most bactericidal drugs exert prolonged postantibiotic effect, so that maintenance of drug level continuously above MIC is not essential.

With bacteriostatic AMAs, the bacteria start multiplying again when drug level falls below MIC, which may result in relapse of infection.

3. *Sensitivity of the organism:* Assessed on the basis of MIC values (seldom determined for dental infections) and consideration of post-antibiotic effect.

4. *Relative toxicity:* Obviously, a less toxic antibiotic is preferred, e.g. a β-lactam over an aminoglycoside or erythromycin over clindamycin.

5. *Pharmacokinetic profile:* For optimum action, the antibiotic has to be present at the site of infection in sufficient concentration for an adequate length of time. This depends on their pharmacokinetic characteristics. Most antibiotics are given at 2–4 half-life intervals—thus attaining therapeutic concentrations only intermittently. For many organisms, aminoglycosides and fluoroquinolones produce 'concentration-dependent inhibition'—inhibitory effect depends on the ratio of peak concentration to the MIC; the same daily dose of gentamicin produces better action when given as a single dose than if it is divided into 2–3 portions. On the other hand, β-lactams and macrolides produce 'time-dependent inhibition'—antimicrobial action depends on the length of time the concentration remains above MIC; division of daily dose has better effect. However, the doses should be so spaced that the surviving organisms again start multiplying and a cidal action is exerted.

Penetration to the site of infection also depends on the pharmacokinetic properties of the drug. A drug, which penetrates better and attains higher concentration, is likely to be more effective. Penetration of AMAs into bone is generally poor, but clindamycin penetrates very well and is a good choice for purulent osteitis and certain other tooth infections. The fluoroquinolones have excellent tissue penetration—attain high concentrations in soft tissues, lungs, prostate, joints, etc. Ciprofloxacin and rifampin have very good intracellular penetration. Cefuroxime, ceftriaxone, chloramphenicol, ciprofloxacin attain high CSF concentration. On the other hand, penicillins and aminoglycosides penetrate poorly into CSF unless meninges are inflamed. Ampicillin, cephalosporins and erythromycin attain high biliary concentration.

6. *Route of administration:* Many AMAs can be given orally as well as parenterally, but aminoglycosides, penicillin G, carbenicillin, many cephalosporins, vancomycin, etc. have to be given by injection only. For less severe infections, an oral antibiotic is preferable; but for serious infections, e.g. spreading cellulitis, meningitis, septicaemias, a parenteral antibiotic may be chosen.

7. *Evidence of clinical efficacy:* Relative value of different AMAs in treating an infection is decided on the basis of comparative clinical trials. Optimum dosage regimens and duration of treatment are also determined on the basis of such trials. Reliable clinical trial data, if available, is the final guide for choice of the antibiotic.

8. *Cost:* Less expensive drugs are to be preferred.

COMBINED USE OF ANTIMICROBIALS

More than one AMAs are frequently used concurrently. This should be done only with a specific purpose and not blindly in the hope that if one is good, two should be better and three should cure almost any infection. The objectives of using antimicrobial combinations are:

1. To achieve synergism Every AMA has a specific effect on selected microorganisms. Depending on the drug pair as well as the organism involved, either synergism (supra-additive effect), additive action, indifference or antagonism may be observed when two AMAs belonging to different classes are used together.

Synergism may manifest in terms of decrease in the MIC of one AMA in the presence of another, or the MICs of both may be lowered. If the MIC of each AMA is reduced to 25% or less, the pair is considered synergistic, 25–50% of each is considered additive and more than 50% of each indicates antagonism. Thus, a synergistic drug sensitizes the organisms to the action of the other member of the pair. This may also manifest as a more rapid lethal action of the combination

than either of the individual members. Synergistic prolongation of postantibiotic effect has also been demonstrated for combinations of β-lactams with aminoglycoside and by addition of rifampin to a variety of antibiotics.

Every combination is unique; the same drugs may be synergistic for one organism but antagonistic for another. However, general guidelines are:

(a) Two bacteriostatic agents are often additive, but rarely synergistic, i.e. combination of tetracyclines, chloramphenicol, erythromycin, etc. A sulfonamide used with trimethoprim is a special case where supra-additive effect is obtained because of sequential block in folate metabolism of certain bacteria (Ch. 27). The combination often exerts cidal action which is curative in some infections while the individual components are only static or ineffective in these.

Another special example is the combination of a β-lactamase inhibitor clavulanic acid or sulbactam with amoxicillin or ampicillin for β-lactamase producing *H. influenzae, N. gonorrhoeae* and other organisms.

(b) Two bactericidal drugs are frequently additive and sometimes synergistic if the organism is sensitive to both, e.g.:

- Penicillin/ampicillin + streptomycin/gentamicin for enterococcal SABE
- Carbenicillin/ticarcillin + gentamicin for *Pseudomonas* infection, especially in neutropenic patients.
- Rifampin + isoniazid in tuberculosis.

In the above cases, the combination produces faster cure and reduces the chances of relapse by more complete eradication of the pathogen.

(c) Combination of a bactericidal with a bacteriostatic drug may be synergistic or antagonistic depending on the organism. In general (i) If the organism is highly sensitive to the cidal drug—response to the combination is equal to the static drug given alone (apparent antagonism), because cidal drugs act primarily on rapidly multiplying bacteria, while the static drug retards multiplication. This has been seen with penicillin + tetracycline/chloramphenicol on pneumococci which are highly sensitive to penicillin. Penicillin + erythromycin for group A streptococci and nalidixic acid + nitrofurantoin for *E. coli* have also shown antagonism.

(ii) If the organism has low sensitivity to the cidal drug—synergism may be seen, e.g.:

- Penicillin + sulfonamide for actinomycosis
- Streptomycin + chloramphenicol for *K. pneumoniae* infection
- Rifampin + dapsone in leprosy

Thus, wherever possible, synergistic combinations may be used to treat infections that are normally difficult to cure. Full doses of individual drugs are given for this purpose.

2. To reduce severity or incidence of adverse effects This is possible only if the combination is synergistic so that the doses can be reduced. This is needed for AMAs with low safety margin, which when used alone in effective doses, produce unacceptable toxicity, e.g. Streptomycin + penicillin G for SABE due to *Strep. faecalis.*

3. To prevent emergence of resistance Mutation conferring resistance to one AMA is independent of that conferring resistance to another. If the incidence of resistant mutants of a bacillus infecting an individual for drug P is 10^{-5} and for drug Q is 10^{-7}, then only one out of 10^{12} bacilli will be resistant to both. The chances of its surviving host defence and causing a relapse would be meagre.

This principle of using two or more AMAs together is valid primarily for chronic infections needing prolonged therapy; has been widely employed in tuberculosis, leprosy and now adopted for *H. pylori,* HIV as well. It is of little value in most acute and short-lived infections. However, rifampin given with ciprofloxacin prevents *Staph. aureus* resistance to the latter.

4. To broaden the spectrum of antimicrobial action This is needed in:

(a) *Treatment of mixed infection* Bronchiectasis, peritonitis, certain urinary tract infections, brain abscesses, diabetic foot infection, bedsores, gynaecological infections and many orodental infections are mixed infections. Often, aerobic and anaerobic organisms sensitive to different drugs are involved. Obviously, two or more AMAs have to be used to cover the pathogens. Drugs should be chosen on the basis of bacteriological diagnosis and sensitivity pattern, and should be employed in full doses. Clindamycin or metronidazole are generally included to cover anaerobes. It may sometimes be possible to find a single agent effective against all the causative organisms.

(b) *Initial treatment of severe infections* Where bacterial diagnosis is not known; drugs covering gram-positive and gram-negative (in certain situations anaerobes as well), e.g. ampicillin + gentamicin; cephalosporin or erythromycin + an aminoglycoside ± metronidazole or clindamycin, may be given together. Rational combinations increase the certainty of curing the infection in the first attempt, but should be continued only till bacteriological data become available. When the organism and its sensitivity has been determined, severity of infection is in itself not an indication for combination therapy. Combinations should not be used as a substitute for accurate diagnosis.

(c) *Topically* Generally, AMAs which are not used systemically, are poorly absorbed from the local site and cover a broad range of gram-positive and gram-negative bacteria are combined for topical application, e.g. bacitracin, neomycin, polymyxin B.

Disadvantages of antimicrobial combinations

1. They foster a casual rather than rational outlook in the diagnosis of infections and choice of AMA.
2. Increased incidence and variety of adverse effects. Toxicity of one agent may be enhanced by another, e.g. vancomycin + tobramycin and gentamicin + cephalothin produce exaggerated kidney failure.
3. Increased chances of superinfections.
4. If inadequate doses of nonsynergistic drugs are used —emergence of resistance may be promoted.
5. Increased cost of therapy.

PROPHYLACTIC USE OF ANTIMICROBIALS

This refers to the use of AMAs for preventing the setting in of an infection or suppressing contacted infection before it becomes clinically manifest. AMAs are frequently given prophylactically; but in a number of circumstances, this is at best wasteful if not harmful. The difference between treating and preventing infections is that treatment is directed against a specific organism infecting an individual patient, while prophylaxis is often against all organisms capable of causing infection.

Antimicrobial prophylaxis is highly successful when it is directed against specific organisms, e.g. use of benzathine penicillin to prevent streptococcal infection responsible for rheumatic fever; isoniazid ± rifampicin to prevent tuberculosis in contacts, or chloroquine/mefloquine to prevent malaria in travellers to endemic areas. On the other hand, when it is intended to prevent infection in general, antibiotic prophylaxis often serves no purpose, may even be deleterious by increasing the likelihood of resistant infections. It is not possible to prevent all infections at all times in all individuals. Use of antibiotics in viral upper respiratory infections to prevent secondary bacterial invasion; to cover clean elective surgery or normal labour; to prevent chest infection in unconscious patients falls in this category.

Though the merit of antibiotic prophylaxis in certain high-risk situations has been questioned, it is frequently given in case of:

(a) Dirty contaminated wounds (e.g. from roadside accidents).

(b) Catheterization/instrumentation of urinary tract, endoscopies.

(c) Chronic obstructive lung disease: to prevent acute exacerbation.
(d) Immunocompromised patients.
(e) Surgical wound infection.

Antimicrobial prophylaxis in dentistry

This is warranted for two distinct purposes viz. (a) prevention of local wound infection, and (b) prevention of distant infection (e.g. bacterial endocarditis) in predisposed patients following dental procedures.

Prophylaxis of dental wound infection

Wound infection occurs due to microbial contamination of the surgical site. It is important for the dental surgeon to see that the wound left after tooth extraction, etc. does not get infected. Use of sterile instruments, cross-infection control measures (antiseptic/disinfectant, etc.) and good surgical technique to minimise tissue damage, haematoma and devascularization are the primary, and often the only measures needed. In addition, systemic antimicrobial prophylaxis is advocated in selected situations.

Prophylaxis should be employed only when there is a clear risk of wound infection that outweighs the possible drawbacks of antibiotic use. In general, antibiotic prophylaxis is not required for routine dental surgery, except in patients at special risk. Simple extractions and minor periodontal procedures in otherwise healthy subjects are associated with very low risk of wound infection. Incidence of postoperative infection is quite low even after difficult surgery such as removal of impacted third molar, and antimicrobial prophylaxis is not required. However, it may be given when surgery involves extensive instrumentation, bone cutting or is prolonged. It has been found that the incidence of postoperative infection is higher when oral surgery had lasted 2 hours or more. Prophylaxis should also be given for procedures in which a prosthesis is inserted into the bone or soft tissue, such as dental implants. Extensive reconstructive surgery of upper or lower jaw also warrants antibiotic prophylaxis.

All orodental procedures which disturb/damage mucosa including extractions, scaling, etc. need to be covered by prophylaxis in diabetics, corticosteroid recipients and other immunocompromised subjects.

The selection of drug, dose, timing and duration of prophylactic medication is crucial. It is important that the antibiotic is not started prematurely and is not continued beyond the time when bacteria have access to the surgical wound. Administration of the AMA has to be so timed that peak blood levels occur when clot is forming in the surgical wound. Thus, most of the oral drugs are given 1 hour before tooth extraction or other short procedures, while i.v. or i.m. drugs are given just prior to it. Most of the AMAs do not penetrate the clot once it is formed and is older than 3 hours. Thus, late and prolonged presence of the antibiotic in circulation serves no purpose, but can foster resistant organisms. In case of prolonged dental surgery, the antibiotic may be repeated i.v. during the procedure.

To be maximally effective, a relatively high dose of the AMA is selected which yields peak blood levels several times higher than MIC for the common oral pathogens. Because the resident oral flora is generally the source of the infecting organism for dental surgery wounds, the prophylactic AMA should be active against gram-positive cocci and oral anaerobes. Being bactericidal and safe, amoxicillin is generally the first choice drug. The commonly employed antibiotics for prevention of wound infection in dentistry are listed in the box.

Prophylaxis of distant infection

Injury to a mucosa that is laden with bacteria induces some of these into the bloodstream. Transient bacteraemia occurs regularly during dental extraction, scaling, intraligamentary local anaesthetic injection, root canal treatment, placement of dental implant or any other procedure in which the gingival margin is

Oral (single dose given 1 hour before procedure)

1.	Amoxicillin	2 g (50 mg/kg)	
2.	Cephalexin	2 g (50 mg/kg)	
3.	Cefadroxil	2 g (50 mg/kg)	
4.	Clindamycin (20 mg/kg)	600 mg	For patients allergic to penicillin
5.	Azithromycin (15 mg/kg)	500 mg	

Parenteral (single injection just before procedure)

1. Ampicillin 2 g (50 mg/kg) i.m/i.v
2. Cefazolin 1 g (25 mg/kg) i.v.
3. Clindamycin 600 mg (20 mg/kg) i.v. for penicillin allergic patients

manipulated. The blood-borne bacteria can cause life-threatening endocarditis in subjects with postrheumatic or congenital endocardial abnormalities such as mitral stenosis and other valvular defects, artificial heart valves or previous history of bacterial endocarditis. As such, it is imperative that the above-mentioned orodental procedures are covered with antibiotic prophylaxis in susceptible individuals.

Though prophylaxis has also been advocated by some for subjects with hip/knee joint replacement and other orthopedic prosthesis, this is considered unnecessary by others because of lack of evidence that prosthetic joint gets infected following dental procedures. However, due to serious nature of infection at these sites, prophylaxis may be given to patients at special risk such as recent joint replacement, past history of prosthetic joint infection and patients with rheumatoid arthritis.

The same antibiotics and regimens described above for prevention of dental wound infection can be employed for prophylaxis of distant infections. However, since patients with prosthetic heart valves, those with history of bacterial endocarditis in the past and those to be operated under general anaesthesia are considered to be at greater risk and have a poorer prognosis if they develop bacterial endocarditis, it has been advocated that gentamicin 120 mg (2 mg/kg) i.m./i.v. may be given just before the dental procedure in addition to amoxicillin (or its substitute) and another dose of amoxicillin 500 mg (12.5 mg/kg) be repeated 6 hours after the procedure.

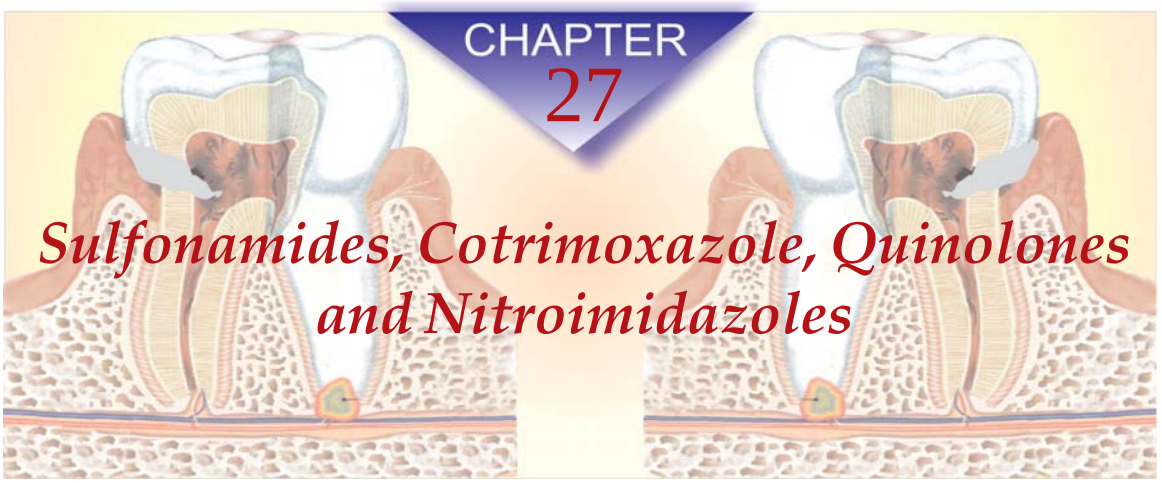
Another regimen used in patients allergic to penicillin is vancomycin 1 g (20 mg/kg) i.v. over 2 hours + gentamicin 120 mg (2 mg/kg) i.m./i.v. just before the procedure.

Antiseptic rinse with chlorhexidine (0.2%) held in the mouth for 1 minute just before dental treatment has been advocated as an adjuvant measure because it has been shown to reduce the severity of bacteraemia following dental extraction.

FAILURE OF ANTIMICROBIAL THERAPY

Antimicrobials may fail to cure an infection/fever, or there may be relapses. This is rare when antimicrobial therapy was begun, in the first place, on sound clinical and/or bacteriological basis. When a real or apparent failure of the antimicrobial regimen occurs, the diagnosis and therapy should be reviewed. One of the following causes will usually be identified:

1. Improper selection of drug, dose, route or duration of treatment.
2. Treatment begun too late.
3. Failure to take necessary adjuvant measures, e.g. drainage of abscesses, empyema, etc.; removal of renal stones, other foreign bodies; cavity closure; control of diabetes, etc.
4. Poor host defence—as in leukaemias, neutropenia and other causes; especially if bacteriostatic AMA is used.
5. Infecting organism present behind barriers, such as vegetation on heart valves (SABE), inside the eye ball, blood-brain barrier.

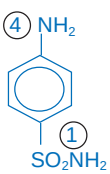


CHAPTER 27

Sulfonamides, Cotrimoxazole, Quinolones and Nitroimidazoles

SULFONAMIDES

Sulfonamides were the first antimicrobial agents (AMAs) effective against pyogenic bacterial infections. Sulfonamido-chrysoidine (Prontosil Red) was one of the dyes included by Domagk to treat experimental streptococcal infection in mice and found it to be highly effective. He subsequently cured his daughter of streptococcal septicaemia (which was 100% fatal at that time) by prontosil. By 1937, it became clear that prontosil was broken down in the body to release sulfanilamide which was the active antibacterial agent. A large number of sulfonamides were produced and used extensively, but because of rapid emergence of bacterial resistance and the availability of many safer and more effective antibiotics, their current utility is limited, except in combination with trimethoprim (as cotrimoxazole) or pyrimethamine (for malaria).



SULFANILAMIDE

Chemistry All sulfonamides may be considered to be derivatives of sulfanilamide (p-aminobenzene sulfonamide). Individual members differ in the nature of N^1 (Sulfonamido N) substitution, which governs solubility, potency and pharmacokinetic property. A free amino group in the para position (N^4) is required for antibacterial activity.

Sulfonamides that are still of clinical interest are:

1. *Short acting (4–8 hr)*: Sulfadiazine
2. *Intermediate acting (8–12 hr)*: Sulfamethoxazole, Sulfamoxole
3. *Long acting (~7 days)*: Sulfadoxine, Sulfamethopyrazine
4. *Special purpose sulfonamides*: Sulfacetamide sod., Sulfasalazine, Mafenide, Silver sulfadiazine

Antibacterial spectrum

Sulfonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria. However, bactericidal concentrations may be attained in urine. Sensitivity patterns among microorganisms have changed from time to time and place to place. Those still sensitive are:

many *Strepto. pyogenes*, *Haemophilus influenzae*, *H. ducreyi*, *Calymmatobacterium granulomatis*, *Vibrio cholerae* and a few gonococci, meningococci, pneumococci, *Escherichia coli*, and *Shigella*, but majority are resistant.

Chlamydiae: trachoma, lymphogranuloma venereum, inclusion conjunctivitis.

Actinomyces, Nocardia and *Toxoplasma*.

Mechanism of action Many bacteria synthesize their own folic acid (FA) of which p-aminobenzoic acid (PABA) is a constituent, and is taken up from the medium. Sulfonamides being structural analogues of PABA, inhibit bacterial folate synthetase → FA is not formed and a number of essential metabolic reactions suffer. Sulfonamides competitively inhibit the union of PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydrofolic acid. Also, being chemically similar to PABA, the sulfonamide may itself get incorporated to form an altered folate which is metabolically injurious.

Human cells also require FA, but they utilize preformed FA supplied in diet and are unaffected by sulfonamides. Evidences in favour of this mechanism of action of sulfonamides are:

(a) PABA, in small quantities, antagonizes the antibacterial action of sulfonamides.
(b) Only those microbes which synthesize their own FA, and cannot take it from the medium are susceptible to sulfonamides.

Pus and tissue extracts contain purines and thymidine which decrease bacterial requirement for FA and antagonize sulfonamide action. Pus is also rich in PABA.

Resistance to sulfonamides Most bacteria are capable of developing resistance to sulfonamides. Prominent among these are gonococci, pneumococci, *Staph. aureus*, meningococci, *E. coli, Shigella* and some *Strep. pyogenes, Strep. viridans* and anaerobes. The resistant mutants either:

(a) produce increased amounts of PABA, or
(b) their folate synthetase enzyme has low affinity for sulfonamides, or
(c) adopt an alternative pathway in folate metabolism.

When an organism is resistant to one sulfonamide, it is resistant to them all. No cross resistance between sulfonamides and other AMAs has been noted. Development of resistance has markedly limited the clinical usefulness of this class of compounds.

Pharmacokinetics Sulfonamides are rapidly and nearly completely absorbed from g.i.t. Extent of plasma protein binding differs considerably (10–95%) among different members. The highly protein bound members are longer acting. Sulfonamides are widely distributed in the body—enter serous cavities easily. The free form of sulfadiazine attains the same concentration in CSF as in plasma. They cross placenta freely.

The primary pathway of metabolism of sulfonamides is acetylation at N^4 by nonmicrosomal enzyme, primarily in liver. There are slow and fast acetylators, but the difference is mostly insufficient to be clinically significant. The extent of metabolism differs for different members. The acetylated derivative is inactive, but can contribute to the adverse effects. It is generally less soluble in acidic urine than the parent drug—may precipitate and cause crystalluria.

Sulfonamides are excreted mainly by the kidney through glomerular filtration. Both renal tubular secretion and reabsorption also occur. The more lipid-soluble members are highly reabsorbed in the tubule, therefore are longer acting.

Sulfadiazine It is the prototype of the general purpose sulfonamides which is rapidly absorbed orally and rapidly excreted in urine. It has good penetrability in brain and CSF—was the preferred compound for meningitis.
Dose: 0.5 g QID to 2 g TDS; SULFADIAZINE 0.5 g tab.

Sulfamethoxazole It has slower oral absorption and urinary excretion—intermediate duration of action, t½ in adults averages 10 hours. It is the preferred compound for combining with trimethoprim because the t½ of both is similar. However, a high fraction is acetylated, which is relatively insoluble—crystalluria can occur.
Dose: 1 g BD for 2 days, then 0.5 g BD.
GANTANOL 0.5 g tab.

Sulfadoxine, Sulfamethopyrazine These are ultralong acting compounds, action lasting > 1 week because of high plasma protein binding and slow renal excretion (t½ 5–9 days). They attain low plasma concentration (of free form) and are not suitable for treatment of acute

pyogenic infections. They are used in combination with pyrimethamine in the treatment of malaria, *Pneumocystis carinii* pneumonia in AIDS patients and in toxoplasmosis. Because they have caused serious cutaneous reactions, large-scale use of the combination for prophylaxis of malaria is not recommended.

Sulfacetamide sod. It is a highly soluble compound yielding neutral solution which is only mildly irritating to the eye in concentrations up to 30%. It is used topically for ocular infections due to susceptible bacteria and chlamydia.
LOCULA, ALBUCID 10%, 20%, 30% eye drops, 6% eye oint.

Sulfasalazine (*see* p.281, 308) used in ulcerative colitis and rheumatoid arthritis.

Mafenide It is not a typical sulfonamide, because a —CH_2— bridge separates the benzene ring and the amino group. It is used only topically. In contrast to typical sulfonamides, it is active in the presence of pus and against *Pseudomonas*, clostridia which are not inhibited by typical sulfonamides. It has been mainly employed for burn dressing to prevent infection, but not to treat already infected cases.

Silver sulfadiazine Used topically as 1% cream, it is active against a large number of bacteria and fungi, even those resistant to other sulfonamides, e.g. *Pseudomonas*. It slowly releases silver ions which appear to be largely responsible for the antimicrobial action. It is considered to be one of the most effective drugs for preventing infection of burnt surfaces and chronic ulcers and is well tolerated. However, it is not good for treating established infection.

Adverse effects

Adverse effects to sulfonamides are relatively common. These are:

- Nausea, vomiting and epigastric pain.
- Crystalluria is dose related but infrequent now. Precipitation in urine can be minimized by taking plenty of fluids and by alkalinizing the urine in which sulfonamides and their acetylated derivatives are more soluble.
- Hypersensitivity reactions occur in 2–5% patients. These are mostly in the form of rashes, urticaria and drug fever. Photosensitization is reported. Stevens-Johnson syndrome and exfoliative dermatitis are more common with long-acting agents.
- Hepatitis, unrelated to dose, occurs in 0.1% patients.
- Topical use of sulfonamides is not recommended because of risk of contact sensitization. However, ocular use is permitted.
- Sulfonamides cause haemolysis in a dose-dependent manner in individuals with G-6-PD deficiency. Neutropenia and other blood dyscrasias are rare.

Interactions Sulfonamides inhibit the metabolism (possibly displace from protein binding also) of phenytoin, tolbutamide and warfarin—enhance their action.
They displace methotrexate from binding and decrease its renal excretion—toxicity can occur.

Uses

Systemic use of sulfonamides alone (not combined with trimethoprim or pyrimethamine) is rare now. Though they can be employed for suppressive therapy of chronic urinary tract infection, for streptococcal pharyngitis, gum infection and as second choice drug in lymphogranuloma venereum; such uses are outmoded.

Ocular sulfacetamide sod. (10–30%) is a cheap alternative in trachoma/inclusion conjunctivitis, though additional systemic azithromycin or tetracycline therapy is required for eradication of the disease. Topical silver sulfadiazine or mafenide are used for preventing infection on burn surfaces.

COTRIMOXAZOLE

The fixed dose combination of trimethoprim and sulfamethoxazole is called *cotrimoxazole.* Trimethoprim is a diaminopyrimidine related to the antimalarial drug pyrimethamine which selectively inhibits *bacterial* dihydrofolate reductase (DHFRase). Cotrimoxazole introduced in 1969 causes sequential block of folate metabolism as depicted in Fig. 27.1. Trimethoprim is >50,000 times more active against bacterial DHFRase than against the mammalian enzyme. Thus, human folate metabolism is not interfered at antibacterial concentrations of trimethoprim. Individually, both sulfonamide and

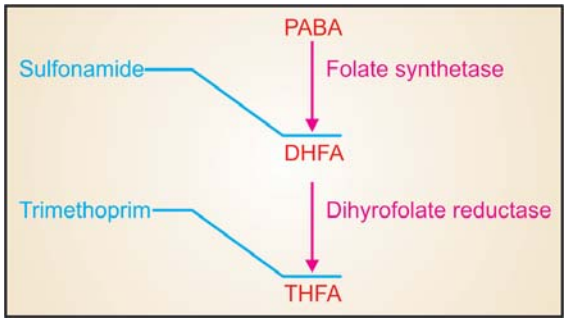


Fig. 27.1: Sequential block in bacterial folate metabolism

trimethoprim are bacteriostatic, but the combination becomes cidal against many organisms. Maximum synergism is seen when the organism is sensitive to both the components, but even when it is moderately resistant to one component, the action of the other may be enhanced.

Sulfamethoxazole was selected for combining with trimethoprim because both have nearly the same t½ (~ 10 hr). Optimal synergy in case of most organisms is exhibited at a concentration ratio of sulfamethoxazole 20 : trimethoprim 1, the MIC of each component may be reduced by 3–6 times. This ratio is obtained in the plasma when the two are given in a dose ratio of 5 : 1, because trimethoprim enters many tissues, has a larger volume of distribution than sulfamethoxazole and attains lower plasma concentration. However, the concentration ratio in many tissues is less than 20 : 1. Trimethoprim adequately crosses blood-brain barrier and placenta, while sulfamethoxazole has a poorer entry. Moreover, trimethoprim is more rapidly absorbed than sulfamethoxazole—concentration ratios may vary with time. Trimethoprim is 40% plasma protein bound, while sulfamethoxazole is 65% bound. Trimethoprim is partly metabolized in liver and excreted in urine.

Spectrum of action Antibacterial spectra of trimethoprim and sulfonamides overlap considerably. Additional organisms covered by the combination are—*Salmonella typhi*, *Serratia*, *Klebsiella*, *Enterobacter*, *Yersinia enterocolitica*, *Pneumocystis carinii* and many sulfonamide-resistant strains of *Staph. aureus*, *Strep. pyogenes*, *Shigella*, enteropathogenic *E. coli*, *H.influenzae*, gonococci and meningococci.

Resistance Bacteria are capable of acquiring resistance to trimethoprim mostly through mutational or plasmid mediated acquisition of a DHFRase having lower affinity for the inhibitor. However, resistance to the combination has been slow to develop compared to either drug alone. Widespread use of the combination has resulted in reduced responsiveness of over 20% originally sensitive strains.

Adverse effects All adverse effects seen with sulfonamides can be produced by cotrimoxazole.

- Nausea, vomiting, stomatitis, headache and rashes are the usual manifestations.
- Folate deficiency (megaloblastic anaemia) is infrequent, occurs only in patients with marginal folate levels.
- Blood dyscrasias occur rarely.

It should not be given during pregnancy: trimethoprim being an antifolate, there is theoretical teratogenic risk. Neonatal haemolysis and methaemoglobinaemia can occur if it is given near term.

- Patients with renal disease may develop uraemia. Dose should be reduced in moderately severe renal impairment.
- A high incidence (up to 50%) of fever, rash and bone marrow hypoplasia due to cotrimoxazole has been reported among AIDS patients with *Pneumocystis carinii* infection.
- The elderly are also at greater risk of bone marrow toxicity from cotrimoxazole.
- Diuretics given with cotrimoxazole have produced a higher incidence of thrombocytopenia.

Preparations SEPTRAN, SEPMAX, BACTRIM, CIPLIN, ORIPRIM, SUPRISTOL, FORTRIM

Trimethoprim	*Sulfamethoxazole*
80 mg +	400 mg tab: 2 BD for 2 days then 1 BD.
160 mg +	800 mg tab: double strength (DS); 1 BD.
20 mg +	100 mg pediatric tab.
40 mg +	200 mg per 5 ml susp; infant 2.5 ml (not to be used in newborns), children 1–5 yr 5 ml, 6–12 year 10 ml (all BD).

160 mg + 800 mg per 3 ml for i.m. injection 12 hourly. (CIPLIN, ORIPRIM-IM)
80 mg + 400 mg per 5 ml for i.v. injection (WK-TRIM, ORIPRIM-IV) 10–15 ml BD.

Cotrimazine It is a combination of trimethoprim with sulfadiazine. Its utility is similar to that of cotrimoxazole.

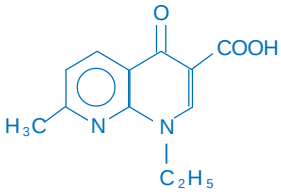
Trimethoprim *Sulfadiazine*
90 mg + 410 mg: TRIGLOBE, ULTROX tab and per 10 ml susp.; 2 tab BD for 2 days, then 1 BD.
180 mg + 820 mg: TRIGLOBE FORTE, ULTROX DS tabs.

Uses

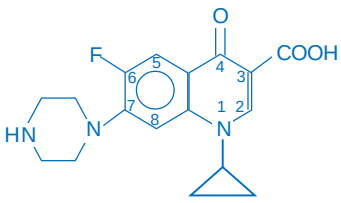
The popularity of cotrimoxazole for treatment of systemic infections has declined. It is still useful in tonsillitis, pharyngitis, sinusitis, otitis media, chronic bronchitis, etc. but is only occasionally employed for orodental infections, especially in patients allergic to β-lactam antibiotics. Urinary tract infections, both acute as well as recurrent cases and those with prostatitis are its major indications now. Many cases of bacterial diarrhoeas and dysentery respond to cotrimoxazole. Initially, it was an effective alternative to chloramphenicol for typhoid fever, but many strains of *S.typhi* are resistant now. Cotrimoxazole is an alternative drug for chancroid, granuloma inguanale and for protecting neutropenic patients. Used in high doses, it is a first line drug for *Pneumocystis carinii* pneumonia in AIDS patients.

QUINOLONES

These are synthetic antimicrobials having a quinolone structure that are active primarily against gram-negative bacteria, though newer fluorinated compounds also inhibit gram-positive ones. The first member *Nalidixic acid* introduced in mid-1960s had usefulness limited to urinary and g.i. tract infections because of low potency, modest blood and tissue levels, limited spectrum and high frequency of bacterial resistance. A breakthrough was achieved in the early 1980s by fluorination of the quinolone structure at position 6 and introduction of a piperazine



Nalidixic acid



Ciprofloxacin

substitution at position 7 resulting in derivatives called *fluoroquinolones* with high potency, expanded spectrum, slow development of resistance, better tissue penetration and good tolerability.

Nalidixic acid

It is active against gram-negative bacteria, especially coliforms: *E. coli, Proteus, Klebsiella, Enterobacter, Shigella* but not *Pseudomonas*. It acts by inhibiting bacterial DNA gyrase and is bactericidal. Resistance to nalidixic acid develops rather rapidly.

Nalidixic acid is absorbed orally, highly plasma protein bound and partly metabolized in liver: one of the metabolites is active. It is excreted in urine with a plasma t½ ~8 hrs. Concentration of the free drug in plasma and most tissues attained with the usual doses is non-therapeutic for systemic infections (MIC values for most susceptible bacteria just approach the 'break-point' concentration). However, high concentration attained in urine (20–50 times that in plasma) is lethal to the common urinary pathogens.

Adverse effects These are relatively infrequent, consist mostly of g.i. upset and rashes.
Most important toxicity is neurological—headache, drowsiness, vertigo, visual disturbances,

occasionally seizures (especially in children). Phototoxicity is rare. Individuals with G-6-PD deficiency may develop haemolysis.

Dose: 0.5–1 g TDS or QID; GRAMONEG, WINTOMYLON, URODIC, 0.5 g tab, 0.3 g/5 ml syrup.

Use: Nalidixic acid is primarily used as a urinary antiseptic. Nitrofurantoin should not be given concurrently—antagonism occurs.

It has also been employed in diarrhoea caused by *Proteus*, *E. coli*, *Shigella* or *Salmonella*.

FLUOROQUINOLONES

These are quinolone antimicrobials having one or more fluorine substitutions. The 'first generation' fluoroquinolones (FQs) introduced in 1980s have one fluoro substitution. In the 1990s, compounds with additional fluoro and other substitutions have been developed—further extending antimicrobial activity to gram-positive cocci and anaerobes, and/or confering metabolic stability (longer t½). These are referred to as 'second generation' FQs.

First generation fluoroquinolones	
Norfloxacin	Ofloxacin
Ciprofloxacin	Pefloxacin

Second generation fluoroquinolones	
Lomefloxacin	Levofloxacin
Sparfloxacin	Gatifloxacin
	Moxifloxacin

Mechanism of action The FQs inhibit the enzyme bacterial DNA gyrase, which nicks double-stranded DNA, introduces negative supercoils and then reseals the nicked ends. This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription. The DNA gyrase consists of two A and two B subunits; A subunit carries out nicking of DNA, B subunit introduces negative supercoils and then A subunit reseals the strands. FQs bind to A subunit with high affinity and interfere with its strand cutting and resealing function. Recent evidence indicates that in gram-positive bacteria the major target of FQ action is a similar enzyme *topoisomerase IV* which nicks and separates daughter DNA strands after DNA replication. Greater affinity for topoisomerase IV may confer higher potency against gram-positive bacteria. The bactericidal action probably results from digestion of DNA by exonucleases whose production is signalled by the damaged DNA.

In place of DNA gyrase or topoisomerase IV, the mammalian cells possess an enzyme topoisomerase II (that also removes positive supercoils) which has very low affinity for FQs—hence the low toxicity to host cells.

Mechanism of resistance Because of the unique mechanism of action, plasmid mediated transferable resistance probably does not occur. Resistance noted so far is due to chromosomal mutation producing a DNA gyrase or topoisomerase IV with reduced affinity for FQs, or due to reduced permeability/increased efflux of these drugs across bacterial membranes. In contrast to nalidixic acid, which selects single step resistant mutants at high frequency, FQ-resistant mutants are not easily selected. Therefore, resistance to FQs has been slow to develop. However, increasing resistance has been reported among *Salmonella*, *Pseudomonas*, staphylococci, gonococci and pneumococci.

Ciprofloxacin (prototype)

It is the most potent first generation FQ active against a broad range of bacteria, the most susceptible ones are the aerobic gram-negative bacilli, especially the Enterobacteriaceae and *Neisseria*. The MIC of ciprofloxacin against these is usually < 0.1 µg/ml, while gram-positive bacteria are inhibited at relatively higher concentrations. The spectrum of action is summarized below:

Highly susceptible

E. coli	*Neisseria gonorrhoeae*
K. pneumoniae	*N. meningitidis*

Enterobacter	*H. influenzae*
Salmonella typhi	*H. ducreyi*
Other *Salmonella*	*Campylobacter jejuni*
Shigella	*Yersinia enterocolitica*
Proteus	*Vibrio cholerae*

Moderately susceptible

Pseudomonas aeruginosa	*Legionella*
Staph. aureus (including *MRSA)*	*Brucella*
	Listeria
Staph. epidermidis	*Bacillus anthracis*
Branhamella catarrhalis	*Mycobact. tuberculosis*

Organisms which have shown low/variable susceptibility are: *Strep. pyogenes, Strep. faecalis, Strep. pneumoniae, Mycoplasma, Chlamydia, Mycobact. kansasii, Mycobact. avium.*

Notable resistant bacteria are: *Bacteroides fragilis, Clostridia*, anaerobic cocci.

The remarkable microbiological features of ciprofloxacin (also other FQs) are:

- Rapidly bactericidal activity and high potency: MBCs are close to MICs.
- Relatively long postantibiotic effect on Enterobacteriaceae, *Pseudomonas* and *Staph.*
- Low frequency of mutational resistance.
- Low propensity to select plasmid type resistant mutants.
- Protective intestinal streptococci and anaerobes are spared.
- Active against many β-lactam and aminoglycoside resistant bacteria.
- Less active at acidic pH.

Pharmacokinetics Ciprofloxacin is rapidly absorbed orally, but food delays absorption, and first pass metabolism occurs. The pharmacokinetic characteristics are given in Table 27.1. The most prominent feature of ciprofloxacin (and other FQs) is high tissue penetrability: concentration in lung, sputum, muscle, bone, prostate and phagocytes exceeds that in plasma, but CSF and aqueous levels are lower. It is excreted primarily in urine, both by glomerular filtration and tubular secretion. Urinary and biliary concentrations are 10–50-fold higher than plasma.

Adverse effects Ciprofloxacin has good safety record: side effects occur in ~10% patients, but are generally mild; withdrawal is needed only in 1.5%.

- Gastrointestinal: nausea, vomiting, bad taste, anorexia. Because gut anaerobes are not affected—diarrhoea is infrequent.
- CNS: dizziness, headache, restlessness, anxiety, insomnia, impairment of concentration and dexterity (caution while driving), tremor. Seizures are rare, occur only at high doses or when predisposing factors are present: possibly reflect GABA antagonistic action of FQs.
- Skin/hypersensitivity: rash, pruritus, photosensitivity, urticaria, swelling of lips, etc. Serious cutaneous reactions are rare.
- Tendonitis and tendon rupture: few cases are reported.

Table 27.1: Pharmacokinetic characteristics and doses of fluoroquinolones

		CIPROFL	*NORFL*	*PEFL*	*OFL*	*LEVOFL*	*LOME*	*SPAR*
1.	Oral bioavailability (%)	60–80	35–45	90–100	85–95	~100	> 90	90
2.	Plasma protein binding (%)	20–35	15	20–30	25	25	10	40
3.	Vol. of distribution (L/kg)	3–4	2	2	1.5	1.3	1.7–2.5	3.6
4.	Percent metabolized	20	25	85	5–10	5	20	60
5.	Elimination t½ (hr)	3–5	4–6	8–14	5–8	8	6–9	15–20
6.	Routes of administration	oral, i.v.	oral	oral, i.v.	oral, i.v.	oral, i.v.	oral	oral
7.	Dose (mg BD) : oral	250–750	400	400	200–400	500 (OD)	400 (OD)	200–400 (OD)
	: i.v.	100–200	—	400	200	500	—	—

On the basis of the finding that administered to immature pups ciprofloxacin (and other FQs) caused cartilage damage in weight bearing joints, the FQs have been contraindicated in children. However, under pressing situations like *Pseudomonas* pneumonia in cystic fibrosis and multi-resistant typhoid, ciprofloxacin was administered to thousands and by now millions of children in India and elsewhere. Though a few cases of joint pain and swelling have been reported, cartilage damage has not occurred. While manufacturers still label 'contraindicated in children', FQs are extensively used among them. Caution may seem prudent.

Interactions

- Plasma concentration of theophylline, caffeine and warfarin are increased by ciprofloxacin (also by norfloxacin and pefloxacin) due to inhibition of metabolism: toxicity of these drugs can occur.
- NSAIDs may enhance the CNS toxicity of FQs; seizures are reported.
- Antacids, sucralfate and iron salts given concurrently reduce absorption of FQs.

CIFRAN, CIPLOX, CIPROBID, QUINTOR, CIPROLET 250, 500, 750 mg tab, 200 mg/100 ml i.v. infusion, 3 mg/ml eye drops.

Uses Ciprofloxacin is effective in a broad range of infections including some difficult to treat ones. Because of wide spectrum bactericidal activity, oral efficacy and good tolerability, it is being extensively employed for blind therapy of any infection, but should not be used for minor cases or where gram-positive organisms and/or anaerobes are primarily causative. As such, it is not a suitable drug for majority of orodental infections. The only specific indication is infection caused by susceptible *Pseudomonas* which is rare in dental practice. Because ofloxacin, gatifloxacin and moxifloxacin are more active against gram-positive bacteria and anaerobes, they have more potential utility in dentistry. Ciprofloxacin may also be used in some mixed infections.

Ciprofloxacin is a very popular drug for many systemic infections, *viz*. urinary tract infection, bacterial gastroenteritis, typhoid fever and carrier state, gonorrhoea caused by penicillinase producing as well as nonpenicillinase producing gonococci, chancroid, skin and soft tissue infections, wound and gynaecological infections, skeletal infections, etc. It is not a primary drug for respiratory tract infections, but can be used to treat those caused by susceptible bacteria. In combination with other antibiotics, ciprofloxacin has been used for serious infections like gram-negative septicaemias, meningitis, etc. It is a frequent component of combination chemotherapy for multidrug resistant tuberculosis.

Norfloxacin It is less potent than ciprofloxacin: MIC values for most gram-negative bacteria are 2–4 times higher. Many *Pseudomonas* and gram-positive organisms are not inhibited at clinically attained concentrations. Moreover, it attains lower concentration in tissues. It is metabolized as well as excreted unchanged in urine.

Norfloxacin is primarily used for urinary and genital tract infections. It is also good for bacterial diarrhoeas.

NORBACTIN, NORFLOX 200, 400, 800 mg tab, 3 mg/ml eye drops; UROFLOX, NORILET 200, 400 mg tab.

Pefloxacin It is the methyl derivative of norfloxacin; more lipid soluble, completely absorbed orally, penetrates tissues better and attains higher plasma concentrations. Passage into CSF is greater than other FQs—preferred for meningeal infections. It is highly metabolized—partly to norfloxacin which contributes to its activity. Pefloxacin has longer t½: cumulates on repeated dosing achieving plasma concentrations twice as high as after a single dose. Because of this, it is effective in many systemic infections in addition to those of the urinary and g.i. tract. Dose of pefloxacin needs to be reduced in liver disease but not in renal insufficiency.

PELOX, 200, 400 mg tab, to be taken with meals; 400 mg/5 ml inj (to be diluted in 100–250 ml of glucose solution but not saline since it precipitates in presence of Cl^- ions), PERTI, 400 mg tab.

Ofloxacin This FQ is intermediate between ciprofloxacin and norfloxacin in activity against gram-negative bacteria, but is comparable to or more potent than ciprofloxacin for gram-positive

organisms and certain anaerobes; better suited for orodental infections. Good activity against *Chlamydia* and *Mycoplasma* has been noted: it is an alternative drug for nonspecific urethritis, cervicitis and atypical pneumonia. It also inhibits *M. tuberculosis*; can be used in place of ciprofloxacin. It is highly active against *M. leprae:* is being used in alternative multidrug therapy regimens.

Ofloxacin is relatively lipid soluble; oral bioavailability is high: attains higher plasma concentrations. Food does not interfere with its absorption. It is excreted largely unchanged in urine; dose needs to be reduced in renal failure.

Ofloxacin is comparable to ciprofloxacin in the therapy of systemic and mixed infections. It is particularly suitable for chronic bronchitis and other respiratory or ENT infections. Inhibition of theophylline metabolism is less marked.

Gonorrhoea has been treated with a single 200 mg dose. It is also useful in nongonococcal urethritis.

ZANOCIN, TARIVID 100, 200, 400 mg tab; 200 mg/100 ml i.v. infusion, ZENFLOX also 50 mg/5 ml susp.

Levofloxacin It is the levoisomer of ofloxacin having improved activity against *Strep. pneumoniae* and some other gram-positive and gram-negative bacteria. Anaerobes are moderately susceptible. Oral bioavailability of levofloxacin is nearly 100%; oral and i.v. doses are similar. It is mainly excreted unchanged and a single daily dose is sufficient.

Theophylline, warfarin, cyclosporine and zidovudine pharmacokinetics has been found to remain unchanged during levofloxacin treatment. The primary indication of levofloxacin is community-acquired pneumonia and exacerbations of chronic bronchitis. High cure rates have been noted in sinusitis, pyelonephritis and skin/soft tissue infections as well.

TAVANIC, GLEVO 500 mg tab, 500 mg/100 ml inj.

Lomefloxacin It is a second generation difluorinated quinolone more active against some gram-negative bacteria and *Chlamydia*. Because of longer t½ and persistence in tissues, it is suitable for single daily administration. It is primarily excreted unchanged in urine; dose needs to be reduced in renal insufficiency. Interaction with theophylline has not been noted, but warfarin levels are increased.

LOMEF-400, LOMEDON, LOMADAY 400 mg tab.

Sparfloxacin This second generation difluorinated quinolone has enhanced activity against gram-positive bacteria (especially *Strep. pneumoniae, Staphylococcus, Enterococcus*), *Bacteroides fragilis,* other anaerobes and mycobacteria. Its major indications include pneumonias, exacerbations of chronic bronchitis, sinusitis and other ENT infections. Reports suggest good efficacy in tuberculosis, *Mycobacterium avium* infection in AIDS patients and in leprosy. Also used for chlamydial infections. It does not alter the pharmacokinetics of theophylline and warfarin. However, it has caused a higher incidence of phototoxic reactions: recipients should be cautioned not to go out in the sun. Slight prolongation of QTc interval has been noted in 3% recipients; should be avoided in patients taking cisapride, tricyclic antidepressants, phenothiazines, class IA and class III antiarrhythmics, etc. Because of longer t½, it is suitable for single daily dosing.

TOROSPAR 200, 400 mg tab; SPARTA, SPARQUIN, SPARDAC 100, 200 mg tab.

Gatifloxacin Another 2nd generation FQ that has excellent activity against *Strep. pneumoniae,* many atypical respiratory pathogens including *Chlamydia pneumoniae* and certain anaerobes. A greater affinity for topoisomerase IV may be responsible for improved activity against gram-positive cocci. The major indication of gatifloxacin is community-acquired pneumonia, exacerbation of chronic bronchitis, and other upper/lower respiratory tract infections. Significant activity against gram-positive cocci and anaerobes has prompted its use in dental infections as well.

Dose: 400 mg on 1st day, followed by 200–400 mg OD, oral or i.v. MYGAT 200,400 mg tab, 400 mg/200 ml inj; GATIQIN 200, 400 mg tab, GAITY 200, 400 mg tab, 400 mg/40 ml inj.

Gatifloxacin has the potential to cause tachycardia and prolong QTc interval; contraindicated in hypokalaemia and with other drugs that can prolong QT. Phototoxicity, CNS effects and swelling over face are other side effects.

Moxifloxacin It is also a long-acting 2nd generation FQ having high activity against *Str. pneumoniae*, other gram-positive bacteria including β-lactam/macrolide resistant ones and some anaerobes. Bacterial topoisomerase IV is the major target of action. Moxifloxacin is primarily used for pneumonias, bronchitis, sinusitis, otitis media, etc. and has been tried in orodental infections as an alternative drug. Side effects are similar to other FQs. It should not be given to patients predisposed to seizures and to those receiving proarrhythmic drugs. Phototoxicity occurs only rarely.

Dose: 400 mg OD; MOXIF 400 mg tab.

NITROIMIDAZOLES

Metronidazole

Metronidazole, the prototype member of this class was introduced in 1959 for trichomonas vaginitis and later found to be a broad-spectrum antiprotozoal drug against *Entamoeba histolytica* and *Giardia lamblia*. Its efficacy in anaerobic bacterial infection was a chance discovery, and it is now extensively used to treat oral and other anaerobic infections. Several congeners of metronidazole have been subsequently produced, of which *Tinidazole, Secnidazole, Ornidazole* and *Satranidazole* are in clinical use. Many anaerobic bacteria, such as *Bact. fragilis, Bact. melaninogenicus, Fusobacterium, Clostridium perfringens, Cl. difficile, Peptococcus, Peptostreptococcus, Prevotella, Veillonella, Campylobacter, Helicobacter pylori* and spirochetes are susceptible to metronidazole. Though it does not directly inhibit the helminth *Dracunculus medinensis*, extraction of the worm from under the skin is facilitated. It does not affect aerobic bacteria. Clinically significant resistance has not developed among *E. histolytica*, but decreased responsiveness of *T. vaginalis* has been observed in some areas. Anaerobic bacteria can also develop metronidazole resistance, but this is not a clinical problem except in case of *H. pylori*.

Metronidazole is selectively toxic to anaerobic microorganisms. After entering the cell by diffusion, its nitro group is reduced by certain redox proteins operative only in anaerobic microbes to highly reactive nitro radical which exerts cytotoxicity by damaging DNA and other critical biomolecules. DNA helix destabilization and strand breakage has been observed in susceptible organisms. Aerobic environment attenuates cytotoxicity of metronidazole by inhibiting its reductive activation. Anaerobes which develop metronidazole resistance have been found deficient in the mechanism that generates reactive nitro radical from it.

Metronidazole has been found to inhibit cell-mediated immunity, to induce mutagenesis and to cause radiosensitization.

Pharmacokinetics Metronidazole is almost completely absorbed from the small intestines: little unabsorbed drug reaches the colon. It is widely distributed in the body, attaining therapeutic concentration in vaginal secretion, semen, saliva and CSF. It is metabolized in liver primarily by oxidation and glucuronide conjugation, and excreted in urine. Plasma t½ is 8 hrs.

Adverse effects Side effects to metronidazole are relatively frequent and unpleasant but mostly nonserious.

- Anorexia, nausea, bitter or metallic taste and abdominal cramps are the most common. Looseness of stool is occasional.
- Less frequent side effects are—headache, glossitis, dryness of mouth, dizziness, rashes and transient neutropenia.
- Prolonged administration may cause peripheral neuropathy and CNS effects. Seizures have followed very high doses.
- On i.v. injection, thromboflebitis of injected vein occurs if the solution is not well diluted.

Metronidazole is contraindicated in neurological disease, blood dyscrasias, first trimester of pregnancy (though no teratogenic effect has yet

been demonstrated, its mutagenic potential warrants caution) and chronic alcoholism.

Interactions A disulfiram-like intolerance to alcohol occurs among some patients taking metronidazole; they should be instructed to avoid drinking.

Enzyme inducers (phenobarbitone, rifampin) may reduce its therapeutic effect.

Cimetidine can reduce metronidazole metabolism: its dose may need to be decreased.

Metronidazole enhances warfarin action by inhibiting its metabolism; prothrombin time of patients taking warfarin should be monitored when metronidazole is prescribed. It has been found to decrease renal elimination of lithium.

Preparations

FLAGYL, METROGYL, METRON, ARISTOGYL ALDEZOLE 200, 400 mg tab, 200 mg/5 ml susp. (as benzoyl metronidazole: tasteless); 500 mg/100 ml i.v. infusion; UNIMEZOL 200, 400 mg tabs, 200 mg/5 ml susp.

Uses

Metronidazole in a dose of 200–400 mg TDS (15–30 mg/kg/day) is extensively used to treat orodental infections, because anaerobic bacteria are frequently involved. Certain anaerobes not inhibited by penicillin/amoxicillin are susceptible to metronidazole. It is the drug of choice for acute necrotizing ulcerative gingivitis in which it is often combined with either penicillinV, amoxicillin, erythromycin or tetracycline. The response is rapid with disappearance of the causative spirochete-fusobacterium complex from the lesions and resolution of pain, bleeding, ulceration and bad breath within 2 to 3 days. A 5-day course is often sufficient. Periodontitis, pericoronitis, acute apical infections and some endodontic infections also respond well to metronidazole given for 5–7 days. Because it is not active against aerobic and facultative bacteria, metronidazole is mostly combined with a penicillin, cephalosporin or macrolide antibiotic.

Metronidazole is an effective drug for anaerobic bacterial infections that occur at other sites as well, e.g. following colorectal/pelvic surgery, appendicectomy, brain abscesses, endocarditis, etc. Because these are serious and often mixed infections, metronidazole is generally given i.v. (15 mg/kg over 1 hr) and combined with gentamicin or a 2nd/3rd generation cephalosporin. Oral metronidazole is the drug of choice for antibiotic associated pseudomembranous enterocolitis caused by *Cl. difficile*. Used along with clarithromycin/amoxicillin and a proton pump inhibitor, metronidazole is a component of triple drug therapy for eradication of *H. pylori* in patients with peptic ulcer/nonulcer dyspepsia.

The most important clinical use of metronidazole is to treat protozoal infections. It is the drug of choice for all forms of amoebic infection, including acute dysentery, chronic intestinal amoebiasis and liver abscess. It is also a first line drug for intestinal giardiasis and trichomonas vaginitis. Nonspecific bacterial vaginosis also responds to oral metronidazole.

Tinidazole It is an equally efficacious congener of metronidazole, similar to it in every way except:

- Metabolism is slower; t½ is ~12 hours; duration of action is longer; thus, it is more suited for single dose or once daily therapy of amoebiasis, giardiasis and trichomoniasis.
- Some comparative trails in amoebiasis have reported higher cure rates.
- It is claimed to be better tolerated; the incidence of side effects is lower: metallic taste (2%), nausea (1%), rash (0.2%).

TINIBA 300, 500, 1000 mg tabs; 800 mg/400 ml i.v. infusion; TRIDAZOLE, 300, 500 mg tab; FASIGYN 0.5 g and 1 g tab.

For orodental infections, tinidazole has been used in a dose of 0.5 g (10 mg/kg) BD for 5 days. In other serious anaerobic infections the recommended dose is 2 g orally followed by 0.5 g BD for 5 days. In case oral treatment is not possible, 800 mg can be infused slowly i.v. daily till oral therapy is instituted. A single 2 g (oral) or 0.8 g (i.v.) dose is given for prophylaxis of anaerobic infection before colorectal surgery.

Secnidazole A congener of metronidazole with the same spectrum of activity and potency.

Absorption after oral administration is rapid and complete, but metabolism is slower resulting in a plasma t½ of 17–29 hours. A single 2 g dose has been found to yield cure rates equal to multiple doses of metronidazole and tinidazole. Side effect profile is similar to metronidazole and reported incidence is 2–10%. It has not been used in dentistry to any significant extent.

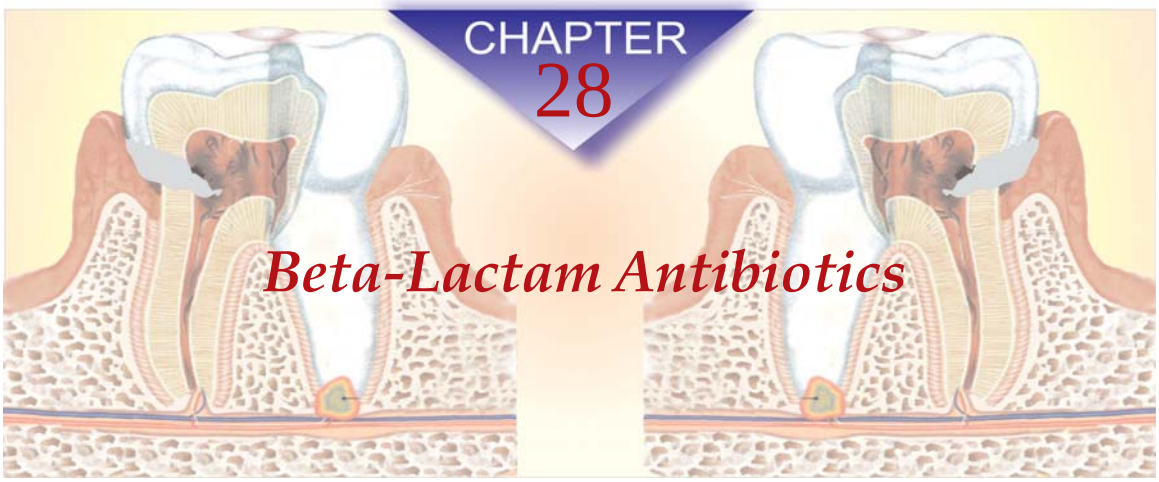
SECNIL, SECZOL 0.5, 1.0 g tabs; NOAMEBA-DS 1.0 g tab.

Ornidazole Activity similar to metronidazole, but it is slowly metabolized—has longer t½ (12–14 hr). Dose and duration of regimens for amoebiasis, giardiasis, trichomoniasis, anaerobic infections and bacterial vaginosis resemble those for tinidazole. Side effect profile is also similar.

DAZOLIC 500 mg tab, 500 mg/100 ml vial for i.v. infusion.
ORNIDA 500 mg tab, 125 mg/5 ml susp.

Satranidazole Another nitroimidazole having longer t½ (14 hr) and greater potency. Advantages claimed are: better tolerability—no nausea, vomiting or metallic taste, absence of neurological and disulfiram-like reactions and that it does not produce the acetamide metabolite which is a weak carcinogen. Its role in dental infections has not been defined.

SATROGYL 300 mg tab.



CHAPTER 28

Beta-Lactam Antibiotics

These are antibiotics having a β-lactam ring. The two major groups are penicillins and cephalosporins that are the most commonly used antibiotics in dentistry. Monobactams and carbapenems are the newer additions.

PENICILLINS

Penicillin was the first antibiotic to be used clinically in 1941. It is a miracle that the least toxic drug of its kind was the first to be discovered. It was originally obtained from the fungus *Penicillium notatum*, but the present source is a high yielding mutant of *P. chrysogenum*.

Chemistry and properties The penicillin nucleus consists of fused thiazolidine and β-lactam rings to which side chains are attached through an amide linkage (Fig. 28.1). Penicillin G (PnG), having a benzyl side chain (at R), is the original penicillin used clinically.

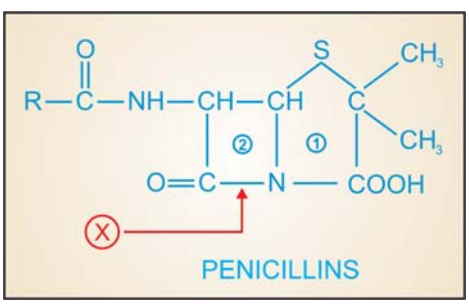


Fig. 28.1: Chemical structure of penicillins. (1) Thiazolidine ring; (2) Beta-lactam ring; (X) Bond which is broken by penicillinase

The side chain of natural penicillin can be split off by an amidase to produce 6-aminopenicillanic acid. Other side chains can then be attached to it resulting in different semisynthetic penicillins with unique antibacterial activities and different pharmacokinetic profiles.

At the carboxyl group attached to the thiazolidine ring, salt formation occurs with Na^+ and K^+; these salts are more stable than the parent acid. Sod. PnG is highly water soluble. It is stable in the dry state, but solution deteriorates rapidly at room temperature, though remains stable at 4°C for 3 days. Therefore, PnG solutions are always prepared freshly. PnG is also thermolabile and acid labile.

Unitage 1 U of crystalline sod. benzyl penicillin = 0.6 µg of the standard preparation. Thus 1 g = 1.6 million units or 1 MU = 0.6 g.

Mechanism of action

All β-lactam antibiotics interfere with the synthesis of bacterial cell wall. The bacteria synthesize UDP-N-acetyl muramic acid pentapeptide, called 'Park nucleotide' (because Park in 1957 found it to accumulate when susceptible *Staphylococcus* was grown in the presence of penicillin) and UDP-N-acetyl glucosamine. The peptidoglycan residues are linked together forming long strands

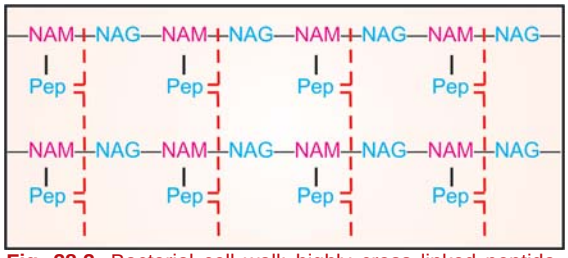


Fig. 28.2: Bacterial cell wall: highly cross linked peptidoglycan structure; NAM— N-acetyl muramic acid, NAG— N-acetyl glucosamine, Pep— Tetrapeptide

and UDP is split off. The final step is cleavage of the terminal D-alanine of the peptide chains by transpeptidases; the energy so released is utilized for establishment of cross linkages between peptide chains of the neighbouring strands (Fig. 28.2). This cross linking provides stability and rigidity to the cell wall.

The β-lactam antibiotics inhibit the transpeptidases so that cross linking (which maintains the close knit structure of the cell wall) does not take place. These enzymes and related proteins constitute the *penicillin binding proteins (PBPs)* which have been located in the bacterial cell membrane. Each organism has several PBPs and PBPs obtained from different species differ in their affinity towards different β-lactam antibiotics. This fact probably explains their differing sensitivity to the various β-lactam antibiotics.

When bacteria divide in the presence of a β-lactam antibiotic—cell wall deficient (CWD) forms are produced. Because the interior of the bacterium is hyperosmotic, the CWD forms swell and burst → bacterial lysis. This is how β-lactam antibiotics exert bactericidal action. Under certain conditions and in case of certain organisms, bizarre shaped or filamentous forms, which are incapable of multiplying, result. Grown in hyperosmotic medium, globular 'giant' forms or *protoplasts* are produced. Lytic effect of these antibiotics may also be due to derepression of some bacterial autolysins which normally function during cell division.

Rapid cell wall synthesis occurs when the organisms are actively multiplying; β-lactam antibiotics are more lethal in this phase.

The peptidoglycan cell wall is unique to bacteria. No such substance is synthesized (particularly, D-alanine is not utilized) by higher animals. This is why penicillin is practically nontoxic to man.

In gram-positive bacteria, the cell wall is almost entirely made of peptidoglycan, which is >50 layers thick and extensively cross linked, so that it may be regarded as a single giant mucopeptide molecule. In gram-negative bacteria, it consists of alternating layers of lipoprotein and peptidoglycan (each layer 1–2 molecule thick with little cross linking). This may be the reason for higher susceptibility of the gram-positive bacteria to PnG.

Blood, pus, and tissue fluids do not interfere with the antibacterial action of β-lactam antibiotics.

PENICILLIN-G (BENZYL PENICILLIN)

Antibacterial spectrum PnG is a narrow spectrum antibiotic; activity is limited primarily to gram-positive bacteria and few others.

Cocci: *Streptococci* (except *viridans*, group D or enterococci) are highly sensitive, so are many pneumococci. *Staph. aureus*, though originally very sensitive, has acquired resistance to such an extent that it must be counted out of PnG spectrum. Gram-negative cocci—*Neisseria gonorrhoeae* and *N. meningitidis* are susceptible to PnG, though increasing number of gonococci have developed partial and others high degree resistance.

Bacilli: Gram-positive bacilli—majority of *B. anthracis, Corynebacterium diphtheriae,* and practically all *Clostridia (tetani* and others), *Listeria* are highly sensitive, so are spirochetes (*Treponema pallidum* and others), but *Bacteroides fragilis* is largely resistant, though *Bact. melaninogenicus* is susceptible. Other anaerobes involved in orodental infections and responsive to PnG are fusobacteria, peptostreptococci, *Eubacterium*, *Campylobacter*, *Prevotella* and *Porphyromonas*.

Actinomyces israelii is only moderately sensitive. Majority of gram-negative bacilli (except a few

E. coli, Proteus), *Mycobacterium tuberculosis*, rickettsiae, chlamydiae, protozoa, fungi and viruses are totally insensitive to PnG.

Bacterial resistance Many bacteria are inherently insensitive to PnG because in them the target enzymes and PBPs are located deeper under lipoprotein barrier where PnG is unable to penetrate or have low affinity for PnG. The primary mechanism of acquired resistance is production of penicillinase.

Penicillinase It is a narrow spectrum β-lactamase which opens the β-lactam ring and inactivates PnG and some closely related congeners. Majority of *Staphylococci* and some strains of gonococci, *B. subtilis, E. coli, H. influenzae* and few other bacteria produce penicillinase. The gram-positive penicillinase producers elaborate large quantities of the enzyme which diffuses into the surroundings and can protect other inherently sensitive bacteria. In gram-negative bacteria, penicillinase is found in small quantity, but is strategically located inbetween the lipoprotein and peptidoglycan layers of the cell wall. Staphylococcal penicillinase is inducible, and methicillin is an important inducer; while in gram-negative organisms, it is mostly a constitutive enzyme.

Some resistant bacteria become *penicillin tolerant* and not penicillin destroying. Their target enzymes are altered to have low affinity for penicillin, e.g. highly resistant pneumococci isolated in some areas have altered PBPs. The methicillin-resistant *Staph. aureus* (MRSA) have acquired a PBP which has very low affinity for β-lactam antibiotics. The low level penicillin-resistant gonococci are less permeable to the drug, while high degree resistant ones produce penicillinase, as do highly resistant *H. influenzae*. Both these appear to have acquired the penicillinase plasmid by conjugation or transduction and then propagated by selection.

The gram-negative bacteria have 'porin' channels formed by specific proteins located in their outer membrane. Permeability of various β-lactam antibiotics through these channels differs: ampicillin and other members which are active against gram-negative bacteria cross the porin channels much better than PnG. Some gram-negative bacteria become resistant by loss or alteration of porin channels.

Pharmacokinetics

Penicillin G is acid labile—destroyed by gastric acid. As such, less than 1/3rd of an oral dose is absorbed in the active form. A larger fraction is absorbed by infants and the elderly because of lower gastric acidity. Absorption of sod. PnG from i.m. site is rapid and complete; peak plasma level is attained in 30 min. It is distributed mainly extracellularly; reaches most body fluids, but penetration in serous cavities and CSF is poor. However, in the presence of inflammation (sinovitis, meningitis, etc.) adequate amounts may reach these sites. About 60% is plasma protein bound. It is little metabolized because of rapid excretion.

The pharmacokinetics of PnG is dominated by very rapid renal excretion; about 10% by glomerular filtration and the rest by tubular secretion. The plasma t½ of PnG in healthy adult is 30 min. Neonates have imperfect tubular secretion—t½ is longer; it approaches adult value at 3 months and then is even shorter during childhood. Aged and those with renal failure excrete penicillin slowly. Tubular secretion of PnG can be blocked by probenecid—higher and longer lasting plasma concentrations are achieved. Probenecid has also been shown to decrease the volume of distribution of penicillins.

Preparations and dose

1. *Sod. penicillin G (crystalline penicillin) injection*: 0.5–5 MU i.m./i.v. 6–12 hourly. It is available as dry powder in vials to be dissolved in sterile water at the time of injection.

BENZYL PEN 0.5, 1 MU inj.

Repository penicillin G injections These are insoluble salts of PnG which must be given by deep i.m. (never i.v.) injection. They release PnG

slowly at the site of injection, which then meets the same fate as soluble PnG.

1. *Procaine penicillin G inj.* 0.5–1 MU i.m. 12–24 hourly as aqueous suspension. Plasma concentrations attained are lower, but are sustained for 1–2 days; PROCAINE PENICILLIN-G 0.5, 1 MU dry powder in vial.

Fortified procaine penicillin G inj: contains 3 lac U procaine penicillin and 1 lac U sod. penicillin G to provide rapid as well as sustained blood levels. FORTIFIED P.P. INJ 3+1 lac U vial.

2. *Benzathine penicillin G* 0.6–2.4 MU i.m. every 2–4 weeks as aqueous suspension. It releases penicillin extremely slowly—plasma concentrations are very low but remain effective for prophylactic purposes for up to 4 weeks. PENIDURE-LA (long acting), LONGACILLIN, PENCOM, 0.6, 1.2, 2.4 MU as dry powder in vial.

Adverse effects

PenicillinG is one of the most nontoxic antibiotics; up to 100 MU (60 g) has been injected in a day without any direct toxicity.

Local irritancy and direct toxicity Pain at i.m. injection site, nausea on oral ingestion and thrombophlebitis of injected vein are dose-related expressions of irritancy.

Toxicity to the brain may be manifested as mental confusion, muscular twitchings, convulsions and coma, when very large doses (> 20 MU) are injected i.v.; especially in patients with renal insufficiency. Bleeding has also occurred with such high doses due to interference with platelet function. Intrathecal injection of PnG is no longer recommended because it has caused arachnoiditis and degenerative changes in spinal cord. Accidental i.v. injection of procaine penicillin produces CNS stimulation, hallucinations and convulsions due to procaine. Being insoluble, it may also cause microembolism.

Hypersensitivity These reactions are the major problem in the use of penicillins. An incidence of 1–10% is reported. Individuals with an allergic diathesis are more prone to develop penicillin reactions. PnG is the most common drug implicated in drug allergy.

Frequent manifestations are—rash, itching, urticaria and fever. Wheezing, angioneurotic edema, serum sickness and exfoliative dermatitis are less common. Anaphylaxis is rare (1 to 4 per 10,000 patients) but may be fatal. Fear of causing anaphylactic shock has severely restricted the use of injected PnG in general practice.

All forms of natural and semisynthetic penicillins can cause allergy, but it is more commonly seen after parenteral than oral administration. Incidence is highest with procaine penicillin: procaine is itself allergenic. The course of penicillin hypersensitivity is unpredictable, i.e. an individual who tolerated penicillin earlier may show allergy on subsequent administration and *vice versa*.

There is partial cross sensitivity between different types of penicillins; an individual who has exhibited immediate type of hypersensitivity—urticaria, angioedema, bronchospasm, anaphylaxis or serum sickness with one penicillin should not be given any other type of penicillin. However, if the earlier reaction had been only a rash, penicillin may be given cautiously—often no untoward effect is seen. History of penicillin allergy must be elicited before injecting it. A scratch test or intradermal test (with 2–10 U) may be performed first. On occasions, this itself has caused fatal anaphylaxis. Testing with benzylpenicilloyl-polylysine is safer. However, a negative intradermal test does not rule out delayed hypersensitivity. It should also be realised that presence of antibodies to penicillin does not mean allergy to it, because practically everyone who receives penicillin develops antibodies to it.

For the development of antibodies, penicillin or a product of it (mostly penicilloyl moiety—major determinant) acts as a hapten. There are many minor determinants as well.

Topical use of penicillin is highly sensitizing (contact dermatitis and other reactions). Therefore, all topical preparations of penicillin (inclu-

ding eye ointment) have been banned, except for use in eye as solution in case of gonococcal ophthalmia.

If a patient is allergic to penicillin, it is best to use an alternative antibiotic. Hyposensitization by the injection of increasing amounts of penicillin intradermally at hourly intervals may be tried if there is no other choice.

Superinfections These are rare with PnG because of its narrow spectrum; though bowel, respiratory and cutaneous microflora does undergo changes.

Jarisch-Herxheimer reaction Penicillin injected in a syphilitic patient (particularly secondary syphilis) may produce shivering, fever, myalgia, exacerbation of lesions, even vascular collapse. This is due to sudden release of spirochetal lytic products and lasts for 12–72 hours. It does not recur and does not need interruption of therapy. Aspirin and sedation afford relief of symptoms.

Uses

Penicillin G is the drug of choice for infections caused by organisms susceptible to it, unless the patient is allergic to this antibiotic. However, use has declined very much due to fear of causing anaphylaxis.

1. Dental infections Parenteral PnG remains effective in majority of common infections encountered in dentistry, particularly those arising as a sequelae of carious lesions and are caused by both aerobic and anaerobic bacteria. At ordinary doses {0.5 – 2 MU i.m. 6 hourly (sod. PnG) or 12–24 hourly (procaine PnG)} it can be used for periodontal abscess, periapical abscess, pericoronitis, acute suppurative pulpitis, necrotizing ulcerative gingivitis, oral cellulitis, etc. Penicillin G can also be employed prophylactically to cover dental procedures in predisposed patients. However, many originally susceptible oral pathogens have acquired penicillin resistance and dental (as well as medical) practitioners are too scared to inject PnG unless there is no other choice. Therefore, in dental practice, use of PnG is very much restricted.

2. General medical uses Other medical conditions treated with PnG are:

a. Streptococcal infections: pharyngitis, tonsillitis, otitis media, scarlet fever, rheumatic fever, etc. For bacterial endocarditis caused by viridans streptococci, high doses (20–40 MU/day) are required in combination with gentamicin.
b. Pneumococcal infections (pneumonia, meningitis) only if the infecting strain is found to be sensitive to PnG.
c. Meningococcal meningitis and other infections.
d. Gonorrhoea caused by nonpenicillinase producing *N. gonorrhoeae* that are still sensitive to PnG.
e. Syphilis: benzathine penicillin is the drug of choice for all stages because *T. pallidum* has not developed penicillin resistance.
f. Diphtheria , tetanus and other rare infections like gas gangrene, anthrax, actinomycosis.

Prophylactic uses of PnG are:

- To prevent recurrence of rheumatic fever: benzathine penicillin is the preparation of choice.
- Surgical prophylaxis (in combination with gentamicin).
- To protect agranulocytosis patients (an aminoglycoside may also be given).

SEMISYNTHETIC PENICILLINS

Semisynthetic penicillins are produced by chemically combining specific side chains (in place of benzyl side chain of PnG) or by incorporating specific precursors in the mould cultures. Thus, procaine penicillin and benzathine penicillin are salts of PnG and *not* semisynthetic penicillins. The aim of producing semisynthetic penicillins has been to overcome the shortcomings of PnG, which are:

1. Poor oral efficacy.
2. Susceptibility to penicillinase.
3. Narrow spectrum of activity.
4. Hypersensitivity reactions (this has not been overcome in any preparation).

In addition, some β-lactamase inhibitors have been developed which themselves are not antibacterial but augment the activity of penicillins against β-lactamase producing organisms.

CLASSIFICATION

1. *Acid-resistant alternative to penicillin G* Phenoxymethyl penicillin (Penicillin V).
2. *Penicillinase-resistant penicillins* Methicillin, Cloxacillin.
3. *Extended spectrum penicillins*
   (a) *Aminopenicillins:* Ampicillin, Bacampicillin, Amoxicillin.
   (b) *Carboxypenicillins*: Carbenicillin, Ticarcillin.
   (c) *Ureidopenicillins*: Piperacillin, Mezlocillin.

β-*lactamase inhibitors* Clavulanic acid, Sulbactam.

ACID-RESISTANT ALTERNATIVE TO PENICILLIN-G

Phenoxymethyl penicillin (Penicillin V) It differs from PnG only in that it is acid stable; oral absorption is better; peak blood level is reached in 1 hour and plasma t½ is 30–60 min.

The antibacterial spectrum of penicillin V is identical to that of PnG, but it is about 1/5 the as active against *Neisseria*, other gram-negative bacteria and anaerobes. Oral penicillinV is a suitable drug to treat majority of nonserious dental infections and trench mouth. However, it cannot be depended upon for more serious infections. Other conditions treated with penicillin V are streptococcal pharyngitis, sinusitis, otitis media and minor pneumococcal infections. It can be employed for prophylaxis of rheumatic fever when an oral drug has to be selected.

Dose: 250–500 mg, infants 60 mg, children 125–250 mg; given 6 hourly, (250 mg = 4 lac U). CRYSTAPEN-V, KAYPEN, 125, 250 mg tab, 125 mg/5 ml dry syr—for reconstitution., PENIVORAL 65, 130 mg tab.

PENICILLINASE-RESISTANT PENICILLINS

These congeners have side chains that protect the β-lactam ring from attack by staphylococcal penicillinase. However, this also partially protects the bacteria from the β-lactam ring: nonpenicillinase producing organisms are less sensitive to these drugs than to PnG. Their only indication is infections caused by penicillinase producing *Staphylococci* for which they are the drugs of choice except in areas where methicillin-resistant *Staph. aureus* (MRSA) has become prevalent. They are not resistant to gram-negative β-lactamases.

Methicillin It is highly penicillinase resistant but not acid resistant—must be injected. It is also an inducer of penicillinase production.

Methicillin-resistant *Staph. aureus* (MRSA) have emerged in many areas. These are insensitive to all penicillinase-resistant penicillins and to other β-lactams as well as to erythromycin, aminoglycosides and tetracyclines. They have altered PBPs which do not bind penicillins. The drug of choice for these organisms is vancomycin/linezolid, but ciprofloxacin can also be used.

Haematuria, albuminuria and reversible interstitial nephritis are the specific adverse effects of methicillin. It has been largely replaced by cloxacillin.

Cloxacillin It has an isoxazolyl side chain and is highly penicillinase as well as acid resistant. It is less active against PnG sensitive organisms: should not be used as its substitute. It is more active than methicillin against penicillinase producing *Staph*, but not against MRSA. Because staphylococcal infections are rare in the oral cavity, cloxacilin is infrequently used in dentistry.

Cloxacillin is incompletely but dependably absorbed from oral route, especially if taken in empty stomach. It is > 90% plasma protein bound. Elimination occurs primarily by kidney, also partly by liver. Plasma t½ is about 1 hour.

Dose: 0.25–0.5 g orally every 6 hours; for severe infections 0.25–1 g may be injected i.m. or i.v.—higher blood levels are produced.

KLOX 0.25, 0.5 g cap, 125 mg/3 g dry syr, 0.25, 0.5 g inj; BIOCLOX, CLOCILIN 0.25, 0.5 g cap; 0.25, 0.5 g/vial inj.

Oxacillin, Dicloxacillin, Flucloxacillin (Floxacillin) are other isoxazolyl penicillins, similar to cloxacillin.

EXTENDED SPECTRUM PENICILLINS

These semisynthetic penicillins are active against a variety of gram-negative bacilli as well. They can be grouped according to their spectrum of activity.

1. Aminopenicillins

This group, led by ampicillin, has an amino substitution in the side chain. Some are prodrugs and all have quite similar antibacterial spectra. None is resistant to penicillinase or to other β-lactamases.

Ampicillin It is active against all organisms sensitive to PnG; in addition, many gram-negative bacilli, e.g. *H. influenzae, E. coli, Proteus, Salmonella* and *Shigella* are inhibited. However, due to widespread use, many of these have developed resistance; usefulness of this antibiotic has decreased considerably.

Ampicillin is more active than PnG for *Strep. viridans* and enterococci; equally active for pneumococci, gonococci and meningococci (penicillin-resistant strains are resistant to ampicillin as well); but less active against other gram-positive cocci. Penicillinase producing *Staph.* are not affected, as are other gram-negative bacilli, such as *Pseudomonas, Klebsiella*, indole positive *Proteus* and anaerobes like *Bacteroides fragilis.*

Pharmacokinetics Ampicillin is not degraded by gastric acid; oral absorption is incomplete but adequate. Food interferes with absorption. It is partly excreted in bile and reabsorbed—enterohepatic circulation occurs. However, primary channel of excretion is kidney, but tubular secretion is slower than for PnG; plasma t½ is 1 hour.

Dose: 0.5–2 g oral/i.m./i.v. depending on severity of infection, every 6 hours; children 25–50 mg/kg/day.

AMPILIN, ROSCILLIN, BIOCILIN 250, 500 mg cap; 125, 250 mg/5 ml dry syr; 100 mg/ml pediatric drops; 250, 500 mg and 1.0 g per vial inj.

Uses

Because of their broader spectrum of action covering both gram-positive and gram-negative aerobic as well as anaerobic bacteria that are mostly causative agents of dental infections, aminopenicillins are one of the commonest antibiotics used in dentistry. Amoxicillin is generally preferred over ampicillin because it produces higher and more sustained blood levels as well as a lower incidence of diarrhoea, but ampicillin can be used for the same indications.

The general medical indications of ampicillin are:

1. Urinary tract infections: response rate has declined now due to emergence of resistant strains.
2. Respiratory tract infections: bronchitis, sinusitis, otitis media, etc.
3. Meningitis: not as dependable now due to resistance; a 3rd generation cephalosporin or chloramphenicol is combined with it.
4. Gonorrhoea caused by nonpenicillinase producing *N. gonorrhoeae* can be treated with a single oral dose 3.5 g + 1 g probenecid.
5. Bacillary dysentery due to *Shigella*: fewer cases respond now.
6. Typhoid fever: infrequently used now due to widespread resistance.
7. Cholecystitis: responds well.
8. Subacute bacterial endocarditis: preferred over PnG.
9. Septicaemias: combined with gentamicin or 3rd generation cephalosporin.

Adverse effects Diarrhoea is frequent after oral administration of ampicillin. It is incompletely absorbed—the unabsorbed drug irritates the lower intestines as well as causes marked alteration of bacterial flora.

It produces a high incidence (up to 10%) of rashes, especially in patients with AIDS, EB virus infections or lymphatic leukaemia. Concurrent administration of allopurinol also increases the incidence of rashes. Sometimes, the rashes may not be allergic but toxic in nature.

Patients with a history of immediate type of hypersensitivity to PnG should not be given ampicillin as well.

Interactions Hydrocortisone inactivates ampicillin if mixed in the i.v. solution.

By inhibiting colonic flora, it may interfere with deconjugation and enterohepatic cycling of oral contraceptives → failure of oral contraception.

Probenecid retards renal excretion of ampicillin.

Bacampicillin It is an ester of ampicillin which is nearly completely absorbed from the g.i.t. It is a prodrug and is largely hydrolysed during absorption. Thus, higher plasma levels are attained. Tissue penetration is also claimed to be better. It does not markedly disturb intestinal ecology—incidence of diarrhoea is claimed to be lower.

Dose: 400–800 mg BD; PENGLOBE 200, 400 mg tab.

Note: A fixed dose combination of ampicillin + cloxacillin (AMPILOX and others) containing 250 mg of each per cap or per vial inj. is vigorously promoted for postoperative, skin and soft tissue, respiratory, urinary and other infections. This combination is not synergistic since cloxacillin is not active against gram-negative bacteria and does not inhibit gram-negative β-lactamases, while ampicillin is not active against staphylococci. Thus, for any given infection, one of the components is useless but adds to the cost and adverse effects. Since the amount of the drug which is actually going to act in any individual patient is halved (when the combination is used), efficacy is reduced and chances of selecting resistant strains is increased. Both drugs are ineffective against MRSA. As such, this combination is needed only when mixed staphylococcal and gram-negative infection is proven, which is very infrequent. Blind therapy with this combination is irrational and harmful.

Amoxicillin It is a close congener of ampicillin (but not a prodrug); similar to it in all respects except:

- Oral absorption is better; food does not interfere with absorption; higher and more sustained blood levels are produced.
- Incidence of diarrhoea is less.
- It is less active against *Shigella* and *H. influenzae.*

Many physicians now prefer it over ampicillin for typhoid, bronchitis, urinary infections, SABE and gonorrhoea. Amoxicillin is one of the most frequently used antibiotics for treatment of dental infections since majority of cases resolve with 250–500 mg TDS given for 5 days. It is also the first choice drug for prophylaxis of local wound infection as well as distant infection (endocarditis) following dental surgery in susceptible patients (*see* p 366).

Dose: 0.25–1 g TDS oral/i.m.; AMOXYLIN, NOVAMOX, SYNAMOX 250, 500 mg cap, 125 mg/5 ml dry syr. AMOXIL, MOX 250, 500 mg caps; 125 mg/5 ml dry syr; 250, 500 mg/vial inj. MOXYLONG: Amoxicillin 250 mg + probenecid 500 mg tab (also 500 mg + 500 mg DS tab).

2. Carboxy penicillins

Carbenicillin The special feature of this penicillin congener is its activity against *Pseudomonas aeruginosa* and indole positive *Proteus* which are not inhibited by PnG or aminopenicillins. It is less active against *Salmonella*, *E. coli* and *Enterobacter*, while *Klebsiella* and gram-positive cocci are unaffected by it. *Pseudomonas* strains less sensitive to carbenicillin have developed in some areas, especially when inadequate doses have been used.

Carbenicillin is neither penicillinase resistant nor acid resistant. It is inactive orally and is excreted rapidly in urine (t½ 1 hr). It is used as sodium salt in a dose of 1–2 g i.m. or 1–5 g i.v. every 4–6 hours. At the higher doses, enough Na may be administered to cause fluid retention and CHF in patients with borderline renal or cardiac function.

High doses have also caused bleeding by interferring with platelet function. This appears to result from perturbation of agonist receptors on platelet surface.

PYOPEN, CARBELIN 1 g, 5 g, per vial inj.

The indications for carbenicillin are—serious infections caused by *Pseudomonas* or *Proteus*, e.g. burns, urinary tract infection, septicaemia, but piperacillin is now preferred. It is often used together with gentamicin. Orodental infections are rarely caused by *Pseudomonas*; if at all they occur in immunocompromised patients. These may be treated with carbenicillin or piperacillin.

Ticarcillin It is more potent than carbenicillin against *Pseudomonas*, but other properties are similar to it.

3. Ureidopenicillins

Piperacillin This antipseudomonal penicillin is about 8 times more active than carbenicillin. It has good activity against *Klebsiella* and is used mainly in neutropenic/immunocompromised patients having serious gram-negative infections and in burns. Elimination t½ is 1 hour. Concurrent use of gentamicin or tobramycin is advised.

Dose: 100–150 mg/kg/day in 3 divided doses (max 16 g/day) i.m. or i.v. The i.v. route is preferred when > 2 g is to be injected.

PIPRAPEN 1 g, 2 g vials; PIPRACIL 2 g, 4 g vials for inj; contains 2 mEq Na^+ per g.

Mezlocillin It has activity similar to ticarcillin against *Pseudomonas* and inhibits *Klebsiella* as well. It is given parenterally primarily for infections caused by enteric bacilli.

BETA-LACTAMASE INHIBITORS

β-lactamases are a family of enzymes produced by many gram-positive and gram-negative bacteria that inactivate β-lactam antibiotics by opening the β-lactam ring. Different β-lactamases differ in their substrate affinities. Two inhibitors of this enzyme *clavulanic acid* and *sulbactam* are available for clinical use.

Clavulanic acid Obtained from *Streptomyces clavuligerus*, it has a β-lactam ring but no antibacterial activity of its own. It inhibits a wide variety (class II to class V) of β-lactamases (but not class I cephalosporinase) produced by both gram-positive and gram-negative bacteria.

Clavulanic acid is a 'progressive' inhibitor: binding with β-lactamase is reversible initially, but becomes covalent later—inhibition increasing with time. Called a 'suicide' inhibitor, it gets inactivated after binding to the enzyme. It permeates the outer layers of the cell wall of gram-negative bacteria and inhibits the periplasmically located β-lactamase.

Pharmacokinetics Clavulanic acid has rapid oral absorption and a bioavailability of 60%; can also be injected. Its elimination t½ of 1 hr and tissue distribution matches amoxicillin with which it is used (called coamoxiclav). However, it is eliminated mainly by glomerular filtration and its excretion is not affected by probenecid. Also, it is largely hydrolysed and decarboxylated before excretion, while amoxicillin is primarily excreted unchanged by tubular secretion.

Uses Addition of clavulanic acid re-establishes the activity of amoxicillin against β-lactamase producing resistant *Staph. aureus* (but not MRSA that have altered PBPs), *Peptococcus*, *H. influenzae*, *N. gonorrhoeae*, *E. coli*, *Proteus*, *Klebsiella*, *Salmonella*, *Shigella* and *Bact. fragilis*. Amoxicillin sensitive strains are not affected by the addition of clavulanic acid. Coamoxiclav is indicated for:

- Skin and soft tissue infections, intra-abdominal and gynaecological sepsis, urinary, biliary and respiratory tract infections: especially when empiric antibiotic therapy is to be given for hospital-acquired infections.
- Dental infections caused by β-lactamase producing bacteria.
- Gonorrhoea (including PPNG), single dose amoxicillin 3 g + clavulanic acid 0.5 g + probenecid 1 g is highly curative.

AUGMENTIN, ENHANCIN, AMONATE: Amoxicillin 250 mg + clavulanic acid 125 mg tab; 1–2 tab TDS, severe infections 4 tabs 6 hourly.

Also AUGMENTIN: Amoxicillin 1 g + clavulanic acid 0.2 g vial and 0.5 g + 0.1 g vial; inject 1 vial deep i.m. or i.v. 6–8 hourly for severe infections.

It is more expensive than amoxicillin alone.

Adverse effects are the same as for amoxicillin alone; g.i. tolerance is poorer—especially in children. Other side effects are *Candida* stomatitis/vaginitis and rashes. Some cases of hepatic injury have been reported with the combination.

Sulbactam It is a semisynthetic β-lactamase inhibitor, related chemically as well as in activity to clavulanic acid. It is also a progressive inhibitor, highly active against class II to V but poorly active against class I β-lactamase. On weight basis, it is 2–3 times less potent than clavulanic acid for most types of the enzyme, but the same level of inhibition can be obtained at the higher concentrations achieved clinically. Sulbactam does not induce chromosomal β-lactamases, while clavulanic acid can induce some of them.

Oral absorption of sulbactam is inconsistent. Therefore, it is preferably given parenterally. It has been combined with ampicillin for use against β-lactamase producing resistant strains. Absorption of its complex salt with ampicillin—*sultamicillin tosylate* is better, which is given orally. Indications are:

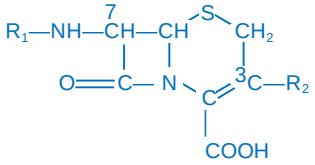
- PPNG gonorrhoea; sulbactam *per se* inhibits *N. gonorrhoeae*.
- Mixed aerobic-anaerobic infections, tooth abscess, intra-abdominal, gynaecological, surgical and skin/ soft tissue infections, especially those acquired in the hospital.

SULBACIN, AMPITUM: Ampicillin 1 g + sulbactam 0.5 g per vial inj; 1–2 vial deep i.m. or i.v. injection 6–8 hourly. Sultamicillin tosylate: BETAMPORAL, SULBACIN 375 mg tab.

Pain at site of injection, thrombophlebitis of injected vein, rash and diarrhoea are the main adverse effects.

CEPHALOSPORINS

These are a group of semisynthetic antibiotics derived from 'cephalosporin-C' obtained from a fungus *Cephalosporium*. They are chemically related to penicillins; the nucleus consists of a β-lactam ring fused to a dihydrothiazine ring, (7-aminocephalosporanic acid). By addition of different side chains at position 7 of β-lactam ring (altering spectrum of activity) and at position 3 of dihydrothiazine ring (affecting pharmacokinetics), a large number of semisynthetic compounds have been produced. These have been conventionally divided into 4 generations. This division has a chronological sequence of development, but more importantly, takes into consideration the overall antibacterial spectrum as well as potency.



Cephalosporin

First generation

Parenteral	*Oral*
Cefazolin	Cephalexin
	Cephradine
	Cefadroxil

Second generation

Parenteral	*Oral*
Cefuroxime	Cefaclor
Cefoxitin*	Cefuroxime axetil

*Not available in India

Third generation

Parenteral	*Oral*
Cefotaxime	Cefixime
Ceftizoxime	Cefpodoxime proxetil
Ceftriaxone	Cefdinir
Ceftazidime	Ceftibuten
Cefoperazone	

Fourth generation

Parenteral
Cefepime
Cefpirome

All cephalosporins are bactericidal and have the same mechanism of action as penicillin, i.e. inhibition of bacterial cell wall synthesis. However, they bind to different proteins than those which bind penicillins. This may explain differences in spectrum, potency and lack of cross resistance.

Acquired resistance to cephalosporins could have the same basis as for penicillins, i.e.:

(a) alteration in target proteins (PBPs) reducing affinity for the antibiotic.
(b) impermeability to the antibiotic so that it does not reach its site of action.
(c) elaboration of β-lactamases which destroy specific cephalosporins (cephalosporinases).

Though the incidence is low, resistance has been developed by some organisms, even against the third generation compounds. Individual cephalosporins differ in their:

(a) Antibacterial spectrum and relative potency against specific organisms.
(b) Susceptibility to β-lactamases from different organisms.
(c) Pharmacokinetic properties—many have to be injected, some are oral; majority are not metabolized but are excreted rapidly by the

kidney and have short t½s, probenecid inhibits their tubular secretion.

(d) Local irritancy on i.m. injection; few cannot be injected i.m.

FIRST GENERATION CEPHALOSPORINS

These were developed in the 1960s , have high activity against gram-positive but weaker against gram-negative bacteria.

Cefazolin It is active against most PnG sensitive organisms, i.e. streptococci (*pyogenes* as well *viridans*), gonococci, meningococci, *C. diphtheriae*, *H.influenzae*, clostridia, and *Actinomyces*. It is more active against *Klebsiella* and *E. coli* but quite susceptible to staphylococcal β-lactamase. It can be given i.m. (less painful) as well as i.v. and has a longer t½ (2 hours) due to slower tubular secretion; attains higher concentration in plasma and in bile. It is the preferred parenteral first generation cephalosporin, especially for surgical prophylaxis.

Dose: 0.25 g 8 hourly (mild cases), 1 g 6 hourly (severe cases) i.m. or i.v.

ALCIZON, ORIZOLIN 0.25 g, 0.5 g, 1 g per vial inj.

Cephalexin It is an orally effective first generation cephalosporin, similar in spectrum to cefazolin, but less active against *H. influenzae*. It is little bound to plasma proteins, attains high concentration in bile and is excreted unchanged in urine; t½ ~60 min. It is one of the commonly used cephalosporins; finds place in dentistry as an alternative to amoxicillin.

Dose: 0.25–1 g 6–8 hourly (children 25–100 mg/kg/day).

CEPHACILLIN 250, 500 mg cap; SPORIDEX, ALCEPHIN, CEPHAXIN 250, 500 mg cap, 125 mg/5 ml dry syr., 100 mg/ml pediatric drops.

ALCEPHIN-LA: Cephalexin + probenecid (250 + 250 mg and 500 + 500 mg) tabs.

Cephradine Another orally active drug, almost identical to cephalexin, but less active against some organisms. Oral administration has caused diarrhoea as side effect. It is available for parenteral use also.

Dose: 0.25–1 g 6–12 hourly oral/i.m/i.v.

CEFLAD 0.25, 0.5, 1 g per vial inj.

Cefadroxil A close congener of cephalexin; has good tissue penetration including that in alveolar bone (tooth socket); exerts more sustained action at the site of infection; can be given 12 hourly despite a t½ of 1 hr. It is excreted unchanged in urine, but dose need be reduced only if creatinine clearance is < 50 ml/min. The antibacterial activity of cefadroxil and indications are similar to those of cephalexin; frequently selected for dental infections.

Dose: 0.5–1 g BD. DROXYL 0.5, 1 g tab, 250 mg/5 ml syr; CEFADROX 0.5 g cap, 125 mg/5 ml syr and 250 mg kid tab; KEFLOXIN 0.5 g cap, 0.25 g Distab, 125 mg/5 ml susp.

SECOND GENERATION CEPHALOSPORINS

These were developed subsequent to the first generation compounds and are more active against gram-negative organisms, with some members active against anaerobes.

Cefoxitin It is more active against *Serratia*, indole positive *Proteus* and particularly *B. fragilis*. It is highly resistant to β-lactamases produced by gram-negative bacteria. The main value of cefoxitin is in the treatment of anaerobic and mixed obstetric/surgical infections, lung abscess; dose 1–2 g i.m./i.v. every 6–8 hrs.

Cefuroxime It is resistant to gram-negative β-lactamases: has high activity against organisms producing these enzymes including PPNG and ampicillin-resistant *H. influenzae*, while retaining significant activity on gram-positive cocci and certain anaerobes. It is well tolerated by i.m. route and attains relatively higher CSF levels. The most important use is in meningitis caused by *H. influenzae*, meningococci, pneumococci, and for single dose i.m. therapy of gonorrhoea due to PPNG.

CEFOGEN, SUPACEF, FUROXIL 250 mg and 750 mg/vial inj; 0.75–1.5 g i.m. or i.v. 8 hourly, children 30–100 mg/kg/day.

Cefuroxime axetil This ester of cefuroxime is effective orally, though absorption is incomplete. The activity depends on *in vivo* hydrolysis and release of cefuroxime. Because of activity on anaerobes, it is frequently chosen for dental infections.

Dose: 250–500 mg BD, children half-dose; CEFTUM, SPIZEF 125, 250, 500 mg cap, tab and 125 mg/5 ml susp.

Cefaclor It retains significant activity by the oral route and is more active than the first generation compounds against *H. influenzae*, *E. coli*, *Pr. mirabilis* and anaerobes found in oral cavity.
KEFLOR, VERCEF, DISTACLOR 250 mg cap, 125 and 250 mg distab, 125 mg/5 ml dry syr, 50 mg/ml ped. drops.

THIRD GENERATION CEPHALOSPORINS

These compounds introduced in the 1980s have highly augmented activity against gram-negative Enterobacteriaceae; some inhibit *Pseudomonas* as well. All are highly resistant to β-lactamases from gram-negative bacteria. However, they are less active on gram-positive cocci and anaerobes.

Cefotaxime It is the prototype of the third generation cephalosporins; exerts potent action on aerobic gram-negative as well as some gram-positive bacteria, but is not so active on anaerobes (particularly *Bact. fragilis*), *Staph. aureus* and *Ps. aeruginosa*. Prominent indications are meningitis caused by gram-negative bacilli (attains relatively high CSF levels), life-threatening resistant/hospital-acquired infections, septicaemias and infections in immunocompromised patients; dose 1–2 g i.m. or i.v. 6–12 hourly (children 50–100 mg/kg/day). It is also utilized for single dose therapy (1 g i.m. + 1 g probenecid oral) of PPNG urethritis, but is not dependable for *Pseudomonas* infections.

Cefotaxime is deacetylated in the body; the metabolite exerts weaker but synergistic action with the parent drug. The plasma t½ of cefotaxime is 1 hr, but is longer for the deacetylated metabolite—permitting 12 hourly doses in many situations.
OMNATAX, ORITAXIM, CLAFORAN 0.25, 0.5, 1.0 g per vial inj.

Ceftizoxime It is similar in antibacterial activity and indications to cefotaxime, but is not metabolized—excreted by the kidney at a slower rate; t½ 1.5–2 hr.
Dose 0.5–1 g i.m./i.v. 8 or 12 hourly.
CEFIZOX, EPOCELIN 0.5 and 1 g per vial inj.

Ceftriaxone The distinguishing feature of this cephalosporin is its longer duration of action (t½ 8 hr), permitting once or at the most twice daily dosing. Penetration into CSF is good, and it is eliminated equally in urine and bile.

Ceftriaxone has shown high efficacy in a wide range of serious infections including bacterial meningitis (especially in children), multiresistant typhoid fever, complicated urinary tract infection, abdominal sepsis and septicaemias. A single dose of 250 mg i.m. has proven curative in gonorrhoea including PPNG and in chancroid.

Hypoprothrombinaemia and bleeding are specific adverse effects. Haemolysis is reported.
OFRAMAX, MONOCEF, MONOTAX 0.25, 0.5, 1.0 g per vial inj;1–2 g i.v. or i.m./day.
Meningitis: 4 g followed by 2 g i.v. (children 75–100 mg/kg) once daily for 7–10 days.
Typhoid: 4 g i.v. daily × 2 days followed by 2 g/day (children 75 mg/kg) till 2 days after fever subsides.

Ceftazidime The most prominent feature of this third generation cephalosporin is its high activity against *Pseudomonas*. It has been specifically used in febrile neutropenic patients with haematological malignancies, burn, etc. Its activity against Enterobacteriaceae is similar to that of cefotaxime, but it is less active on *Staph. aureus*, other gram-positive cocci and anaerobes like *Bact. fragilis*. Its plasma t½ is 1.5–1.8 hr.

Neutropenia, thrombocytopenia, rise in plasma transaminases and blood urea have been reported.
Dose: 0.5–2 g i.m. or i.v. every 8 hr, children 30 mg/kg/day. Resistant typhoid 30 mg/kg/day.
FORTUM, CEFAZID, ORZID 0.25, 0.5 and 1 g per vial inj.

Cefoperazone Like ceftazidime, it differs from other third generation compounds in having stronger activity on *Pseudomonas* and weaker activity on other organisms. It is good for *S. typhi* and *B. fragilis* also, but more susceptible to β-lactamases. The indications are—severe urinary, biliary, respiratory, skin-soft tissue infections, meningitis and septicaemias. It is primarily excreted in bile; t½ is 2 hr. It has hypoprothrombinaemic action but does not affect platelet function. A disulfiram-like reaction with alcohol has been reported.

MAGNAMYCIN 0.25 g, 1, 2 g inj; CEFOMYCIN, NEGAPLUS 1 g inj; 1-2 g i.m./i.v. 12 hourly.

Cefixime It is an orally active third generation cephalosporin highly active against Enterobacteriaceae, *H. influenzae, Strep. pyogenes, Strep. pneumoniae* and is resistant to many β-lactamases. However, it is not active on *Staph. aureus* and *Pseudomonas*. It is longer acting (t½ 3 hr) and has been used in a dose of 200–400 mg BD for respiratory, urinary and biliary infections. Stool changes and diarrhoea are the most prominent side effects.
TOPCEF, ORFIX 100, 200 mg tab/cap, CEFSPAN 100 mg cap, 100 mg/5 ml syr.

Cefpodoxime proxetil It is the orally active ester prodrug of 3rd generation cephalosporin cefpodoxime. In addition to being highly active against Enterobacteriaceae and streptococci, it inhibits *Staph. aureus*. It is used mainly for respiratory, urinary, skin and soft tissue infections.
Dose: 200 mg BD (max 800 mg/day)
CEFOPROX 100, 200 mg tab, 100 mg/5 ml dry syr; CEPODEM 100, 200 mg tab, 50 mg/5 ml susp.

Cefdinir This orally active 3rd generation cephalosporin has good activity against many β-lactamase producing organisms. Most respiratory pathogens including gram-positive cocci are susceptible. Its indications are pneumonia, acute exacerbations of chronic bronchitis, ENT and skin infections.
Dose: 300 mg BD
SEFDIN, ADCEF 300 mg cap, 125 mg/5ml susp.

Ceftibuten Another oral 3rd generation cephalosporin, active against both gram-positive and gram-negative bacteria, and stable to β-lactamases. It is indicated in respiratory, urinary and gastrointestinal infections.
Dose: 200 mg BD or 400 mg OD.
PROCADAX 400 mg cap, 90 mg/5 ml powder for oral suspension.

FOURTH GENERATION CEPHALOSPORINS

Cefepime Developed in 1990s, this 4th generation cephalosporin has antibacterial spectrum similar to that of 3rd generation compounds, but is highly resistant to β-lactamases, hence active against many bacteria resistant to the earlier drugs. *Ps. aeruginosa* and *Staph. aureus* are also inhibited. Due to high potency and extended spectrum, it is effective in many serious infections like hospital-acquired pneumonia, febrile neutropenia, bacteraemia, septicaemia, etc.
Dose: 1–2 g i.v. 8–12 hourly; KEFAGE 0.5, 1.0 g inj.

Cefpirome This 4th generation cephalosporin has become available for the treatment of serious and resistant hospital-acquired infections including septicaemias, lower respiratory tract infections, etc. Its zwitterion character permits better penetration through porin channels of gram-negative bacteria. It is resistant to many β-lactamases; inhibits type 1 β-lactamase producing Enterobacteriaceae and it is more potent against gram-positive and some gram-negative bacteria than the 3rd generation compounds.
Dose: 1–2 g i.m./i.v. 12 hourly;
CEFROM, CEFORTH 1 g inj.

Adverse effects

Cephalosporins are generally well tolerated but are more toxic than penicillin.

1. *Pain* after i.m. injection occurs with many. This is so severe with cephalothin as to interdict i.m. route, but many others can be injected i.m. (*see* individual compounds). Thrombophlebitis can occur on i.v. injection.

2. *Diarrhoea* due to alteration of gut ecology or irritative effect is more common with oral cephradine and parenteral cefoperazone (it is significantly excreted in bile).

3. *Hypersensitivity reactions* caused by cephalosporins are similar to penicillin, but incidence is lower. Rashes are the most frequent manifestation, but anaphylaxis, angioedema, asthma and urticaria have also occurred. About 10% patients allergic to penicillin show cross reactivity with cephalosporins. Those with a history of immediate type of reactions to penicillin should better not be given a cephalosporin. Skin tests for sensitivity to cephalosporins are unreliable.

A positive Coombs' test occurs in many but haemolysis is rare.

4. *Nephrotoxicity* is highest with cephaloridine, which consequently has been withdrawn. Cephalothin and a few others have low-grade nephrotoxicity which may be accentuated by pre-existing renal disease, concurrent administration of an aminoglycoside or loop diuretic.

5. *Bleeding* occurs with cephalosporins having a methylthiotetrazole or similar substitution at position 3 (cefoperazone, ceftriaxone). This is due to hypoprothrombinaemia caused by the same mechanism as warfarin and is more common in patients with cancer, intra-abdominal infection or renal failure.

6. Neutropenia and thrombocytopenia are rare adverse effects reported with ceftazidime and some others.

7. A disulfiram-like interaction with alcohol has been reported with cefoperazone.

Uses

A. *Dental infections:* There are no compelling indications for cephalosporins in dentistry except as alternative to penicillin/amoxicillin, especially in patients who develop rashes or other milder allergic reactions (but not immediate type of hypersensitivity), and in cases with penicillin/amoxicillin-resistant infection. As such, they are used to a lesser extent than penicillins. Only oral antibiotics are routinely employed in dentistry, while parenteral ones are reserved for serious and fulminating infections. Therefore, the orally active 1st and 2nd generation cephalosporins are mainly prescribed for orodental infections. The first generation agents like cephalexin or cephadroxil are used because of their high activity against gram-positive aerobic bacteria and their good penetration into alveolar bone (like tooth socket). Though they do not directly kill anaerobes, removal of aerobic organisms improves oxygen availability at the local site, especially in alveolar bone, and indirectly checks growth of anaerobes.

The 2nd generation compounds like cefuroxime axetil and cefaclor are the only ones with good activity against oral anaerobes, and are the preferred cephalosporins for dental indications. Cephalosporins are specially valuable for orodental infections caused by *Klebsiella*, which though rare, may occur in neutropenic patients. Anaerobes are less prominent in acute gingival cellulitis which often responds rapidly to cephalosporins. Cephalexin and cephadroxil are alternatives to amoxicillin for prophylaxis of local wound infection as well as bacterial endocarditis following dental surgery in predisposed patients.

B. *General medical uses:* Cephalosporins are now extensively used in medicine.

1. As alternatives to PnG in allergic patients (other than immediate hypersensitivity), one of the first generation compounds may be used.
2. Respiratory, urinary and soft tissue infections caused by gram-negative organisms, especially *Klebsiella, Proteus, Enterobacter, Serratia*.
3. Penicillinase producing staphylococcal infections.
4. Septicaemias caused by gram-negative organisms: an aminoglycoside may be combined with a cephalosporin.
5. Surgical prophylaxis: Cefazolin is employed for most types of surgeries.
6. Meningitis caused by *H. influenzae*, Enterobacteriaceae: cefuroxime, cefotaxime and ceftriaxone have been specially used. Ceftazidime + gentamicin is the most effective therapy for *Pseudomonas* meningitis.
7. Gonorrhoea caused by penicillinase producing organisms: ceftriaxone is a first choice drug for single dose therapy. Cefuroxime and cefotaxime have also been used for this purpose. For chancroid also, a single dose is as effective as cotrimoxazole or erythromycin given for 7 days.
8. Typhoid: ceftriaxone and cefoperazone are the fastest acting drugs.
9. Mixed aerobic-anaerobic infections seen in cancer patients, those undergoing colorectal surgery, obstetric complications: cefuroxime, cefaclor or one of the third generation compounds is used.

10. Hospital-acquired infections resistant to commonly used antibiotics: cefotaxime, ceftizoxime or a fourth generation drug may work.
11. Prophylaxis and treatment of infections in neutropenic patients: ceftazidime or another third generation compound, alone or in combination with an aminoglycoside.

MONOBACTAMS

Aztreonam It is a novel β-lactam antibiotic in which the other ring is missing (hence monobactam). It inhibits gram-negative enteric bacilli and *H. influenzae* at very low concentrations and *Pseudomonas* at moderate concentrations, but does not inhibit gram-positive cocci or faecal anaerobes. It is resistant to gram-negative β-lactamases. The main indications of aztreonam are hospital-acquired infections originating from urinary, biliary, gastrointestinal and female genital tracts.

Lack of cross sensitivity with other β-lactam antibiotics appears to be the most promising feature of aztreonam: permiting its use in patients allergic to penicillins or cephalosporins. It is eliminated in urine with a t½ of 1.8 hours.

Dose: 0.5–2 g i.m. or i.v. 6–12 hourly.
AZENAM 0.5 g, 1 g, 2 g per vial inj.

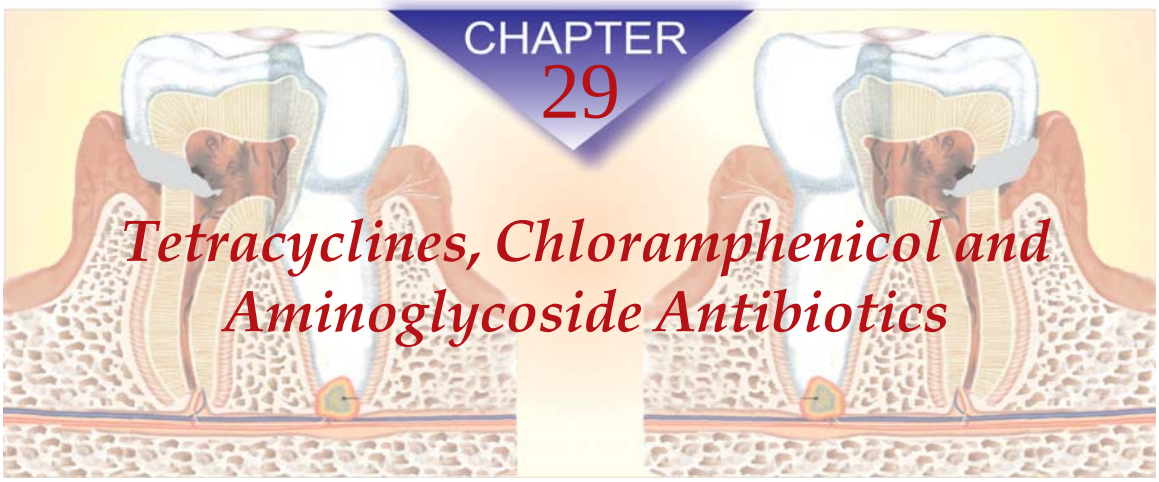
CARBAPENEMS

Imipenem It is an extremely potent and very broad spectrum β-lactam antibiotic whose range of activity includes gram-positive cocci, Enterobacteriaceae, *Ps. aeruginosa, Listeria* as well as anaerobes like *Bact. fragilis* and *Cl. difficile*. It is resistant to most β-lactamases and inhibits penicillinase producing staphylococci.

A limiting feature of imipenem is its rapid hydrolysis by the enzyme dehydropeptidase I located on the brush border of renal tubular cells. An innovative solution to this problem is its combination with *cilastatin*, a reversible inhibitor of dehydropeptidase I, which has matched pharmacokinetics with imipenem (t½ of both is 1 hr) and protects it.

Imipenem-cilastatin 0.5 g i.v. 6 hourly (max 4 g/day) has proved effective in a wide range of serious hospital-acquired infections including those in neutropenic, cancer and AIDS patients. Imipenem-cilastatin monotherapy is as effective as combination of other antibiotics.

Imipenem has propensity to induce seizures at higher doses and in predisposed patients.

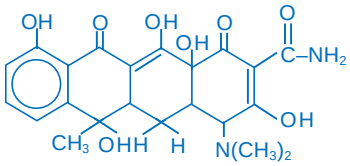


CHAPTER 29

Tetracyclines, Chloramphenicol and Aminoglycoside Antibiotics

TETRACYCLINES

These are a class of antibiotics having a nucleus of four cyclic rings.



TETRACYCLINE

All are obtained from soil actinomycetes. The first to be introduced was chlortetracycline in 1948. It contrasted markedly from penicillin and streptomycin (the other two antibiotics generally available at that time) in being active orally and in affecting a wide range of microorganisms—hence called 'broad-spectrum antibiotic'. Oxytetracycline soon followed; others were produced later, either from mutant strains or semisynthetically.

All tetracyclines are slightly bitter solids which are weakly water soluble, but their hydrochlorides are more soluble. Aqueous solutions are unstable. All have practically the same antimicrobial activity (with minor differences). The subsequently developed members have high lipid solubility, greater potency and some other differences. On the basis of chronology of development, as well as for convenience of description, the still available members can be divided into 3 groups.

Group I
Tetracycline
Oxytetracycline

Group II
Demeclocycline

Group III
Doxycycline
Minocycline

Mechanism of action The tetracyclines are primarily bacteriostatic; inhibit protein synthesis by binding to 30S ribosomes in susceptible organism. Subsequent to such binding, attachment of aminoacyl-t-RNA to the mRNA-ribosome complex is interferred with (Fig. 29.1). As a result, the peptide chain fails to grow.

The sensitive organisms have an energy dependent active transport process which concentrates tetracyclines intracellularly. In gram-negative bacteria tetracyclines diffuse through porin channels as well. The more lipid-soluble members (doxycycline, minocycline) enter by passive diffusion also (this is partly responsible for their higher potency). The carrier involved in active transport of tetracyclines is absent in the host cells. Moreover, protein synthesizing apparatus of host cells is less sensitive to tetracyclines. These two factors are responsible for the selective toxicity of tetracyclines for the microbes.

Antimicrobial spectrum When originally introduced, tetracyclines inhibited practically all types of pathogenic microorganisms except fungi and

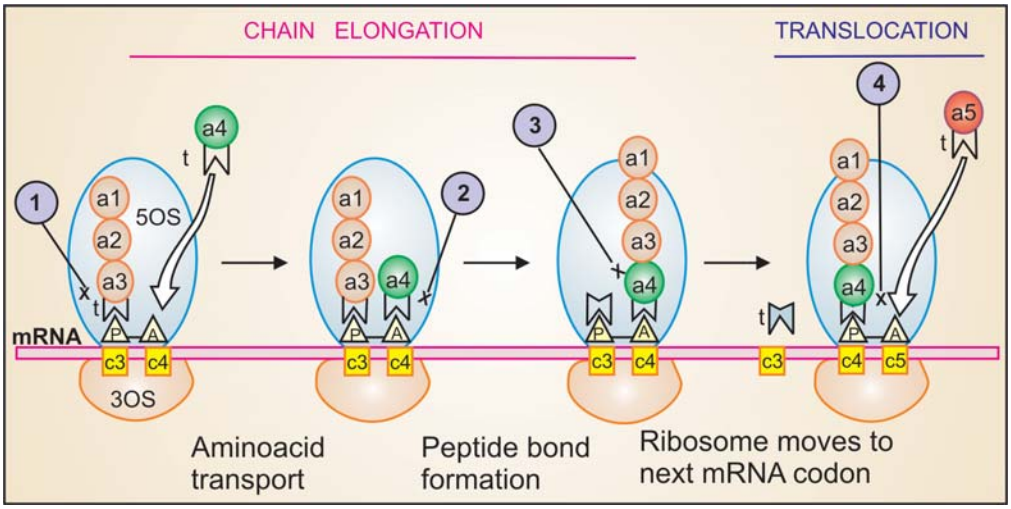


Fig. 29.1: Bacterial protein synthesis and the site of action of antibiotics

The messenger RNA (mRNA) attaches to the 30S ribosome. The initiation complex of mRNA starts protein synthesis and polysome formation. The nacent peptide chain is attached to the peptidyl (P) site of the 50S ribosome. The next amino acid (a) is transported to the acceptor (A) site of the ribosome by its specific tRNA which is complementary to the base sequence of the next mRNA codon (C). The nacent peptide chain is transferred to the newly attached amino acid by peptide bond formation. The elongated peptide chain is shifted back from the 'A' to the 'P' site and the ribosome moves along the mRNA to expose the next codon for amino acid attachment. Finally, the process is terminated by the termination complex and the protein is released.

(1) Aminoglycosides bind to several sites at 30S and 50S subunits as well as to their interface—freeze initiation, interfere with polysome formation and cause misreading of mRNA code. (2) Tetracyclines bind to 30S ribosome and inhibit aminoacyl tRNA attachment to the 'A' site. (3) Chloramphenicol binds to 50S subunit—interferes with peptide bond formation and transfer of peptide chain from 'P' site. (4) Erythromycin and clindamycin also bind to 50S ribosome and hinder translocation of the elongated peptide chain back from 'A' site to 'P' site and the ribosome does not move along the mRNA to expose the next codon. Peptide synthesis may be prematurely terminated.

viruses; hence the name 'broad-spectrum antibiotic'. However, promiscous and often indiscriminate use has gradually narrowed the field of their usefulness.

1. Cocci: All gram-positive and gram-negative cocci were originally sensitive, but now many *Strep. pyogenes, Staph. aureus* and enterococci have become resistant. Responsiveness of *Strep. pneumoniae* has decreased somewhat. Tetracyclines (especially minocycline) are still active against many *N. gonorrhoeae* and *N. meningitidis*.
2. Most gram-positive bacilli, e.g. *Clostridia* and other anaerobic bacilli, *Listeria, Corynebacteria, Propionibacterium acnes, B. anthracis* are inhibited but not *Mycobacteria*, except some atypical ones.
3. Sensitive gram-negative bacilli are—*H. ducreyi, Calymmatobacterium granulomatis, V. cholerae, Yersinia pestis, Y. enterocolitica, Campylobacter, Helicobacter pylori, Brucella, Pasteurella multocida, F. tularensis* and many anaerobes; some *H. influenzae* have become insensitive.

Enterobacteriaceae are now largely resistant. Notable bacilli that are not inhibited are *Pseudomonas aeruginosa, Proteus, Klebsiella, Salmonella typhi* and many *Bact. fragilis*. MIC against anaerobes is relatively higher.

4. Spirochetes, including *T. pallidum* and *Borrelia* are quite sensitive.
5. All rickettsiae (typhus, etc.) and chlamydiae are highly sensitive.
6. *Mycoplasma* and *Actinomyces* are moderately sensitive.
7. *Entamoeba histolytica* and *Plasmodia* are inhibited at high concentrations.

Resistance Resistance to tetracyclines develops slowly in a graded manner. In such bacteria, usually the tetracycline concentrating mechanism becomes less efficient or the bacteria acquire capacity to pump it out. Another mechanism is plasmid mediated synthesis of a 'protection' protein which protects the ribosomal binding site from tetracycline. Elaboration of tetracycline inactivating enzymes is an unimportant mechanism of tetracycline resistance. Due to widespread use, tetracycline resistance has become common among gram-positive cocci, *E. coli*, *Enterobacter* and many others. Nearly complete cross resistance is seen among different members of the tetracycline group. However, some organisms not responding to other tetracyclines may be inhibited by therapeutically attained concentrations of minocycline (the most potent agent).

Partial cross resistance between tetracyclines and chloramphenicol has been noted.

Pharmacokinetics

The pharmacokinetic differences between individual tetracyclines are included in Table 29.1. The older tetracyclines are incompletely absorbed from g.i.t.; absorption is better if taken in empty stomach. Doxycycline and minocycline are completely absorbed irrespective of food. Tetracyclines have chelating property—form insoluble and unabsorbable complexes with calcium and other metals. Milk, iron preparations, nonsystemic antacids and sucralfate reduce their absorption. Administration of these substances and tetracyclines should be staggered, if they cannot be avoided altogether.

Table 29.1: Comparative features of tetracyclines

	Group I	*Group II*	*Group III*
	Tetracycline (T) *Oxytetracycline (OxyT)*	*Demeclocycline (Deme)*	*Doxycycline (Doxy)* *Minocycline (Mino)*
1. Source	Oxy T: *S. rimosus* T: semisynthetic	Deme: *S. aureofaciens* (mutant)	Doxy: semisynthetic Mino: semisynthetic
2. Potency	Low	Intermediate	High (Doxy < Mino)
3. Intestinal absorption	T: moderate Oxy T: moderate	Moderate	Complete, No interference by food
4. Plasma protein binding	OxyT: Low T: Intermediate	High	High
5. Elimination	T, Oxy T: Rapid renal excretion	Partial metabolism, slower renal excretion	Doxy: Primarily excreted in faeces as conjugate Mino: Primarily metabolized, excreted in urine and bile
6. Plasma t½	6–10 hr.	16–18 hr.	18–24 hr.
7. Dosage	250–500 mg QID or TDS	300 mg BD	200 mg initially, then 100–200 mg OD
8. Alteration of intestinal flora	Marked	Moderate	Least
9. Incidence of diarrhoea	High	Intermediate	Low
10. Phototoxicity	Low	Deme: Highest	Doxy: High
11. Specific toxicity	OxyT: less tooth discolouration	Deme: more phototoxic, diabetes insipidus	Doxy: low renal toxicity. Mino: Vestibular toxicity, less superinfections

Tetracyclines are widely distributed in the body (volume of distribution > 1 L/kg). Variable degree of protein binding is exhibited by different members. They are concentrated in liver, spleen, gingival tissue and bind to the connective tissue in bone and teeth. Intracellularly, they bind to mitochondria. Minocycline accumulates in body fat. The CSF concentration of most tetracyclines is about 1/4th of plasma concentration, whether meninges are inflamed or not.

Most tetracyclines are primarily excreted in urine by glomerular filtration; dose has to be reduced in renal failure; doxycycline is an exception to this. They are partly metabolized and significant amounts enter bile—some degree of enterohepatic circulation occurs. They are secreted in milk in amounts sufficient to affect the suckling infant.

Enzyme inducers like phenobarbitone and phenytoin enhance metabolism and reduce the t½ of doxycycline.

Administration Oral capsule is the dosage form in which tetracyclines are most commonly administered. The capsule should be taken ½ hr before or 2 hr after food. Dry syrups and other liquid oral preparations have been discontinued to discourage use in children.

Tetracyclines are not recommended by i.m. route because it is painful and absorption from the injection site is poor. Slow i.v. injection may be given in severe cases, but is rarely required now.

A variety of topical preparations (ointment, cream, etc.) are available, but should not be used, because there is high risk of sensitization. However, ocular application is not contraindicated.

Preparations

1. Oxytetracycline: TERRAMYCIN 250, 500 mg cap, 50 mg/ml in 10 ml vials inj; 3% skin oint, 1% eye/ear oint.
2. Tetracycline: ACHROMYCIN, HOSTACYCLINE, RESTECLIN 250, 500 mg cap. 3% skin oint, 1% eye/ear drops and oint.
3. Demeclocycline (Demethylchlortetracycline): LEDERMYCIN 150, 300 mg cap/tab.
4. Doxycycline: TETRADOX, BIODOXI, DOXT, NOVADOX, 100 mg cap.
5. Minocycline: CYANOMYCIN 50, 100 mg caps.

Adverse effects

Irritative effects Tetracyclines can cause epigastric pain, nausea, vomiting and diarrhoea by their irritant property. The irritative diarrhoea is to be distinguished from that due to superinfection. Esophageal ulceration has occurred by release of the material from capsules in the esophagus during swallowing, especially with doxycycline. Intramuscular injection of tetracyclines is very painful; thrombophlebitis of the injected vein can occur, especially on repeated use.

Dose-related toxicity

1. *Liver damage* Fatty infiltration of liver and jaundice occurs occasionally. Oxytetracycline and tetracycline are safer in this regard. Tetracyclines are risky in pregnant women, can precipitate acute hepatic necrosis which may be fatal.

2. *Kidney damage* It is prominent only in the presence of existing kidney disease. All tetracyclines, except doxycycline, accumulate and enhance renal failure. A reversible *Fancony syndrome* like condition is produced by outdated tetracyclines due to proximal tubular damage caused by degraded products—epitetracycline, anhydrotetracycline and epianhydrotetracycline. Exposure to acidic pH, moisture and heat favours such degradation.

3. *Phototoxicity* A sun burn-like or other severe skin reaction on exposed parts is seen in some individuals. A higher incidence has been noted with demeclocycline and doxycycline. Distortion of nails occurs occasionally.

4. *Teeth and bones* Tetracyclines have chelating property. Calcium-tetracycline chelate gets deposited in developing teeth and bone. Given from midpregnancy to 5 months of extrauterine life, the deciduous teeth are affected: brown

discolouration, ill-formed teeth, more susceptible to caries. Tetracyclines given between 3 months and 6 years of age affect the crown of permanent anterior dentition. Repeated courses are more damaging.

Given during late pregnancy or childhood, tetracyclines can cause temporary suppression of bone growth. The ultimate effect on stature is mostly insignificant, but deformities and reduction in height are a possibility with prolonged use.

5. *Antianabolic effect* Tetracyclines reduce protein synthesis and have an overall catabolic effect. They induce negative nitrogen balance and can increase blood urea.

6. *Increased intracranial pressure* is noted in some infants.

7. *Diabetes insipidus* Demeclocycline antagonizes ADH action and reduces urine concentrating ability of the kidney. It has been tried in patients with inappropriate ADH secretion.

8. *Vestibular toxicity* Minocycline has produced ataxia, vertigo and nystagmus, which subside when the drug is discontinued.

Hypersensitivity This is infrequent with tetracyclines. Skin rashes, urticaria, glossitis, pruritus ani and vulvae, even exfoliative dermatitis have been reported. Angioedema and anaphylaxis are extremely rare. Complete cross sensitization is exhibited by different tetracyclines.

Superinfection Tetracyclines are the most common antibiotics responsible for superinfections, because they cause marked suppression of the resident flora.

Though mouth, skin or vagina may be involved, intestinal superinfection by *Candida albicans* is most prominent; pseudomembranous enterocolitis is rare but serious. Higher doses suppress flora more completely—greater chance of superinfection: doses on the lower side of the range should be used whenever possible. The tetracycline should be discontinued at the first sign of superinfection and appropriate therapy instituted.

Doxycycline and minocycline are less liable to cause diarrhoea, because only small amounts reach the lower bowel in the active form.

Precautions

1. Tetracyclines should not be used during pregnancy, lactation and in children.
2. They should be avoided in patients on diuretics: blood urea may rise in such patients.
3. They should be used cautiously in renal or hepatic insufficiency.
4. Preparations should never be used beyond their expiry date.
5. Do not mix injectable tetracyclines with penicillin—inactivation occurs.

Uses

Orodental conditions Tetracyclines are of limited usefulness in treating acute dental infections and are infrequently selected for this purpose. However, they benefit certain forms of periodontal disease by virtue of their broad-spectrum antimicrobial action as well as by suppressing the activity of collagenases derived from neutrophils and fibroblasts that contribute to the gingival inflammation. These collagenase enzymes are Ca^{2+} dependent and tetracyclines chelate Ca^{2+}. In addition, tetracyclines may benefit periodontal inflammation by scavenging free (oxygen) radicals.

Tetracyclines have an important adjuvant role in the management of chronic periodontitis refractory to conventional therapy with local hygienic and surgical measures, and in juvenile periodontitis. In refractory periodontal disease 2-week tetracycline (1 g/day) or doxycycline (0.1–0.2 g/day) therapy controls gingival inflammation and helps to normalise the periodontal microflora from a mixture of anaerobic gram-negative bacilli + spirochetes to the usual one in which gram-positive bacteria predominate. Tetracyclines are highly active against the

Actinobacillus sp. that is held responsible for destruction of gums and bone loss in juvenile periodontitis. Appropriate surgical treatment combined with 2 to 4-week tetracycline therapy halts progression of this disease.

General medical uses Although tetracyclines are broad-spectrum antibiotics, they are employed only for those infections for which a more selective and less toxic AMA is not available. Clinical use of tetracyclines has very much declined due to availability of fluoroquinolones and other efficacious AMAs.

1. Tetracyclines are often employed when the nature and sensitivity of the infecting organism cannot be reasonably guessed, but they are not dependable for empirical treatment of serious/life-threatening infections. They may also be used for initial treatment of *mixed infections*.

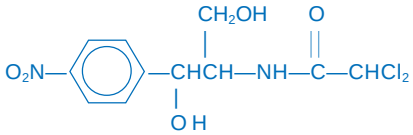
2. Tetracyclines are still the drug of **first choice** in:
(a) Venereal diseases: Lymphogranuloma venereum and granuloma inguinale.
(b) Atypical pneumonia due to *Mycoplasma pneumoniae* and psittacosis.
(c) Cholera: Tetracyclines have adjuvant value by reducing stool volume and limiting the duration of diarrhoea.
(d) Brucellosis: Tetracyclines are combined with gentamicin.
(e) Plague: Tetracyclines are preferred for blind/mass treatment of suspected cases during an epidemic, though streptomycin often acts faster.
(f) Relapsing fever due to *Borrelia recurrentis*.
(g) Rickettsial infections: typhus, rocky mountain spotted fever, Q fever, etc.

3. Tetracyclines are **second choice** drugs:
(a) To penicillin/ampicillin for tetanus, anthrax, actinomycosis and *Listeria* infections.
(b) To ciprofloxacin or ceftriaxone for gonorrhoea in patients allergic to penicillin.
(c) To ceftriaxone for syphilis in patients allergic to penicillin.
(d) To azithromycin for chlamydial infections, e.g. trachoma, nonspecific urethritis/endocervicitis due to *Ch. trachomatis*, pneumonia due to *Ch. pneumoniae.*

4. Other situations in which tetracyclines may be used are:
(a) Urinary tract infections.
(b) Community-acquired pneumonia.
(c) Amoebiasis: along with other amoebicides for chronic intestinal amoebiasis.
(d) As adjuvant to quinine or sulfadoxine-pyrimethamine for chloroquine-resistant *P. falciparum* malaria.
(e) Acne: prolonged therapy with low doses may be used in severe cases.
(f) Chronic obstructive lung disease: prophylactic use may reduce the frequency of exacerbations.

CHLORAMPHENICOL

Chloramphenicol was initially obtained from *Streptomyces venezuelae* in 1947. It was soon synthesized chemically and the commercial product now is all synthetic.



CHLORAMPHENICOL

It is a yellowish white crystalline solid, aqueous solution is quite stable, stands boiling, but needs protection from light. It has a nitrobenzene substitution, which is probably responsible for the antibacterial activity and its intensely bitter taste.

Mechanism of action Chloramphenicol inhibits bacterial protein synthesis by interferring with 'transfer' of the elongating peptide chain to the newly attached aminoacyl-tRNA at the ribosome-mRNA complex. It specifically attaches to the 50S ribosome and thus may hinder the access of aminoacyl-tRNA to the acceptor site for aminoacid incorporation (*see* Fig. 29.1). Probably,

by acting as a peptide analogue, it prevents formation of peptide bonds.

At high doses, it can inhibit mammalian mitochondrial protein synthesis as well. Bone marrow cells are specially susceptible.

Antimicrobial spectrum Chloramphenicol is primarily bacteriostatic, though high concentrations have been shown to exert cidal effect on some bacteria, e.g. *H. influenzae*. It is a broad-spectrum antibiotic, active against the same range of organisms (gram-positive and negative bacteria, rickettsiae, chlamydia, mycoplasma) as tetracyclines. Notable differences between these two are:

(a) Chloramphenicol is highly active against *Salmonella* including *S. typhi*, but resistant strains are now rampant.

(b) It is more active than tetracyclines against *H. influenzae* (though many have now developed resistance), *B. pertussis, Klebsiella* and anaerobes including *Bact. fragilis.*

(c) It is less active against gram-positive cocci, spirochetes, certain Enterobacteriaceae and inactive on *Entamoeba* and *Plasmodia.*

Like tetracyclines, it is ineffective against *Mycobacteria, Pseudomonas*, many *Proteus*, viruses and fungi.

Resistance Most bacteria are capable of developing resistance to chloramphenicol, which generally emerges in a graded manner, as with tetracyclines. Being orally active, broad spectrum and relatively cheap, chloramphenicol was extensively and often indiscriminately used, especially in developing countries, resulting in high incidence of resistance among many gram-positive and gram-negative bacteria.

In many areas, highly chloramphenicol resistant *S. typhi* have emerged due to transfer of R factor by conjugation. Resistance among gram-negative bacteria is generally due to acquisition of R plasmid encoded for an acetyl transferase—an enzyme which inactivates chloramphenicol. Acetyl-chloramphenicol does not bind to the bacterial ribosome. In many cases, this plasmid has also carried resistance to ampicillin and tetracycline. Multidrug-resistant *S. typhi* have arisen.

Decreased permeability into the resistant bacterial cells (chloramphenicol appears to enter bacterial cell both by passive as well as facilitated diffusion) and lowered affinity of bacterial ribosome for chloramphenicol are other mechanisms of resistance. Partial cross resistance between chloramphenicol and erythromycin/clindamycin has been noted, because all these antibiotics bind to 50S ribosome at adjacent sites. Some cross resistance with tetracyclines also occurs, though the latter binds to 30S ribosome.

Pharmacokinetics

Chloramphenicol is rapidly and completely absorbed after oral ingestion. It is 50–60% bound to plasma proteins and very widely distributed: volume of distribution 1 L/kg. It freely penetrates serous cavities and blood-brain barrier: CSF concentration is nearly equal to that of unbound drug in plasma. It crosses placenta and is secreted in bile and milk.

Chloramphenicol is primarily conjugated with glucuronic acid in the liver and little is excreted unchanged in urine. Cirrhotics and neonates, who have low conjugating ability, require lower doses. The metabolite is excreted mainly in urine. Plasma t½ of chloramphenicol is 3–5 hours in adults. It is increased only marginally in renal failure: dose need not be modified.

Administration The commonest route of administration of chloramphenicol is oral—as capsules; 250–500 mg 6 hourly (max. total dose 28 g), children 25–50 mg/kg/day. It is also available for application to eye/ear, but topical use at other sites is not recommended.

CHLOROMYCETIN, ENTEROMYCETIN, PARAXIN, 250 mg, 500 mg cap, 1% eye oint, 0.5% eye drops, 5% ear drops, 1% applicaps.

Chloramphenicol palmitate (CHLOROMYCETIN PALMITATE, ENTEROMYCETIN, PARAXIN 125 mg/5 ml oral susp) is an insoluble tasteless ester of chloramphenicol, which is inactive as such. It is nearly completely hydrolysed in the intestine

by pancreatic lipase and absorbed as free chloramphenicol, but produces lower plasma concentration.

Chloramphenicol succinate (ENTEROMYCETIN, CHLOROMYCETIN SUCCINATE, KEMICETINE 1 g/vial inj, PHENIMYCIN 0.25, 0.5, 1.0 g inj. is the soluble but inactive ester which is used in the parenteral preparations. Intramuscular injection is painful and produces lower blood levels. It is hydrolysed in tissues to the free active form. However, bioavailability even on i.v. injection is only 70% due to renal excretion of the ester before hydrolysis.

Adverse effects

1. *Bone marrow depression* Of all drugs, chloramphenicol is the most important cause of aplastic anaemia, agranulocytosis, thrombocytopenia or pancytopenia. Two forms are recognized:
(a) Non-dose related idiosyncratic reaction: This is rare (1 in 40,000), unpredictable, but serious, often fatal, probably has a genetic basis and is more common after repeated courses. Aplastic anaemia is the most common manifestation. Many victims, even if they survive, develop leukaemias later.
(b) Dose and duration of therapy related myelosuppression: a direct toxic effect, predictable and probably due to inhibition of mitochondrial enzyme synthesis. This is often reversible without long-term sequelae. Liver and kidney disease predisposes to such toxicity.

2. *Hypersensitivity reactions* Rashes, fever, atrophic glossitis, angioedema are infrequent.

3. *Irritative effects* Nausea, vomiting, diarrhoea, pain on injection.

4. *Superinfections* These are similar to tetracyclines, but less common.

5. *Gray baby syndrome* It occurred when high doses (~100 mg/kg) were given prophylactically to neonates, especially premature. The baby stopped feeding, vomited, became hypotonic and respiration became irregular; an ashen gray cyanosis developed, followed by cardiovascular collapse and death.

It occurs because of inability of the newborn to adequately metabolize and excrete chloramphenicol.

Interactions Chloramphenicol inhibits tolbutamide, chlorpropamide, warfarin, cyclophosphamide and phenytoin metabolism. Toxicity can occur if dose adjustments are not done. Phenobarbitone, phenytoin, rifampin enhance chloramphenicol metabolism → reduce its concentration → failure of therapy may occur.

Erythromycin, clindamycin and chloramphenicol can exhibit mutual antagonism of antibacterial action; probably, due to proximity of their binding sites on bacterial 50S ribosome.

Uses

Because of serious (though rare) bone marrow toxicity:
(a) Never use chloramphenicol for minor infections or those of undefined etiology.
(b) Do not use chloramphenicol for infections treatable by other safer antimicrobials.
(c) Avoid repeated courses.
(d) Daily dose not to exceed 2–3 g; duration of therapy to be < 2–3 weeks, total dose in a course < 28 g.
(e) Regular blood counts (especially reticulocyte count) may detect dose-related bone marrow toxicity but not the idiosyncratic type.

In view of the above limitations, there is no indication in dentistry that warrants use of chloramphenicol despite its broad-spectrum antimicrobial action. In general medicine also systemic use of chloramphenicol is restricted to a few conditions.

1. *Enteric fever* Till recently chloramphenicol was the drug of choice for typhoid fever. However, emergence of resistant strains of *S. typhi* has markedly reduced response rate: 50–80% isolates are now chloramphenicol resistant. Many of these are multidrug resistant. Chloramphenicol may still be used if the *S. typhi* strain is known to be sensitive.

Chloramphenicol does not prevent or cure typhoid carrier state. It is only static while cidal action is required to eradicate carrier state.

2. *H. influenzae meningitis* Chloramphenicol is highly efficacious; it has excellent penetrability into CSF. However, the 3rd generation cephalosporins are being increasingly used now.

3. *Anaerobic infections* caused by *Bact. fragilis* and others (wound infections, pelvic and brain abscesses, etc.) respond well to chloramphenicol. However, clindamycin or metronidazole are preferred for these. Penicillin/cephalosporin is generally combined since most are mixed infections.

4. *Intraocular infections* Chloramphenicol given systemically attains high concentration in ocular fluid. It is the preferred drug for endophthalmitis caused by sensitive organisms.

5. *As second choice drug*
(a) to tetracyclines for brucellosis, cholera, rickettsial and chlamydial infections.
(b) to erythromycin for whooping cough.
(c) to penicillin for meningococcal or pneumococcal meningitis, e.g. in patients allergic to penicillin.
(d) to cotrimoxazole for *Shigella dysentery* enteritis.
(e) to fluoroquinolones in urinary tract infections.

6. *Topically* In conjunctivitis, external ear infections—it is highly effective. Topical use on skin or other areas is not recommended because of risk of sensitization.

AMINOGLYCOSIDE ANTIBIOTICS

These are a group of natural and semisynthetic antibiotics having polybasic amino groups linked glycosidically to two or more aminosugar residues. While they are extensively used to treat medical, surgical, gynaecological and other systemic infections, they are seldom employed in dentistry.

Unlike penicillin, which was a chance discovery, aminoglycosides are products of deliberate search for drugs effective against gram-negative bacteria. Streptomycin was the first member discovered in 1944 by Waksman and his colleagues. It assumed great importance because it was active against tubercle bacilli. Others have been produced later; now aminoglycosides are a sizable family. All aminoglycosides are produced by soil actinomycetes and have many common properties.

1. All are used as sulfate salts, which are highly water soluble; solutions are stable for months.
2. They ionize in solution; are not absorbed orally; distribute only extracellularly; do not penetrate brain or CSF.
3. All are excreted unchanged in urine by glomerular filtration.
4. All are bactericidal and more active at alkaline pH.
5. They act by interferring with bacterial protein synthesis.
6. All are active primarily against aerobic gram-negative bacilli, but do not inhibit anaerobes.
7. There is only partial cross resistance among them; an organism resistant to one aminoglycoside may still respond to another.
8. They have relatively narrow margin of safety between therapeutic and toxic concentrations.
9. All exhibit ototoxicity and nephrotoxicity which is tentatively graded in Table 29.2.

Table 29.2: Comparative toxicity of aminoglycoside antibiotics (tentative)

	Systemically used aminoglycoside	*Ototoxicity*		*Nephrotoxicity*
		vestibular	*cochlear*	
1.	Streptomycin	++	±	+
2.	Gentamicin	++	+	++
3.	Kanamycin	+	++	++
4.	Tobramycin	+±	+	+
5.	Amikacin	+	++	++
6.	Sisomicin	++	+	++
7.	Netilmicin	+	+	++

Neomycin and Framycetin are aminoglycosides with high systemic toxicity, therefore, used only topically.

MECHANISM OF ACTION

The aminoglycosides are bactericidal antibiotics, all having the same general pattern of action which may be described in two main steps:
(a) Transport of the aminoglycoside through the bacterial cell wall and cytoplasmic membrane.
(b) Binding to ribosomes resulting in inhibition of protein synthesis.

Transport of aminoglycoside into bacteria is a multistep process. They diffuse across the outer coat of gram-negative bacteria through porin channels. Entry from the periplasmic space across the cytoplasmic membrane is carrier mediated which is linked to the electron transport chain. Thus, penetration is dependent upon maintenance of a polarized membrane and on oxygen dependent active processes. These are inactivated under anaerobic conditions; anaerobes are not sensitive and facultative anaerobes are more resistant when O_2 supply is deficient, e.g. inside big abscesses. Penetration is also favoured by high pH; aminoglycosides are ~20 times more active in alkaline than in acidic medium.

Once inside the bacterial cell, streptomycin binds to 30S ribosomes, but other aminoglycosides bind to additional sites on 50S subunit as well as to 30S-50S interface. They freeze initiation of protein synthesis (*see* Fig. 29.1), prevent polysome formation and promote their disaggregation to monosomes so that only one ribosome is attached to each strand of mRNA. Binding of aminoglycoside to 30S-50S juncture causes distortion of mRNA codon recognition resulting in misreading of the code: one or more wrong amino acids are entered in the peptide chain and/or peptides of abnormal lengths are produced. Different aminoglycosides cause misreading at different levels depending upon their selective affinity for specific ribosomal proteins.

The cidal action of these drugs appears to be based on secondary changes in the integrity of bacterial cell membrane, because other antibiotics which inhibit protein synthesis (tetracyclines, chloramphenicol, erythromycin) are only static. After exposure to aminoglycosides, sensitive bacteria become more permeable; ions, amino acids and even proteins leak out followed by cell death. This probably results from incorporation of the defective proteins into the cell membrane. One of the consequences of aminoglycoside induced alteration of cell membrane is augmentation of the carrier-mediated entry of the antibiotic. This reinforces the lethal action.

The cidal action of aminoglycosides is concentration dependent, i.e. rate of bacterial cell killing is directly related to the ratio of the peak antibiotic concentration to the MIC value. They also exert a long and concentration dependent 'postantibiotic effect'. It has, therefore, been argued that despite their short t½ (2–4 hr), single injection of the total daily dose of aminoglycoside may be more effective and possibly less toxic than its conventional division into 2–3 doses.

MECHANISM OF RESISTANCE

Resistance to aminoglycosides is acquired by one of the following mechanisms:
(a) Acquisition of cell membrane bound inactivating enzymes which phosphorylate/adenylate or acetylate the antibiotic. The conjugated aminoglycosides do not bind to the target ribosomes and are incapable of enhancing active transport like the unaltered drug. These enzymes are acquired mainly by conjugation and transfer of plasmids. Nosocomial microbes have become rich in such plasmids, some of which encode for multidrug resistance. This is the most important mechanism of development of resistance to aminoglycosides. Susceptibility of different aminoglycosides to these enzymes differs. Thus, cross resistance among different members is partial or absent.
(b) Mutation decreasing the affinity of ribosomal proteins that normally bind the aminoglycoside: this mechanism can confer high degree resistance, but operates to a limited extent, e.g. *E. coli* that develop streptomycin resistance by single step mutation do not bind the antibiotic on the polyribosome. Only a few other instances are known. This type of resistance is specific for a particular aminoglycoside.

(c) Decreased efficiency of the aminoglycoside transporting mechanism: either the pores in the outer coat become less permeable or the active transport is interfered. This again is not frequently encountered in the clinical setting. In some *Pseudomonas* which develop resistance, the antibiotic induced 2nd phase active transport has been found to be deficient.

SHARED TOXICITIES

The aminoglycosides produce toxic effects which are common to all members, but the relative propensity differs (*see* Table 29.2).

1. Ototoxicity This is the most important dose and duration of treatment related adverse effect. The vestibular or the cochlear part may be primarily affected by a particular aminoglycoside. These drugs are concentrated in the labyrinthine fluid and are slowly removed from it when the plasma concentration falls. Ototoxicity is greater when plasma concentration of the drug is persistently high and above a threshold value. The vestibular/cochlear sensory cells and hairs undergo concentration dependent destructive changes. Aminoglycoside ear drops can cause ototoxicity when instilled in patients with perforated eardrum; contraindicated in them.

Cochlear damage It starts from the base and spreads to the apex; hearing loss affects the high frequency sound first, then progressively encompasses the lower frequencies. No regeneration of the sensory cells occurs; auditory nerve fibres degenerate in retrograde manner—deafness is permanent. Older patients and those with pre-existing hearing defect are more susceptible. Initially, the cochlear toxicity is asymptomatic; can be detected only by audiometry. Tinnitus then appears, followed by progressive hearing loss. On stopping the drug, tinnitus disappears in 4–10 days, but frequency loss persists.

Vestibular damage Headache is usually first to appear, followed by nausea, vomiting, dizziness, nystagmus, vertigo and ataxia. When the drug is stopped at this stage, it passes into a chronic phase lasting 6 to 10 weeks in which the patient is asymptomatic while in bed and has difficulty only during walking. Compensation by visual and proprioceptive positioning and recovery (often partial) occurs over 1–2 years. Permanency of changes depends on the extent of initial damage and the age of the patient (elderly have poor recovery).

2. Nephrotoxicity It manifests as tubular damage resulting in loss of urinary concentrating power, low g.f.r., nitrogen retention, albuminuria and casts. Aminoglycoside toxicity is related to the total amount of the drug received by the patient. It is more in the elderly and in those with pre-existing kidney disease. Essentially, renal damage caused by aminoglycosides is totally reversible, provided the drug is promptly discontinued. An important implication of aminoglycoside induced nephrotoxicity is reduced clearance of the antibiotic → higher blood levels → enhanced ototoxicity.

3. Neuromuscular blockade All aminoglycosides reduce ACh release from the motor nerve endings: interfere with mobilization of centrally located synaptic vesicles to fuse with the terminal membrane as well as decrease the sensitivity of the muscle end-plates to ACh. Effect of this action is not manifested ordinarily in the clinical use of these drugs. However, apnoea and fatalities have occurred when these antibiotics were put into peritonial or pleural cavities after an operation, especially if a curare-like muscle relaxant had been used during surgery. Rapid absorption from the peritoneum/pleura produces high blood levels and adds to the residual action of the neuromuscular blocker.

Neomycin and streptomycin have higher propensity while tobramycin is least likely to produce this effect. It can be partially antagonized by i.v. injection of a calcium salt. Neostigmine has inconsistent reversing action.

Myasthenic weakness is accentuated by these drugs. Neuromuscular blockers should be used cautiously in patients receiving aminoglycosides.

PRECAUTIONS AND INTERACTIONS

(i) Avoid during pregnancy: risk of foetal ototoxicity.
(ii) Avoid concurrent use of other ototoxic drugs, e.g. high ceiling diuretics, minocycline.
(iii) Avoid concurrent use of other nephrotoxic drugs, e.g. amphotericin B, vancomycin, cyclosporine and cisplatin.
(iv) Cautious use in patients past middle age and in those with kidney damage.
(v) Cautious use of muscle relaxants in patients receiving an aminoglycoside.
(vi) Do not mix aminoglycoside with any drug in the same syringe/infusion bottle.

Streptomycin

It is the oldest aminoglycoside antibiotic obtained from *Streptomyces griseus*; used extensively in the past, but now practically restricted to treatment of tuberculosis. The antimicrobial spectrum of streptomycin is relatively narrow: active primarily against aerobic gram-negative bacilli, but potency is low. Sensitive organisms are—*H. ducreyi, Brucella, Yersinia pestis, Francisella tularensis, Nocardia, Calym. granulomatis, M. tuberculosis*. Only few strains of *E. coli, H. influenzae, V. cholerae, Shigella, Klebsiella*, enterococci and some gram-positive cocci are now inhibited, that too at higher concentrations. All other organisms are unaffected.

Resistance Many organisms develop rapid resistance to streptomycin, either by one-step mutation or by acquisition of plasmid which codes for inactivating enzymes. In the intestinal and urinary tracts, resistant organisms may emerge within 2 days of therapy. *E. coli., H. influenzae, Str. pneumoniae, Str. pyogenes, Staph. aureus* have become largely resistant. If it is used alone, *M. tuberculosis* also become resistant.

Streptomycin dependence Certain mutants grown in the presence of streptomycin become dependent on it. This occurs when the antibiotic induced misreading of the genetic code becomes a normal feature for the organism.

Cross resistance Only partial and often unidirectional cross resistance occurs between streptomycin and other aminoglycosides.

Pharmacokinetics Streptomycin is highly ionized. It is neither absorbed nor destroyed in the g.i.t. However, absorption from injection site in muscles is rapid. It is distributed only extracellularly: volume of distribution (0.3 L/kg) is nearly equal to the extracellular fluid volume. It attains low concentrations in serous fluids like synovial, pleural, etc. Concentrations in CSF and aqueous humour are often non-therapeutic, even in the presence of inflammation. Plasma protein binding is clinically insignificant.

Streptomycin is not metabolized—excreted unchanged in urine. Glomerular filtration is the main channel: tubular secretion and reabsorption are negligible. The plasma t½ is 2–4 hours, but the drug persists longer in tissues. Renal clearance of streptomycin parallels creatinine clearance and is approximately 2/3rd of it. Half-life is prolonged and accumulation occurs in patients with renal insufficiency, in elderly and neonates who have low g.f.r. Reduction in dose or increase in dose interval is essential in these situations.

These pharmacokinetic features apply to all systemically administered aminoglycosides.

Adverse effects About 1/5th patients given streptomycin 1 g BD i.m. experience vestibular disturbances. Auditory disturbances are less common.

Streptomycin has the lowest nephrotoxicity among aminoglycosides. Hypersensitivity reactions are rare; rashes, eosinophilia, fever and exfoliative dermatitis have been noted. Anaphylaxis is very rare. Topical use is contraindicated for fear of contact sensitization.

Superinfections are not significant. Pain at injection site is common. Paraesthesias and scotoma are occasional.

AMBISTRYN-S 0.75, 1 g dry powder per vial for inj.
Acute infections: 1 g (0.75 g in those above 50 yr age) i.m. BD for 7–10 days.
Tuberculosis: 1 g or 0.75 g i.m. OD or twice weekly for 30–60 days.

Uses

Streptomycin is not used in dentistry. Other uses are:

1. Tuberculosis: *see* Ch. 31.
2. Subacute bacterial endocarditis (SABE): Streptomycin (now mostly gentamicin) is given in conjunction with penicillin, because enterococci and *Strep. viridans* have low susceptibility to the latter drug and the combination is synergistic. A 4–6 weeks of treatment is needed.
3. Plague: It effects rapid cure, may be employed in confirmed cases, but tetracyclines have been more commonly used.
4. Tularaemia: Streptomycin is the drug of choice for this rare disease.

In most other situations, e.g. urinary tract infection, peritonitis, septicaemias, etc. where streptomycin was used earlier, gentamicin or one of the newer aminoglycosides is now preferred due to low potency and widespread resistance to streptomycin.

Gentamicin

It was obtained from *Micromonospora purpurea* in 1964; has become the most commonly used aminoglycoside for acute infections. The properties of gentamicin including plasma t½ of 2–4 hours after i.m. injection are the same as described above for streptomycin, but there are following differences:

(a) It is more potent (MIC for most organisms is 4–8 times lower.)

(b) It has a broader spectrum of action: effective against *Ps. aeruginosa* and most strains of *Proteus, E. coli, Klebsiella, Enterobacter, Serratia.*

(c) It is ineffective against *M. tuberculosis, Strep. pyogenes* and *Strep. pneumoniae*, but inhibits many *Strep. faecalis* and some *Staph. aureus*.

(d) It is relatively more nephrotoxic.

Dose: The dose of gentamicin must be precisely calculated according to body weight and level of renal function. For an average adult with normal renal function (creatinine clearance > 100 ml/min), 3–5 mg/kg/day i.m. either as single dose or divided in three 8 hourly doses is recommended.

The daily dose of gentamicin (and other aminoglycosides) should be reduced in patients with impaired renal function according to measured creatinine clearance. A general guideline is:

CL cr (ml/min)	% of daily dose
70	70% daily
50	50% daily
30	30% daily
10–30	60% alternate day
<10	40% alternate day

GARAMYCIN, GENTASPORIN, GENTICYN 20, 60, 80, 240 mg per vial inj; also 0.3% eye/ear drops, 0.1% skin cream.

Use in dentistry Because of its predominantly gram-negative spectrum of activity, inefficacy against anaerobes and need for parenteral administration, gentamicin (and other aminoglycosides) is not employed to treat dental infections. The only application in dentistry is to give gentamicin 2 mg/kg i.m./i.v. (single dose) to supplement amoxicillin or vancomycin for prophylaxis of bacterial endocarditis following dental surgery in patients with prosthetic heart valves or in those having past history of bacterial endocarditis or those to be operated under general anaesthesia.

General medical uses Gentamicin is the cheapest (other than streptomycin) and the first line aminoglycoside antibiotic. However, because of low therapeutic index, its use should be restricted to serious gram-negative bacillary infections.

1. Gentamicin is very valuable for preventing and treating respiratory infections in critically ill patients; in those with impaired host defence (receiving anticancer drugs or high-dose corticosteroids; AIDS; neutropenic), patients in resuscitation wards, with tracheostomy or on respirators; postoperative pneumonias; patients with implants and in intensive care units. It is often combined with a penicillin/cephalosporin or another antibiotic in these situations. However,

resistant strains have emerged in many hospitals and nosocomial infections are less amenable to gentamicin now. Another aminoglycoside (tobramycin, amikacin, sisomicin, netilmicin) is then selected on the basis of the sensitivity pattern.

2. *Pseudomonas, Proteus* or *Klebsiella* infections: burns, urinary tract infection, pneumonia, lung abscesses, osteomyelitis, middle ear infection, septicaemia, etc. are an important area of use of gentamicin. It may be combined with piperacillin or a third generation cephalosporin for serious infections. Topical use on infected burns and in conjunctivitis is permissible.

3. Meningitis caused by gram-negative bacilli. Because this is a serious condition, drug combinations including an aminoglycoside are often used.

4. SABE: gentamicin is more commonly used in place of streptomycin to accompany penicillin.

Kanamycin

Obtained from *S. kanamyceticus* (in 1957), it was the second systemically used aminoglycoside to be developed after streptomycin. It is similar to streptomycin in all respects including lack of activity against *Pseudomonas*. However, it is more toxic, both to the cochlea and to kidney. Hearing loss is more common than vestibular disturbance.

Because of toxicity and narrow spectrum of activity, it has been largely replaced by other aminoglycosides. It is occasionally used as a second line drug in resistant tuberculosis.

Dose: 0.5 g i.m. BD-TDS: KANAMYCIN, KANCIN, KANAMAC 0.5, 1 g inj.

Tobramycin

It was obtained from *S. tenebrarius* in the 1970s. The antibacterial and pharmacokinetic properties, as well as dosage are almost identical to gentamicin, but it is 2–4 times more active against *Pseudomonas* and *Proteus*, including those resistant to gentamicin. However, it is not useful for combining with penicillin in the treatment of enterococcal endocarditis. It should be used only as a reserve alternative to gentamicin. Serious infections caused by *Pseudomonas* and *Proteus* are its only current indications. Ototoxicity and nephrotoxicity is probably lower than gentamicin.

Dose: 3–5 mg/kg day in 1–3 doses.

TOBACIN 20, 60, 80 mg in 2 ml inj. 0.3% eye drops.
TOBRANEG 20, 40, 80 mg per 2 ml inj.

Amikacin

It is a semisynthetic derivative of kanamycin to which it resembles in pharmacokinetics, dose and toxicity. The outstanding feature of amikacin is its resistance to bacterial aminoglycoside inactivating enzymes. Thus, it has the widest spectrum of activity, including many organisms resistant to other aminoglycosides. However, relatively higher doses are needed for *Pseudomonas*, *Proteus* and *Staph.* infections.

The range of conditions in which amikacin can be used is the same as for gentamicin. It is recommended as a reserve drug for hospital acquired gram-negative bacillary infections. It is effective in tuberculosis, but rarely used for this purpose. More hearing loss than vestibular disturbance occurs in toxicity.

Dose: 15 mg/kg/day in 1–3 doses; urinary tract infection 7.5 mg/kg/day.

AMICIN, MIKACIN, MIKAJECT 100 mg, 250 mg, 500 mg in 2 ml inj.

Sisomicin

Introduced in 1980s, it is a natural aminoglycoside from *Micromonospora inyoensis* that is chemically and pharmacokinetically similar to gentamicin, but somewhat more potent on *Pseudomonas*, a few other gram-negative bacilli and β-haemolytic *Streptococci*. It is moderately active on faecal *Streptococci*—can be combined with penicillin for SABE. However, it is susceptible to aminoglycoside inactivating enzymes and offers no advantage in terms of ototoxicity and nephrotoxicity. It can be used interchangeably with gentamicin for the same purposes in the same doses.

ENSAMYCIN, SISOPTIN 50 mg, 10 mg (pediatric) per ml in 1 ml amps.

Netilmicin

This semisynthetic derivative of sisomicin has a broader spectrum of activity than gentamicin. It

is relatively resistant to aminoglycoside inactivating enzymes and thus effective against many gentamicin-resistant strains. It is more active against *Klebsiella*, *Enterobacter* and *Staphylococci*, but less active against *Ps. aeruginosa*.

Pharmacokinetic characteristics and dosage of netilmicin are similar to gentamicin. Experimental studies have shown it to be less ototoxic, but clinical evidence is inconclusive: hearing loss occurs, though fewer cases of vestibular damage have been reported.

A marginal improvement in antibacterial spectrum, clinical efficacy and possibly reduced toxicity indicates that netilmicin could be preferable in critically ill and neutropenic patients, and retain activity in hospitals where gentamicin resistance has spread.

Dose: 4–6 mg/kg/day in 1–3 doses; NETROMYCIN 10, 25, 50 mg in 1 ml, 200 mg in 2 ml and 300 mg in 3 ml inj.

Neomycin

Obtained from *S. fradiae*, it is a wide spectrum aminoglycoside, active against most gram-negative bacilli and some gram-positive cocci. However, *Pseudomonas* and *Strep. pyogenes* are not sensitive. Neomycin is highly toxic to the internal ear (mainly auditory) and to kidney. It is, therefore, not used systemically. It is poorly absorbed from the g.i.t. Oral and topical administration does not ordinarily cause systemic toxicity.

Dose: 0.25–1 g QID oral, 0.3–0.5% topical.

NEOMYCIN SULPHATE 350, 500 mg tab, 0.3% skin oint, 0.5% skin cream, eye oint.

NEBASULF: Neomycin sulph. 5 mg, bacitracin 250 U, sulfacetamide 60 mg/g oint. and powder for surface application.

POLYBIOTIC CREAM: Neomycin sulph. 5 mg, polymyxin 5,000 IU, gramicidin 0.25 mg/g cream.

Uses

1. Topically (often in combination with polymyxin, bacitracin, etc.) for infected wound, ulcers, burn, external ear infections, conjunctivitis.
2. Orally for:

(a) Preparation of bowel before surgery: may reduce postoperative infections.

(b) Hepatic coma: Normally NH_3 is produced by colonic bacteria. This is absorbed and converted to urea by liver. In severe hepatic failure, detoxication of NH_3 does not occur, blood NH_3 levels rise and produce encephalopathy. Neomycin, by suppressing intestinal flora, diminishes NH_3 production and lowers its blood level. However, because of the toxic potential, it is infrequently used for this purpose.

Adverse effects Applied topically neomycin has low sensitizing potential, however, rashes do occur.

Oral neomycin has a damaging effect on intestinal villi—prolonged treatment can induce malabsorption syndrome with diarrhoea and steatorrhoea. Due to marked suppression of gut flora, superinfection by *Candida* can occur.

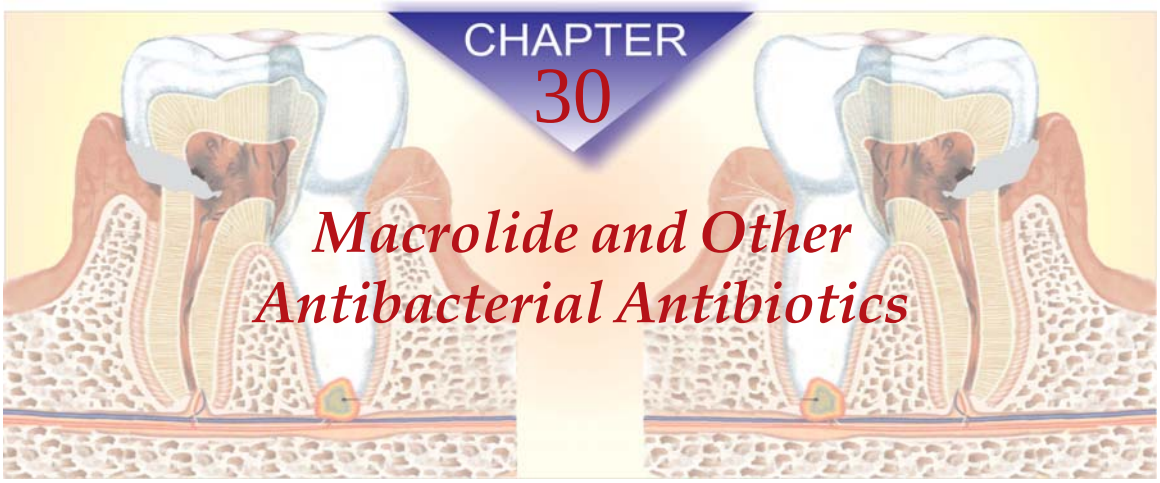
Small amounts that are absorbed from the gut or topical sites are excreted unchanged by kidney. This may accumulate in patients with renal insufficiency—cause further kidney damage and ototoxicity.

Applied to serous cavities (peritoneum), it can cause apnoea due to muscle paralysing action.

Framycetin

Obtained from *S. lavendulae*, it is very similar to neomycin. It is too toxic for systemic administration and is used topically on skin, eye, ear in the same manner as neomycin.

SOFRAMYCIN, FRAMYGEN 1% skin cream, 0.5% eye drops or oint.



CHAPTER 30

Macrolide and Other Antibacterial Antibiotics

MACROLIDE ANTIBIOTICS

These are antibiotics having a macrocyclic lactone ring with attached sugars. *Erythromycin* has been in use from the 1950s, *Roxithromycin*, *Clarithromycin* and *Azithromycin* are the later additions.

ERYTHROMYCIN

It was isolated from *Streptomyces erythreus* in 1952 and is widely employed, mainly as an alternative to penicillin. It is quite frequently prescribed in dentistry. Water solubility of erythromycin is limited, and the solution remains stable only when kept in cold.

Mechanism of action Erythromycin is bacteriostatic at low but cidal at high concentrations. Cidal action also depends on the organism concerned and its rate of multiplication. Sensitive gram-positive bacteria accumulate erythromycin intracellularly by active transport which is responsible for their high susceptibility to this antibiotic. It is several fold more active in alkaline medium, because the nonionized (penetrable) form of the drug is favoured at higher pH.

Erythromycin acts by inhibiting bacterial protein synthesis. It combines with 50S ribosome subunit and interferes with 'translocation' (*see* Fig. 29.1). After peptide bond formation between the newly attached amino acid and the nacent peptide chain at the acceptor (A) site the elongated peptide is translocated back to the peptidyl (P) site, making the A site available for next aminoacyl tRNA attachment. This is prevented by erythromycin and the ribosome fails to move along the mRNA to expose the next codon. As an indirect consequence, peptide chain may be prematurely terminated: synthesis of larger proteins is specifically suppressed.

Antimicrobial spectrum It is narrow, includes mostly gram-positive and a few gram-negative organisms, and overlaps considerably with that of penicillin G. Erythromycin is highly active against *Str. pyogenes* and *Str. pneumoniae, N. gonorrhoeae, Clostridia, C. diphtheriae, Listeria*. Most penicillin-resistant *Staphylococci* and *Streptococci* were initially sensitive, but have now become resistant to erythromycin also.

In addition, *Campylobacter, Legionella, Branhamella catarrhalis, Gardnerella vaginalis* and *Mycoplasma* that are not affected by penicillin are highly sensitive to erythromycin. Few others including oral anaerobes, *H. influenzae, H. ducreyi, B. pertussis, Chlamydia trachomatis, Str. viridans, N. meningitidis* and *Rickettsiae* are moderately sensitive. Enterobacteriaceae, other gram-negative bacilli and *B. fragilis* are not inhibited.

Resistance All cocci readily develop resistance to erythromycin, mostly by mechanisms which

render them less permeable to erythromycin or acquire the capacity to pump it out. Resistant Enterobacteriaceae have been found to produce an erythromycin esterase. Alteration in the ribosomal binding site for erythromycin by plasmid encoded methylase enzyme is yet another mechanism of resistance. All the above types of resistance are plasmid mediated, while change in the 50S ribosome by chromosomal mutation has also been found.

Cross resistance with other macrolides, clindamycin and chloramphenicol occurs because the ribosomal binding sites for all these are proximal to each other.

Pharmacokinetics Erythromycin base is acid labile. To protect it from gastric acid, it is given as enteric coated tablets, from which absorption is incomplete and food delays absorption by retarding gastric emptying. Its acid stable esters are better absorbed.

Erythromycin is widely distributed in the body, enters into abscesses, crosses serous membranes and placenta but not blood-brain barrier. It is 70–80% plasma protein bound, partly metabolized and excreted primarily in bile in the active form. Renal excretion is minor; dose need not be altered in renal failure. The plasma t½ is 1.5 hours, but erythromycin persists longer in tissues.

Preparations and dose

Dose: 250–500 mg 6 hourly (max. 4 g/day), children 30–60 mg/kg/day.

1. Erythromycin (base): ERYSAFE 250, mg tabs, EROMED 333 mg tab, 125 mg/5 ml susp.
2. Erythromycin stearate: blood levels produced are similar to those after erythromycin base. ERYTHROCIN 250, 500 mg tab, 100 mg/5 ml susp., 100 mg/ml ped. drops. ETROCIN, ERYSTER 250 mg tab, 100 mg/5 ml dry syr, EMTHRO 250 mg tab, 125 mg/5 ml susp.
3. Erythromycin estolate (lauryl sulfate): it is relatively acid stable and better absorbed after oral administration. However, concentration of free and active drug in plasma may be the same as after administration of erythromycin base. Certain organisms hydrolyse it to liberate the free form intracellularly and are more susceptible to it. ALTHROCIN 250, 500 mg tab, 125 mg kid tab, 125 mg/5 ml and 250 mg/5 ml dry syr, 100 mg/ml ped. drops, E-MYCIN 100, 250 mg tab, 100 mg/5 ml dry syr; ERYC-S 250 mg tab, 125 mg/5 ml dry syr.
4. Erythromycin ethylsuccinate: well absorbed orally; ERYNATE 100 mg/5 ml dry syr, ERYTHROCIN 100 mg/ml drops, 125 mg/5 ml syr.

Adverse effects Erythromycin base is a remarkably safe drug.

1. *Gastrointestinal* Mild-to-severe epigastric pain is experienced by many patients, especially children, on oral therapy. Diarrhoea is occasional. Erythromycin stimulates motilin receptors in the g.i.t.—thereby induces gastric contractions, hastens gastric emptying and promotes intestinal motility. However, contribution of this action to the g.i. side effects is not known.

2. Very high doses of erythromycin have caused reversible hearing impairment.

3. *Hypersensitivity* Rashes and fever are infrequent. Other allergic manifestations are rare with erythromycin base or esters other than estolate.

Hepatitis with cholestatic jaundice resembling viral hepatitis or extrahepatic biliary obstruction occurs with the estolate ester (rarely with ethyl succinate or stearate ester) after 1–3 weeks. Incidence is higher in pregnant women. It clears on discontinuation of the drug, and is probably due to hypersensitivity to the estolate ester; erythromycin base or other esters can be given to these patients without recurrence. Though the estolate is acid stable, tasteless and better absorbed, it has been banned in some countries (but not in India).

Interaction Erythromycin inhibits hepatic oxidation of many drugs. The clinically significant interactions are—rise in plasma levels of theophylline, carbamazepine, valproate, ergotamine, warfarin, terfenadine, astemizole and cisapride.

Several cases of Q-T prolongation, serious ventricular arrhythmias and death have been reported due to inhibition of CYP3A4 by erythromycin/clarithromycin resulting in high blood levels of concurrently administered terfenadine/astemizole/cisapride (*see* p. 102and 275).

Uses

Dental infections Because erythromycin is orally administered, safe and active against both aerobic and anaerobic gram-positive bacteria commonly infecting dental structures and mouth, it is the second choice drug to penicillins for periodontal/periapical abscesses, necrotizing ulcerative gingivitis, postextraction infections, gingival cellulitis, etc. It is particularly valuable for patients allergic to penicillins, or those with penicillin-resistant infections. However, being bacteriostatic, it is less effective than penicillins in eradicating dental infections caused by penicillin-sensitive bacteria. It is also a good alternative to penicillin for prophylactic uses in dentistry.

General medical uses The most common indications of erythromycin are as a substitute for penicillins in allergic patients for pharyngitis, tonsillitis and other respiratory/ENT infections as well as for prophylaxis of rheumatic fever. It is one of the first choice drugs for atypical pneumonia caused by *Mycoplasma pneumoniae*, diphtheria (antitoxin therapy is the primary measure), early stages of whooping cough and chancroid. It is a second choice drug for Legionnaires' pneumonia, *Campylobacter* enteritis, chlamydial urogenital infections and some skin/soft tissue infections caused by penicillin resistant *Staph. aureus*, but not MRSA.

NEWER MACROLIDES

In an attempt to overcome the limitations of erythromycin like narrow spectrum, gastric intolerance, gastric acid lability, low oral bioavailability, moderate tissue penetration and short half-life, a number of semisynthetic macrolides have been produced, of which roxithromycin, clarithromycin and azithromycin are available.

Roxithromycin It is a semisynthetic long-acting acid stable macrolide whose antimicrobial spectrum resembles closely with that of erythromycin. It is more potent against *Branh. catarrhalis, Gard. vaginalis* and *Legionella* but less potent against *B. pertussis*. Improved enteral absorption and tissue penetration, an average plasma t½ of 12 hours making it suitable for twice daily dosing, as well as better gastric tolerability are its desirable features.

Though its affinity for cytochrome P450 is lower, drug interactions with terfenadine, cisapride and others are not ruled out. Thus, it is an alternative to erythromycin for respiratory, ENT, orodental, skin and soft tissue and genital tract infections with similar efficacy.

Dose: 150–300 mg BD 30 min before meals, children 2.5–5 mg/kg BD;

ROXID, ROXIBID, RULIDE 150, 300 mg tab, 50 mg kid tab, 50 mg /5 ml liquid; ROXEM 50 mg kid tab, 150 mg tab.

Clarithromycin The antimicrobial spectrum of clarithromycin is similar to erythromycin; in addition, it includes *Mycobact. avium* complex (MAC), other atypical mycobacteria, *Mycobact. leprae.* It is more active against sensitive strains of gram-positive cocci, many oral anaerobes like *Bact. melaninogenicus, Peptococcus, Cl. perfringens* (but not *Bact. fragilis*), *Moraxella, Legionella, Mycoplasma pneumoniae* and *Helicobacter pylori*. However, bacteria that have developed resistance to erythromycin are resistant to clarithromycin also.

Clarithromycin is more acid stable than erythromycin, and is rapidly absorbed; oral bioavailability is ~50% due to first pass metabolism; food delays absorption. It has slightly greater tissue distribution than erythromycin and is metabolized by saturation kinetics—t½ is prolonged from 3–6 hours at lower doses to 6–9 hours at higher doses. An active metabolite is produced. About 1/3rd of oral dose is excreted unchanged in urine, but no dose modification is needed in liver disease or in mild-to-moderate kidney failure.

Clarithromycin is indicated in upper and lower respiratory tract infections, orodental infections, sinusitis, otitis media, atypical pneumonia, skin and skin structure infections mostly due to *Strep. pyogenes* and some *Staph. aureus*. Used as a component of triple drug regimen (*see* p. 271) it eradicates *H. pylori* in 1–2 weeks. It is a first line drug in combination

regimens for MAC infection in AIDS patients and a second line drug for other atypical mycobacterial diseases as well as leprosy.

Dose: 250 mg BD for 7 days; severe cases 500 mg BD up to 14 days.

CLARIBID 250, 500 mg tab, 250 mg/5 ml dry syr; CLARIMAC 250, 500 mg tabs; SYNCLAR 250 mg tab, 125 mg/5 ml dry syr.

Side effects of clarithromycin are similar to erythromycin, but gastric tolerance is better. High doses can cause reversible hearing loss. Few cases of pseudomembranous enterocolitis, hepatic dysfunction or rhabdomyolysis are reported. Its safety in pregnancy and lactation is not known. The drug interaction potential is also similar to erythromycin.

Azithromycin This new azalide congener of erythromycin has an expanded spectrum, improved pharmacokinetics, better tolerability and drug interaction profiles. It is more active than other macrolides against *H. influenzae*, and certain anaerobes like *Peptostreptococcus*, few *Clostridia*, but less active against gram-positive cocci. High activity is exerted on respiratory pathogens—*Mycoplasma*, *Chlamydia pneumoniae*, *Legionella*, *Moraxella* and on others like *Campylobacter*, *Ch. trachomatis*, *N. gonorrhoeae*. However, it is not active against erythromycin-resistant bacteria. Penicillinase producing *Staph. aureus* are inhibited but not methicillin-resistant ones. Good activity is noted against MAC.

The remarkable pharmacokinetic properties are acid stability, rapid oral absorption, marked tissue distribution and intracellular penetration. However, absorption is decreased by food. Concentration in most tissues exceeds that in plasma. Particularly high concentrations are attained inside macrophages and fibroblasts: volume of distribution is ~30 L/kg. Slow release from the intracellular sites contributes to its long terminal t½ of >50 hr. It is largely excreted unchanged in bile, renal excretion is < 10%.

Azithromycin can be used in orodental infections in place of erythromycin, particularly in those not tolerating the latter. It is also an alternative for prophylaxis of postdental surgery wound infection/endocarditis in predisposed patients. Because of higher efficacy, better gastric tolerance and convenient once a day dosing, azithromycin is now preferred over erythromycin as first choice drug for infections such as:

(a) *Legionnaires'* pneumonia.

(b) *Chlamydia trachomatis*: nonspecific urethritis and genital infections in both men and women. It is also the drug of choice for chlamydial pneumonia and is being preferred over tetracycline for trachoma in the eye.

The other indications of azithromycin are pharyngitis, tonsillitis, sinusitis, otitis media, pneumonias, acute exacerbations of chronic bronchitis, streptococcal and some staphylococcal skin and soft tissue infections, and gonorrhoea. In combination with at least one other drug it is effective in the prophylaxis and treatment of MAC in AIDS patients. Other potential uses are in typhoid, toxoplasmosis and malaria.

Dose: 500 mg once daily 1 hour before or 2 hours after food, (children above 6 months 10 mg/kg) for 3 days is sufficient for most infections.

AZITHRAL 250, 500 mg cap and 250 mg per 5 ml dry syr; AZIWOK 250 mg cap, 100 mg kid tab, 100 mg/5 ml and 200 mg/5 ml susp. AZIWIN 100, 250, 500 mg tab, 200 mg/5 ml liq. Also AZITHRAL 500 mg inj.

Side effects are mild gastric upset, abdominal pain (less than erythromycin), headache and dizziness. Azithromycin has been found not to interact with hepatic CYP3A4 enzyme. Interaction with theophylline, carbamazepine, warfarin, terfenadine and cisapride is not likely, but cannot be totally ruled out.

Spiramycin This macrolide antibiotic, though available for more than a decade, has been employed only sporadically. It resembles erythromycin in spectrum of activity and properties. Distinctively, it has been found to limit risk of transplacental transmission of *Toxoplasma gondii* infection. Its specific utility is for toxoplasmosis and recurrent abortion in pregnant women.

ROVAMYCIN 1.5 MU, 3 MU tabs, 0.375 MU/5 ml susp.

MISCELLANEOUS ANTIBIOTICS

Clindamycin

It is a lincosamide antibiotic similar in mechanism of action (inhibits protein synthesis by binding

to 50S ribosome) and spectrum of activity to erythromycin with which it exhibits partial cross resistance. It inhibits most gram-positive cocci (including penicillinase producing *Staph.*, but not MRSA), *C. diphtheriae, Nocardia, Actinomyces, Toxoplasma,* but the distinctive feature is its high activity against a variety of anaerobes, especially *Bact. fragilis.* Aerobic gram-negative bacilli, spirochetes, *Chlamydia, Mycoplasma* and *Rickettsia* are not affected.

Oral absorption of clindamycin is good. It penetrates into most skeletal and soft tissues, but not brain and CSF; accumulates in neutrophils and macrophages. It is largely metabolized and metabolites are excreted in urine and bile. The t½ is 3 hr.

Side effects are rashes, urticaria, abdominal pain, but the major problem is diarrhoea and pseudomembranous enterocolitis due to *Clostridium difficile* superinfection which is potentially fatal. The drug should be promptly stopped and metronidazole (alternatively vancomycin) given to treat it.

Because of potential toxicity, use of clindamycin is restricted to anaerobic and mixed infections, especially by *Bact. fragilis* causing abdominal, pelvic and lung abscesses. It is generally combined with an aminoglycoside or cephalosporin. Anaerobic streptococcal and *Cl. perfringens* infections and those involving bone and joints respond well. It has also been employed for prophylaxis in colorectal/pelvic surgery. In AIDS patients it is combined with pyrimethamine for toxoplasmosis. Topically it can be used for infected acne vulgaris.

In the treatment of dental infections, clindamycin is a reserve drug for those caused by anaerobic bacteria in patients who cannot be given a penicillin or a macrolide or for cases not responding to these antibiotics. Because of good penetration into bone clindamycin is particularly suited for dentoalveolar abscesses and other bone infections caused by *Staphylococci* or *Bacteroides*. It is an alternative antibiotic for prophylaxis of endocarditis due to postextraction bacteraemia in patients with damaged heart valves or other risk factors. Because only a single dose is needed for this purpose, there is little risk of pseudomembranous enterocolitis which otherwise is the most important limitation of clindamycin.

Clindamycin, erythromycin and chloramphenicol can exhibit mutual antagonism, probably because their ribosomal binding sites are proximal; binding of one hinders access of the other to its target site. Clindamycin potentiates neuromuscular blockers.

Dose: 150–300 mg QID oral; 200–600 mg i.v. 8 hourly; DALCAP 150 mg cap; CLINCIN 150, 300 mg cap; DALCIN, 150, 300 mg cap, 300 mg/2 ml and 600 mg/4 ml inj.

Lincomycin

It is the forerunner of clindamycin; has similar antibacterial and toxic properties, but is less potent and produces a higher incidence of diarrhoea and colitis—deaths have occurred. Thus, it has been largely replaced by clindamycin.
Dose: 500 mg TDS-QID oral; 600 mg i.m. or by i.v. infusion 6–12 hourly.
LINCOCIN 500 mg cap, 600 mg/2 ml inj; LYNX 250, 500 mg cap, 125 mg/5 ml syr, 300 mg/ml inj in 1, 2 ml amp.

Vancomycin

It is a glycopeptide antibiotic discovered in 1956 as a penicillin substitute that has assumed special significance due to efficacy against MRSA, *Strep. viridans, Enterococcus* and *Cl. difficile*. It is bactericidal to gram-positive cocci, *Neisseria, Clostridia*, oral cavity anaerobes and diphtheroids. However, in hospitals where it has been extensively used for surgical prophylaxis, etc., vancomycin-resistant *Staph. aureus, Enterococcus faecium* and *E. faecalis* have emerged. These nosocomial bacteria are resistant to methicillin and most other antibiotics as well.

Vancomycin acts by inhibiting bacterial cell wall synthesis. It binds to the terminal dipeptide 'D-ala-D-ala' sequence of peptidoglycan units—prevents its release from the carrier so that assembly of the units at the cell membrane and their cross linking to form the cell wall cannot take place. Enterococcal resistance to vancomycin is due to a plasmid mediated alteration of the dipeptide target.

Vancomycin is not absorbed orally. After i.v. administration, it is widely distributed, penetrates serous cavities, inflamed meninges and is excreted mainly unchanged by glomerular filtration with a t½ of 6 hours. Dose reduction is needed in renal insufficiency.

Toxicity: Systemic toxicity of vancomycin is high. It can cause plasma concentration dependent nerve deafness which may be permanent. Kidney damage is also dose related. Other oto and nephrotoxic drugs like aminoglycosides must be very carefully administered when vancomycin is being used. Skin allergy and fall in BP during i.v. injection due to histamine release are the other problems. Rapid i.v. injection has caused chills, fever, urticaria and intense flushing—called 'Red man syndrome'.

Uses: Given orally (125–500 mg 6 hourly), it is the second choice drug to metronidazole for antibiotic associated pseudomembranous enterocolitis caused by *C. difficile*.

Systemic use (500 mg 6 hourly or 1 g 12 hourly infused i.v. over 1 hr) is restricted to serious MRSA infections for which it is the most effective drug, and as a penicillin substitute (in allergic patients) for enterococcal endocarditis along with gentamicin. It is also used in dialysis patients and those undergoing cancer chemotherapy. Penicillin-resistant pneumococcal infections and infection caused by diphtheroids respond very well to vancomycin.

VANCOCIN-CP 150 mg tab, 500 mg/vial inj; VANCOGEN, VANCORID-CP 500 mg/vial inj; VANCOLED 0.5, 1.0 g inj.

Use of vancomycin in dental infections is highly restricted to the few cases that do not respond to other safer antibiotics and are hypersensitive to penicillin. In penicillin allergic patients vancomycin 1 g (20 mg/kg) i.v. infusion is an alternative to amoxicillin for combining with gentamicin for prophylaxis of endocarditis in high-risk patients undergoing dental surgery.

Teicoplanin It is a recently developed glycopeptide antibiotic which in fact is a mixture of 6 similar compounds. It is active against gram-positive bacteria only; mechanism of action and spectrum of activity is similar to vancomycin. Notable features are:

- It is more active than vancomycin against enterococci, and equally active against MRSA.
- Some vancomycin-resistant enterococci but not *Staph. aureus* are susceptible to teicoplanin.
- It can be injected i.m. as well; is excreted by kidney; dose needs to be reduced in renal insufficiency; has a very long t½ (3–4 days).
- Toxicity is less than vancomycin; adverse effects are rashes, fever, granulocytopenia and rarely hearing loss. Reactions due to histamine release are very rare (1 in 2500).

Teicoplanin is indicated in enterococcal endocarditis (along with gentamicin); MRSA and penicillin-resistant streptococcal infections in place of vancomycin.

Dose: 400 mg first day—then 200 mg daily i.v. or i.m.; severe infection 400 mg × 3 doses 12 hourly—then 400 mg daily.

TARGOCID 200, 400 mg per vial inj. for reconstitution.

OXAZOLIDINONE

Linezolid This is the first member of a new class of synthetic AMAs 'Oxazolidinones,' which has become available for the treatment of resistant gram-positive coccal (aerobic and anaerobic) and bacillary infections. It is active against methicillin-resistant and some vancomycin-resistant *Staph. aureus* (VRSA), vancomycin-resistant enterococci (VRE), penicillin-resistant *Strep. pyogenes, Strep. viridans* and *Strep. pneumoniae, Corynebacterium, Listeria, Clostridia* and *Bact. fragilis*. It is primarily bacteriostatic, but can exert cidal action against some streptococci, pneumococci and *B. fragilis*. Gram-negative bacteria are not affected.

Linezolid inhibits bacterial protein synthesis by acting at an early step and a site different from that of other AMAs. It binds to the 23S fraction of the 50S ribosome and interferes with formation of the initiation complex. Binding of linezolid stops protein synthesis before it starts. As such, there is no cross resistance with any other class of AMAs.

Linezolid is rapidly and completely absorbed orally, partly metabolized nonenzymatically and excreted in urine. Plasma t½ is 5 hrs.

Linezolid has been used for skin and soft tissue infections, community-and hospital-acquired pneumonias, bacteraemias and other drug-resistant gram-positive infections by oral and i.v. routes with high cure rates. However, to prevent emergence of resistance to this valuable drug, use should be restricted to serious hospital-acquired pneumonias, febrile neutropenia, wound infections and others caused by multidrug-resistant gram-positive bacteria such as VRE, vancomycin-resistant-MRSA, multiresistant *S. pneumoniae*, etc. Being bacteriostatic, it is not suitable for treatment of enterococcal endocarditis. There are no indications in dentistry for linezolid.

Dose: 600 mg BD, oral/ i.v.; LIZOLID 600 mg tab; LINOX 600 mg tab, 200 mg/100 ml i.v. infusion.

Side effects to linezolid have been few; mostly mild abdominal pain and bowel upset. Occasionally, rash, pruritus, headache, oral/ vaginal candidiasis have been reported, but data are still preliminary. Because linezolid is a MAO inhibitor, interactions with adrenergic/serotonergic drugs and excess dietary tyramine are expected. No cytochrome P450 enzyme related interactions seem likely.

Fusidic acid

It is a narrow spectrum steroidal antibiotic, blocks bacterial protein synthesis and is active against penicillinase producing *Staphylococci* and few other gram-positive bacteria. It is used only topically for boils, folliculitis, sycosis barbae and other cutaneous infections.

FUCIDIN-L, FUCIBACT, FUSIDERM; 2% oint. and cream.

POLYPEPTIDE ANTIBIOTICS

These are low molecular weight cationic polypeptide antibiotics. All are powerful bactericidal agents, but not used systemically due to toxicity. All are produced by bacteria. Clinically used ones are:

Polymyxin B	Bacitracin
Colistin	Tyrothricin

Polymyxin B and Colistin Polymyxin and colistin were obtained in the late 1940s from *Bacillus polymyxa* and *B. colistinus* respectively. They are active against gram-negative bacteria only; all except *Proteus, Serratia* and *Neisseria* are inhibited. Both have very similar range of activity, but colistin is more potent on *Pseudomonas, Salmonella* and *Shigella*.

Mechanism of action They are rapidly acting bactericidal agents; have a detergent-like action on the cell membrane. They have high affinity for phospholipids: the peptide molecules (or their aggregates) orient between the phospholipid and protein films in gram-negative bacterial cell membrane causing membrane distortion or pseudopore formation. As a result, ions, amino acids, etc. leak out. Sensitive bacteria take up more of the antibiotic.

They exhibit synergism with many other AMAs by improving their penetration into the bacterial cell.

Resistance Resistance to these antibiotics has never been a problem. There is no cross resistance with any other AMA.

Adverse effects Little or no absorption occurs from oral route or even from denuded skin (burn, ulcers). Applied topically, they are safe—no systemic effect or sensitization occurs. A rash is rare.

- Given orally, side effects are limited to the g.i.t.—occasional nausea, vomiting, diarrhoea.
- Systemic toxicity of these drugs (when injected) is high: flushing and paresthesias (due to liberation of histamine from mast cells), marked kidney damage, neurological disturbances, neuromuscular blockade.

Preparation and dose

Polymyxin B: (1 mg = 10,000 U)

NEOSPORIN POWDER: 5,000 U with neomycin sulf. 3,400 U and bacitracin 400 U per g.

NEOSPORIN EYE DROPS: 5,000 U with neomycin sulf. 1,700 U and gramicidin 0.25 mg per ml.

NEOSPORIN-H EAR DROPS: 10,000 U with neomycin sulf. 3,400 U and hydrocortisone 10 mg per ml.

Colistin sulfate: 25–100 mg TDS oral; WALAMYCIN 12.5 mg (25,000 i.u.) per 5 ml dry syr, COLISTOP 12.5 mg/5 ml and 25 mg/5 ml dry syr.

Uses

(a) *Topically* Usually in combination with other antimicrobials for skin infections, burns, otitis externa, conjunctivitis, corneal ulcer—caused by gram-negative bacteria including *Pseudomonas*.

(b) *Orally* Gram-negative bacillary (*E. coli*, *Salmonella, Shigella*) diarrhoeas, especially in infants and children; *Pseudomonas* superinfection enteritis.

Bacitracin It is one of the earliest discovered antibiotics from a strain of *Bacillus subtilis*. In contrast to polymyxin, it is active mainly against gram-positive organisms (both

cocci and bacilli). *Neisseria, H. influenzae* and few other gram-negative bacteria are also affected.

It acts by inhibiting cell wall synthesis at a step earlier than that inhibited by penicillin. Subsequently, it increases the efflux of ions by binding to cell membrane. It is bactericidal.

Bacitracin is not absorbed orally. It is not used parenterally because of high toxicity, especially to the kidney. Use is restricted to topical application for infected wounds, ulcers, eye infections—generally in combination with neomycin, polymyxin, etc.

In NEBASULF 250 U/g powder, skin oint, eye oint; in NEOSPORIN 400 U/g powder. (1 U = 26 µg).

It does not penetrate intact skin, therefore, of little value in furunculosis, boils, carbuncles, etc.

Tyrothricin It is a mixture of *gramicidin* and *tyrocidin*, obtained from *Bacillus bravis*. It is active against gram-positive and a few gram-negative bacteria. It acts on cell membrane causing leakage and uncouples oxidative phosphorylation in the bacteria.

Tyrothricin is not absorbed orally and is too toxic for systemic use; causes haemolysis. Used only topically; does not cause sensitization.

TYRODERM: 0.5 mg/g skin cream; PROTHRICIN 0.2 mg/ml topical solution.

TYOTOCIN: 0.05% otic solution with benzocaine 1.25%, antipyrine 5%, hexylresorcinol 0.1%.

URINARY ANTISEPTICS

Some AMAs, in orally tolerated doses, attain antibacterial concentration only in the urinary tract. Like many other drugs, they are concentrated in the kidney tubules, and are used only for urinary tract infection. They have been called *urinary antiseptics* because this may be considered as a form of local therapy. Nitrofurantoin and methenamine are two such agents; infrequently used now. Nalidixic acid (*see* p 372) can also be considered to be a urinary antiseptic.

Nitrofurantoin

It is a primarily bacteriostatic compound, but may be cidal at higher concentrations and in acidic urine: its activity is enhanced at lower pH. It inhibits many gram-negative bacteria, but due to development of resistance, activity is now restricted largely to *E. coli.* Resistance to nitrofurantoin develops slowly and no cross resistance with any other AMA is known. It antagonizes the action of nalidixic acid. Susceptible bacteria appear to enzymatically reduce nitrofurantoin to generate reactive intermediates which damage DNA.

Pharmacokinetics It is well absorbed orally; rapidly metabolized in liver and other tissues; less than half is excreted unchanged in urine; plasma t½ is 30–60 min. Antibacterial concentrations are not attained in blood or tissues. Renal excretion is reduced in azotaemic patients; effective concentrations may not be reached in urine, while toxicity increases: contraindicated in renal failure; also during pregnancy and in neonates.

Adverse effects Commonest is gastrointestinal intolerance—nausea, epigastric pain and diarrhoea.

An acute reaction with chills, fever and leucopenia occurs occasionally.

Peripheral neuritis and other neurological effects are reported with long-term use. Haemolytic anaemia is rare, except in G-6-PD deficiency. Liver damage and a pulmonary reaction with fibrosis on chronic use are infrequent events.

Use The only indication for nitrofurantoin is urinary tract infection, but it is infrequently used now. It can be employed for prophylaxis of urinary tract infection when catheterization or instrumentation of the lower urinary tract is performed.

FURADANTIN 50, 100 mg tab, 25 mg/5 ml susp.

Methenamine (Hexamine)

It is hexamethylene-tetramine; inactive as such; decomposes slowly in acidic urine to release formaldehyde which inhibits all bacteria. This drug exerts no antimicrobial activity in blood and tissues, including kidney parenchyma. Acidic urine is essential for its action; urinary pH must be kept below 5.5 by administering some organic acid which is excreted as such, e.g. mandelic acid or ascorbic acid.

Methenamine is administered in enteric coated tablets to protect it from decomposing in gastric juice. Mandelic acid itself is a urinary antiseptic in high doses by virtue of lowering pH of urine. However, the amount taken with methenamine (as methenamine mandelate) is inadequate in its own right: serves only to promote decomposition of methenamine.

MANDELAMINE 0.5 g, 1 g tab: 1 g TDS or QID with fluid restriction to ensure adequate concentration of formaldehyde in urine.

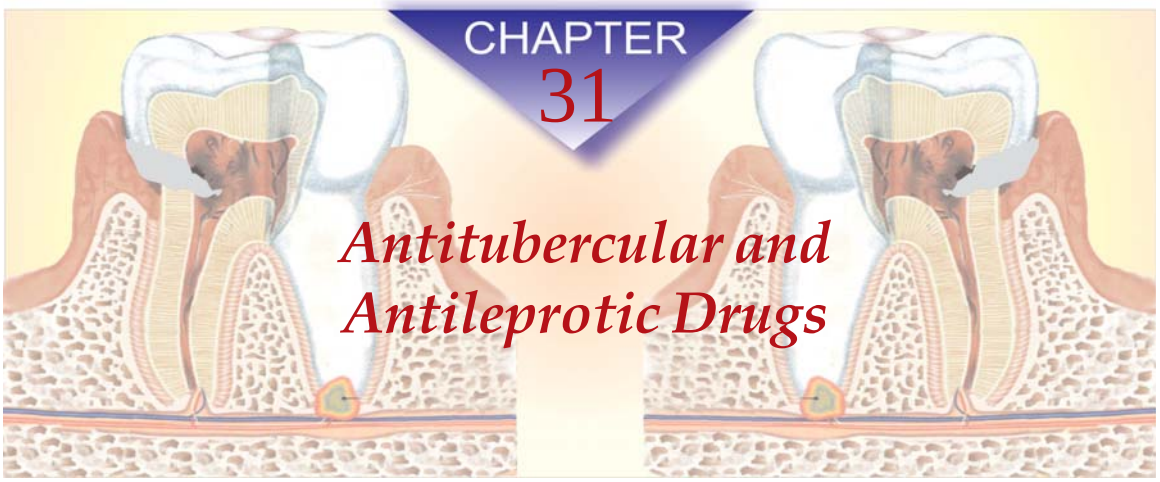
It is not a good drug for acute urinary tract infections or for catheterization prophylaxis. Its use is restricted to chronic, resistant type of urinary tract infections, not involving kidney substance. Resistance to formaldehyde does not occur, but it is not popular now.

Adverse effects Gastritis can occur due to release of formaldehyde in stomach—patient compliance is often poor due to this.

Chemical cystitis and haematuria may develop with high doses given for long periods. CNS symptoms are produced occasionally.

Methenamine mandelate is contraindicated in renal failure (mandelic acid accumulates in blood → acidosis) and in liver disease (the released NH_3 is not detoxified).

Sulfonamides combine chemically with methenamine in urine resulting in antagonism.



CHAPTER 31

Antitubercular and Antileprotic Drugs

ANTITUBERCULAR DRUGS

Tuberculosis is a chronic granulomatous disease and a major health problem in developing countries. About 1/3rd of the world's population is infected with *Mycobact. tuberculosis*. As per ICMR (2001)* estimate > 40% adults in India are infected with TB; nearly 2 million people develop active disease every year and about 0.5 million die from it. A new dimension has got added in the 1980s due to spread of HIV with high prevalence of tuberculosis and *Mycobact. avium* complex (MAC) infection among these patients. Emergence of 'multidrug resistant' (MDR) TB with a reported overall incidence of 13% in 35 countries is threatening the whole future of current antitubercular chemotherapy.

Remarkable progress has been made in the last 60 years since the introduction of *Streptomycin* in 1947 for the treatment of tuberculosis. Besides adding a number of effective drugs, strategies in the management of TB have been improved based on the understanding of biology of this infection, and clear-cut treatment guidelines have been formulated. While dentists are not called upon to treat tuberculosis, they should be familiar with important features of antitubercular drugs and the current therapeutic regimens. According to their clinical utility, the anti-TB drugs can be divided into:

First line: These drugs have high antitubercular efficacy as well as low toxicity; are used routinely.

Second line: These drugs have either low antitubercular efficacy or high toxicity or both; are used in special circumstances only.

First line drugs

1. Isoniazid (H)
2. Rifampin (R)
3. Pyrazinamide (Z)
4. Ethambutol (E)
5. Streptomycin (S)

Second line drugs

1. Thiacetazone (Tzn)
2. Para-aminosalicylic acid (PAS)
3. Ethionamide (Etm)
4. Cycloserine (Cys)
5. Kanamycin (Kmc)
6. Amikacin (Am)
7. Capreomycin (Cpr)

Newer drugs

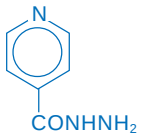
1. Ciprofloxacin
2. Ofloxacin
3. Clarithromycin
4. Azithromycin
5. Rifabutin

Isoniazid (Isonicotinic acid hydrazide, H)

Isonicotinic acid hydrazide (INH, isoniazid) is the antitubercular drug parexcellence, and an

* ICMR Bulletin **31** (3) 37-43, 2001.

essential component of all antitubercular regimens, unless the patient is not able to tolerate it or bacilli are resistant. It is primarily tuberculocidal. Fast multiplying organisms are rapidly killed, but quiescent ones are only inhibited. It acts on extracellular as well as on intracellular TB (bacilli present within macrophages); is equally active in acidic and alkaline medium. It is one of the cheapest antitubercular drugs. However, most atypical mycobacteria are not inhibited by INH.



ISONIAZID

The most plausible mechanism of action of INH is inhibition of synthesis of *mycolic acids* which are unique fatty acid component of mycobacterial cell wall. This may explain the high selectivity of INH for mycobacteria (it is not active against any other microorganism). A gene labelled *inh A* which encodes for a fatty acid synthase enzyme is the likely target of INH action. The sensitive mycobacteria concentrate INH and convert it by a catalase-peroxidase enzyme into an active metabolite that appears to interact with the *inh A* gene.

About 1 in 10^6 tubercle bacilli is inherently resistant to clinically attained INH concentrations. If INH is given alone, such bacilli proliferate selectively and after 2–3 months (sometimes even earlier) an apparently resistant infection emerges. The most common mechanism of INH resistance is by mutation of the catalase-peroxidase gene so that the bacilli do not generate the active metabolite of INH. Resistance may also involve mutation in the target *inh A* gene. Other resistant TB bacilli lose the active INH concentrating process.

Pharmacokinetics INH is completely absorbed orally and penetrates all body tissues, tubercular cavities, placenta and meninges. It is extensively metabolized in liver; most important pathway being acetylation—metabolites are excreted in urine. The rate of INH acetylation shows genetic variation: there are slow and fast acetylators.

INH induced peripheral neuritis appears to be more common in slow acetylators.

Interactions Aluminium hydroxide inhibits INH absorption.

INH inhibits phenytoin, carbamazepine, diazepam and warfarin metabolism: may raise their blood levels.

Adverse effects INH is well tolerated by most patients. Peripheral neuritis and a variety of neurological manifestations (paresthesias, numbness, mental disturbances, rarely convulsions) are the most important dose-dependent toxic effects. These are due to interference with utilization of pyridoxine and its increased excretion in urine. Pyridoxine given prophylactically (10 mg/day) prevents neurotoxicity. INH neurotoxicity is treated by pyridoxine 100 mg/day.

Hepatitis, a major adverse effect of INH, is due to dose-related damage to liver cells and is reversible on stopping the drug. Other side effects are rashes, fever, acne and arthralgia.

ISONEX 100, 300 mg tabs, ISOKIN 100 mg tab, 100 mg per 5 ml liq.

Rifampin (Rifampicin, R)

It is a semisynthetic derivative of rifamycin B obtained from *Streptomyces mediterranei*. Rifampin is bactericidal to *M. tuberculosis* and many other gram-positive and gram-negative bacteria like *Staph. aureus*, *N. meningitidis*, *H. influenzae*, *E. coli*, *Klebsiella*, *Pseudomonas*, *Proteus* and *Legionella*. Against TB bacilli, it is as efficacious as INH and better than all other drugs. It acts best on slowly or intermittently (spurters) dividing *M. tub.* as well as on many atypical mycobacteria. Both extra- and intracellular organisms are affected. It has good sterilizing and resistance preventing actions.

Rifampin inhibits DNA-dependent RNA synthesis. Probably, the basis of selective toxicity is that mammalian RNA polymerase does not avidly bind rifampin.

Mycobacteria and other organisms develop resistance to rifampin rather rapidly. However, the incidence of resistant TB is less than 10^{-7}. Rifampin resistance is nearly always due to mutation in the *repoB* gene (the target of rifampin action) reducing its affinity for the drug. No cross resistance with any other antitubercular drug has been noted.

Pharmacokinetics It is well absorbed orally, widely distributed in the body: penetrates cavities, caseous masses, placenta and meninges. It is metabolized in liver to an active deacetylated metabolite which is excreted mainly in bile; some in urine also. The t½ of rifampin is variable (2–5 hours).

Interactions Rifampin is a microsomal enzyme inducer—enhances its own metabolism as well as that of many drugs including warfarin, oral contraceptives, corticosteroids, sulfonylureas, digitoxin, steroids, HIV protease inhibitors, ketoconazole, etc. Contraceptive failures have occurred.

Adverse effects The incidence of adverse effects is similar to INH.

Hepatitis, a major adverse effect, generally occurs in patients with pre-existing liver disease and is dose related. Other serious but rare reactions are:

- 'Respiratory syndrome': breathlessness which may be associated with shock and collapse.
- Purpura, haemolysis, shock and renal failure.

Minor reactions are:

- 'Cutaneous syndrome': flushing, pruritus + rash, redness and watering of eyes.
- 'Flu syndrome': with chills, fever, headache, malaise and bone pain.
- 'Abdominal syndrome': nausea, vomiting, abdominal cramps with or without diarrhoea.

Urine and secretions may become orange-red—but this is harmless.

Other uses of rifampin are:

(i) Leprosy.

(ii) Prophylaxis of *Meningococcal* and *H. influenzae* meningitis and carrier state.

(iii) Second/third choice drug for MRSA, diphtheroids and *Legionella* infections.

(iv) Combination of doxycycline and rifampin is the first line therapy of brucellosis.

RCIN 150, 300, 450, 600 mg caps, 100 mg/5 ml susp. RIMACTANE, RIMPIN 150, 300, 450 mg caps, 100 mg/5 ml syr.; RIFAMYCIN 450 mg cap, ZUCOX 300,450, 600 mg tabs.

Pyrazinamide (Z)

Chemically similar to INH, pyrazinamide (Z) was developed parallel to it in 1952. It is weakly tuberculocidal but more active in acidic medium. It is highly lethal to intracellularly located bacilli as well as to those at sites showing an inflammatory response (pH is acidic at both these locations). It has good sterilizing activity and is highly effective during the first 2 months of therapy when inflammatory changes are present. Its use has enabled regimens to be shortened and risk of relapse to be reduced. Mechanism of antimycobacterial action of Z resembles INH. Resistance to Z develops rapidly if it is used alone, and is due to mutation in the gene which encodes for the enzyme generating the active metabolite of Z.

Pyrazinamide is absorbed orally, widely distributed, has good penetration in CSF, extensively metabolized in liver and excreted in urine; plasma t½ 6–10 hours.

Hepatotoxicity is the most important dose-related adverse effect, but it appears to be less common in the Indian population than in Western countries.

Hyperuricaemia is due to inhibition of uric acid secretion in kidney: gout can occur.

Other adverse effects are arthralgia, flushing, rashes, fever and loss of diabetes control.

PYZINA 0.5, 0.75, 1.0 g tabs, 0.3 g kid tab; PZA-CIBA 0.5, 0.75 g tabs, 250 mg/5 ml syr; RIZAP 0.75, 1.0 g tabs

Ethambutol (E)

Ethambutol is selectively tuberculostatic and clinically as active as S. Fast multiplying bacilli

are more susceptible as are many atypical mycobacteria. Added to the triple drug regimen of RHZ, it has been found to hasten the rate of sputum conversion and to prevent development of resistance.

The mechanism of action of E is not fully understood, but it has been found to inhibit arabinogalactan synthesis and to interfere with mycolic acid incorporation in mycobacterial cell wall. Resistance to E develops slowly; in many cases it is due to alteration in the target gene. No cross resistance with any other antitubercular drug has been noted.

About 3/4th of an oral dose of E is absorbed. It is distributed widely but penetrates meninges incompletely and is temporarily stored in RBCs. Less than ½ of E is metabolized. It is excreted in urine by glomerular filtration and tubular secretion; plasma t½ is ~4 hrs.

Patient acceptability of E is very good and side effects are few. Loss of visual acuity/colour vision, field defects due to optic neuritis is the most important dose and duration of therapy dependent toxicity. Because young children may be unable to report early visual impairment, it should not be used below 6 years of age. Ethambutol produces few other symptoms: nausea, rashes, fever, neurological changes are infrequent.

MYCOBUTOL, MYAMBUTOL, COMBUTOL 0.2, 0.4, 0.6, 0.8, 1.0 g tabs.

Streptomycin (S)

The pharmacology of streptomycin is described in Ch. 29. It was the first clinically useful antitubercular drug. It is tuberculocidal, but less effective than INH or rifampin; acts only on extracellular bacilli (because of poor penetration into cells). It penetrates tubercular cavities, but does not cross to the CSF, and has poor action in acidic medium.

Resistance develops rapidly to streptomycin. In case of S resistant infection, it must be stopped at the earliest because of chances of S dependence. Most atypical mycobacteria are unaffected by S.

Popularity of S in the treatment of tuberculosis has declined due to need for i.m. injections and lower margin of safety because of ototoxicity.

Thiacetazone (Tzn, Amithiozone)

Thiacetazone is a tuberculostatic, low efficacy drug; does not add to the therapeutic effect of H, S or E, but delays resistance to these drugs. It is orally active, and primarily excreted unchanged in urine with a t½ of 12 hr. The major adverse effects of Tzn are hepatitis, exfoliative dermatitis, Stevens-Johnson syndrome and rarely bone marrow depression. The common side effects are anorexia, abdominal discomfort, loose motions and minor rashes. A mild anaemia persists till Tzn is given. Tzn is a reserve antitubercular drug, sometimes added to INH in alternative regimens.

Dose: 150 mg OD in adults, 2.5 mg/kg in children, as combined tablet with isoniazid.

Para-amino salicylic acid (PAS)

It is related to sulfonamides—chemically as well as in mechanism of action, but is not active against other bacteria: selectivity may be due to difference in the affinity of folate synthetase of TB and other bacteria for PAS.

PAS is tuberculostatic and one of the least active drugs: does not add to the efficacy of more active drugs that are given with it; only delays development of resistance—probably, by directly inhibiting episomal resistance transfer. Resistance to PAS is slow to develop.

It is absorbed completely by the oral route and distributed all over except in CSF. About 50% PAS is acetylated; competes with acetylation of INH—prolongs its t½. It is excreted rapidly by glomerular filtration and tubular secretion; t½ is short, ~1 hour.

Patient acceptability of PAS is poor because of frequent anorexia, nausea and epigastric pain. Other adverse effects are rashes, fever, malaise, goiter, liver dysfunction and blood dyscrasias.

Ethionamide (Etm)

It is a tuberculostatic drug of moderate efficacy that acts on both extra- and intracellular organisms. Atypical mycobacteria are sensitive. Resistance to Etm develops rapidly. It is absorbed orally, distributes all over including CSF, completely metabolized and has a short duration of action (t½ 2–3 hr).

Anorexia, nausea, vomiting and abdominal upset are common. Other side effects are aches and pains, rashes, hepatitis, peripheral or optic neuritis, mental disturbances and impotence. It is seldom used; only in case of resistance to better tolerated drugs.

Cycloserine (Cys)

It is an antibiotic obtained from *S. orchidaceus*, and is a chemical analogue of D-alanine: inhibits bacterial cell wall synthesis by inactivating the enzymes which recemize L-alanine and link two D-alanine residues. Cys is tuberculostatic and inhibits some other gram-positive bacteria, *E. coli*, *Chlamydia* also.

It is absorbed orally, diffuses all over, CSF concentration is equal to that in plasma. About 1/3 of a dose is metabolized, rest is excreted unchanged by kidney. The CNS toxicity of Cys is high—sleepiness, headache, tremor and psychosis. It is rarely used; only in resistant cases.

Kanamycin, Amikacin and Capreomycin are more toxic antibiotics used as reserve drugs in rare cases not responding to the usual therapy, or infection by atypical mycobacteria. All exhibit similar ototoxicity and nephrotoxicity.

NEWER DRUGS

Ciprofloxacin, Ofloxacin (*see* Ch. 27 for description) The fluoroquinolones are a useful new addition to the antitubercular drugs. Ciprofloxacin, ofloxacin, moxifloxacin and sparfloxacin are active against *M. tuberculosis* as well as *M. avium* complex (MAC) and *M. fortuitum*. They penetrate cells and kill mycobacteria lodged in macrophages also. Because of their good tolerability, ciprofloxacin and ofloxacin are being increasingly included in combination regimens against MDR tuberculosis and MAC infection in HIV patients. They are also being used to supplement ethambutol + streptomycin in cases when H, R, Z have been stopped due to hepatotoxicity. However, neither ciprofloxacin nor ofloxacin have enhanced the sterilizing ability of long-term regimens containing H and R.

Clarithromycin, Azithromycin (*See* Ch. 30) These newer macrolide antibiotics are active against most nontubercular mycobacteria including MAC, *M. fortuitum*, *M. Kansasii* and *M. marinum.* Clarithromycin has been used to a greater extent because its MIC values are lower, but azithromycin may be equally efficacious due to its higher tissue and intracellular levels. In AIDS patients, life-long therapy is required—may cause ototoxicity.

Rifabutin It is related to rifampin in structure and mechanism of action; but less active against *M. tuberculosis* and more active against MAC. Only partial cross resistance occurs between the two. Rifabutin is used for prophylaxis of MAC infection in AIDS patients. For the treatment of established MAC infection, it has been added to ethambutol + clarithromycin/azithromycin.

TREATMENT OF TUBERCULOSIS

The therapy of tuberculosis has undergone remarkable change. The conventional 12–18-month treatment has been largely replaced by more effective and less toxic 6-month treatment which also yields higher completion rates.

The goals of antitubercular chemotherapy are:

(a) *Kill dividing bacilli* Drugs with early bactericidal action rapidly reduce bacillary load in the patient and achieve quick sputum negativity so that the patient is non-contagious to the community: transmission of TB is interrupted. This also affords quick symptom relief.

(b) *Kill persisting bacilli* To effect cure and prevent relapse. This depends on sterilizing capacity of the drug.

(c) *Prevent emergence of resistance* So that the bacilli remain susceptible to the drugs.

The relative activity of the first line drugs in achieving these goals differs, e.g. H and R are the most potent bactericidal drugs active against all populations of TB bacilli, while Z acts best on intracellular bacilli and those at inflamed sites—has very good sterilizing activity. On the other hand, S is active only against rapidly multiplying extracellular bacilli. E is bacteriostatic—mainly serves to prevent resistance and may hasten sputum conversion. The general principles of antitubercular chemotherapy are:

- Use of any single drug in tuberculosis results in the emergence of resistant organisms and relapse in almost 3/4th patients. A combination of two or more drugs must be used.
- Isoniazid and R are the most efficacious drugs; their combination is definitely synergistic—duration of therapy is shortened

Table 31.1: Recommended doses of antitubercular drugs@

Drug	Daily dose		3 × per week dose	
	mg/kg	For > 50 kg	mg/kg	For > 50 kg
Isoniazid (H)	5 (4–6)	300 mg	10 (8–12)	600 mg
Rifampin (R)	10 (8–12)	600 mg	10 (8–12)	600 mg
Pyrazinamide (Z)	25 (20–30)	1500 mg	35 (30–40)	2000 mg
Ethambutol (E)	15 (15–20)	1000 mg	30 (25–35)	1600 mg
Streptomycin (S)	15 (12–18)	1000 mg£	15 (12–18)	1000 mg

@ The WHO guidelines also describe a twice weekly dosage schedule, but do not recommend it.
£ Dose to be reduced to 750 mg above 50 yr age and to 500 mg above 65 yr age; also in patients with renal impairment.

from > 12 months to 9-months. Addition of Z for the initial 2 months further reduces duration of treatment to 6 months.

- A single daily dose of all first line anti-tubercular drugs is preferred. The 'directly observed treatment short course' (DOTS) was recommended by the WHO in 1995.
- Response is fast in the first few weeks as the fast dividing bacilli are eliminated rapidly. Symptomatic relief is evident within 2–4 weeks. The rate of bacteriological, radiological and clinical improvement declines subsequently. Bacteriological cure takes much longer.

SHORT COURSE CHEMOTHERAPY (SCC)

These are regimens of 6–9 month duration which have been found to be highly efficacious. After several years of experience a WHO expert group has framed clear-cut treatment guidelines* (1997) for different categories of TB patients. The dose of first line anti-TB drugs has been standardized on body weight basis and is applicable to both adults and children (Table 31.1).

All regimens have an *initial intensive phase* lasting for 2–3 months aimed to rapidly kill the TB bacilli, bring about sputum conversion and afford symptomatic relief. This is followed by a *continuation phase* lasting for 4–6 months during which the remaining bacilli are eliminated so that relapse does not occur. Treatment of TB is categorized into 4 categories by site and severity of disease, sputum smear positivity/negativity and history of previous treatment. The category-wise treatment regimens are summarized in Table 31.2.

Table 31.2: Category-wise alternative treatment regimens for tuberculosis (WHO 1997)

TB category	Initial phase (daily/ 3×per week)	Continuation phase	Total duration
I	2 HRZE (S)	4 HR/4 H_3R_3	6
		or 6 HE	8
II	2 HRZES +	5 HRE or	8
	1 HRZE	5 $H_3R_3E_3$	8
III	2 HRZ	4 HR/4 H_3R_3	6
		or 6 HE	8
IV	Chronic case:	See text	

Explanation of standard code

- Each anti-TB drug has a standard abbreviation (H, R, Z, E, S).
- The numeral before a phase is the duration of that phase in months.
- The numeral in subscript (e.g. H_3 R_3) is number of doses of that drug per week. If there is no subscript numeral, then the drug is given daily.

Category I This category includes:

- New (untreated) smear positive pulmonary TB.
- New smear negative pulmonary TB with extensive parenchymal involvement.
- New cases of severe forms of extrapulmonary TB, *viz.* meningitis, miliary, pericarditis, peritonitis, bilateral or extensive pleural effusion, spinal, intestinal, genitourinary TB.

* Treatment of tuberculosis: Guidelines for National Programmes, Second Edition (1997), WHO, Geneva.

Initial phase Four drugs HRZ + E or S are given daily or thrice weekly for 2 months. The Revised National Tuberculosis Control Programme (RNTCP) has been launched in India in 1997, which is implementing DOTS. Out of the WHO recommended regimens, the RNTCP has decided to follow thrice weekly regimen, since it is equally effective, saves drugs and effort, and is more practical.

Continuation phase Two drugs HR for 4 months or HE for 6 months are given. When both H and R are used, thrice weekly regimen is permissible. Under the RNTCP, thrice weekly treatment with H and R is given for 4 months. This phase is extended to 6–7 months (total duration 8–9 months) for TB meningitis, miliary and spinal disease.

Category II These are smear positive failure, relapse and interrupted treatment cases. These patients may have resistant bacilli and are at greater risk of developing MDR-TB.

Initial phase All 5 first line drugs are given for 2 months followed by 4 drugs (HRZE) for another month. Continuation phase is started if sputum is negative, but 4 drug treatment is continued for another month if sputum is positive at 3 months.

Continuation phase Three drugs (HRE) are given for 5 months either daily or thrice weekly (only thrice weekly under the RNTCP).

Category III These are new cases of smear negative pulmonary TB with limited parenchymal involvement or less severe forms of extrapulmonary TB, *viz,* lymph node TB, unilateral pleural effusion, bone (excluding spine), peripheral joint or skin TB.

Initial phase Three drugs (HRE) given for 2 months are enough because the bacillary load is smaller.

Continuation phase This is similar to category I, i.e. 4 months daily/thrice weekly HR or 6 months daily HE therapy. Under the RNTCP, only thrice weekly HR regimen is followed.

Category IV These are chronic cases who have remained or have become smear positive after completing fully supervised retreatment (Category II) regimen. These are most likely MDR cases. Multidrug resistant (MDR) TB is defined as resistance to both H and R and may be any number of other anti-TB drugs. MDR-TB has a more rapid course (some die in 4–16 weeks). Treatment of these cases is difficult because the second line drugs are less efficacious, less convenient, more toxic and more expensive.

Choice of therapy depends on drugs used in the earlier regimen, dosage and regularity with which they were taken, presence of associated disease like AIDS/diabetes/leukaemia/silicosis, and whether sensitivity of the pathogen to various drugs is known (by *in vitro* testing) or unknown.

The actual regimen is devised according to the features of the individual patient.

Tuberculosis in pregnant / breastfeeding women HRZ and E are safe to the foetus. Standard 6-month regimen 2 HRZ + 4 HR should be given. E can be added during late but not early pregnancy. Treatment of TB should not be withheld or delayed because of pregnancy. All anti-TB drugs are compatible with breastfeeding.

Chemoprophylaxis This is indicated in:
(a) Contacts of open cases who show recent Mantoux conversion.
(b) Children with positive Mantoux and a TB patient in the family.
(c) Neonate of tubercular mother.
(d) Patients of leukaemia, diabetes, silicosis, or those who are HIV positive and show a positive Mantoux.

The drug generally used for prophylaxis has been H 300 mg (10 mg/kg in children) daily for 6–12 months. Now because of high incidence of H resistance, a combination of H (5 mg/kg) and R (10 mg/kg) given for 6 months is preferred.

Tuberculosis in AIDS patients The association of HIV and TB infection is a serious problem.

HIV positive cases have more severe and more infectious TB. HIV infection is the strongest risk factor for making latent TB overt.

In case of *M. tuberculosis* infection, drugs used are the same as in non-HIV cases. Short course chemotherapy must be immediately started on diagnosis of TB. The initial 2 HRZE phase is followed by a continuation phase of HR for 7 months (total 9 months). Alternatively, 3 drugs HRE are used for 4 months in the continuation phase.

Mycobacterium avium complex (MAC): infection is particularly common in HIV patients. The most effective regimen is clarithromycin + ethambutol ± rifabutin. Azithromycin may be substituted in place of clarithromycin.

ANTILEPROTIC DRUGS

Leprosy, caused by *Mycobacterium leprae*, has been considered incurable since ages and bears a social stigma. However, due to development of effective antileprotic drugs, it is entirely curable now, but deformities/defects already incurred may not reverse. Though certain forms of leprosy produce oral/dental lesions, chemotherapy of leprosy is not managed by dentists. Only a brief account of the antileprotic drugs is therefore relevant. The antileprotic drugs are:

1.	*Sulfone*	Dapsone (DDS)
2.	*Phenazine derivative*	Clofazimine
3.	*Antitubercular drugs*	Rifampin, Ethionamide
4.	*Other antibiotics*	Ofloxacin, Minocycline, Clarithromycin

Dapsone (DDS)

It is diamino diphenyl sulfone (DDS), the simplest, oldest, cheapest, most active and most commonly used member of its class.

Dapsone is chemically related to sulfonamides and has the same mechanism of action, i.e. inhibition of PABA incorporation into folic acid; its antibacterial action is antagonized by PABA. It is leprostatic at very low concentrations. Specificity for *M.leprae* may be due to difference in the affinity of its folate synthetase.

Dapsone resistance among *M. leprae* was first noted in 1964. It has increased and has necessitated use of multidrug therapy (MDT). However, the peak serum concentration of dapsone after 100 mg/day dose exceeds MIC for *M. leprae* by nearly 500 times; it continues to be active against low to moderately resistant bacilli.

Dapsone is completely absorbed after oral administration and is widely distributed in the body. It is concentrated in skin (especially lepromatous skin), muscle, liver and kidney.

Dapsone is acetylated as well as glucuronide and sulfate conjugated in liver. The plasma t½ of dapsone is variable, though often > 24 hrs. The drug is cumulative due to retention in tissues and enterohepatic circulation. Elimination takes 1–2 weeks or longer.

Dapsone is generally well tolerated at doses 100 mg/day or less.

Mild haemolytic anaemia is common. It is a dose-related toxicity—reflects oxidising property of the drug. Patients with G-6-PD deficiency are more susceptible.

Gastric intolerance—nausea and anorexia are frequent.

Other side effects are methaemoglobinaemia, headache, paresthesias, mental symptoms and drug fever.

Cutaneous reactions include allergic rashes, hypermelanosis, phototoxicity.

Lepra reaction.

Other use In combination with pyrimethamine dapsone can be used for chloroquine-resistant malaria.

Clofazimine (Clo)

It is a dye with leprostatic and antiinflammatory properties; acts probably by interfering with template function of DNA. When used alone, resistance to clofazimine develops in 1–3 years.

Clofazimine is orally active. It accumulates in many tissues, especially in fat, in crystalline form.

The t½ is 70 days so that intermittent therapy is possible.

It has been used as a component of multidrug therapy of leprosy. Because of its antiinflammatory property, it is valuable in lepra reaction.

In the doses employed for multidrug therapy (MDT) clofazimine is well tolerated. The major disadvantage is reddish-black discolouration of skin, especially on exposed parts. Discolouration of hair and body secretions may also occur. Dryness of skin and itching is often troublesome. Conjunctival pigmentation may create cosmetic problem.

Enteritis with intermittent loose stools, nausea, abdominal pain, anorexia and weight loss can occur.

Rifampin (R)

It is an important antitubercular drug; also bactericidal to *M. leprae*; rapidly renders leprosy patients noncontagious. Up to 99.99% *M. leprae* are killed in 3–7 days. However, it is not satisfactory if used alone—some bacilli persist even after prolonged treatment—resistance develops. It has been included in the multidrug therapy of leprosy and shortens duration of treatment. The 600 mg monthly dose used in leprosy is relatively nontoxic and does not induce metabolism of other drugs. It should not be given to patients with hepatic or renal dysfunction.

Ethionamide This antitubercular drug has significant antileprotic activity, but causes hepatotoxicity in ~ 10% patients. It has been used as an alternative to clofazimine.

Ofloxacin Many trials have evaluated ofloxacin as a component of MDT and found it to hasten the bacteriological and clinical response. However, it is not included in the standard treatment protocols, but can be used in alternative regimens in case rifampin cannot be used, or to shorten the duration of treatment.

Minocycline Because of high lipophilicity, this tetracycline is active against *M. leprae*. A dose of 100 mg/day produces peak blood levels that exceed MIC against *M. leprae* by 10–20 times. In one trial minocycline 100 mg daily monotherapy rendered all 8 patients of lepromatous leprosy negative for *M. leprae* after 8 weeks. It is being tried in alternative MDT regimens.

Clarithromycin It is the only macrolide antibiotic with significant activity against *M. leprae*. However, it is less bactericidal than rifampin. Monotherapy with clarithromycin 500 mg daily caused 99.9% bacterial killing in 8 weeks. It is being included in alternative MDT regimens.

TREATMENT OF LEPROSY

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae*; primarily affecting skin, mucous membranes and nerves. It is a major health problem in India which has 1/3rd of total leprosy patients in the world. The National Leprosy Control Programme was launched in 1955, and has been changed to National Leprosy Eradication Programme (NLEP) in 1982.

Two polar types—lepromatous (LL) and tuberculoid (TT) with 4 intermediate forms—borderline (BB), borderline lepromatous (BL), borderline tuberculoid (BT) and indeterminate (I) of the disease are recognized.

For operational purposes, leprosy has been divided into:

Paucibacillary leprosy (PBL) (Non-infectious): This includes TT, BT, I and polyneuritic.

Multibacillary leprosy (MBL) (Infectious): This includes LL, BL and BB.

Multidrug therapy (MDT) of leprosy

Multidrug therapy with rifampin, dapsone and clofazimine was introduced by the WHO in 1981. This was implemented under the NLEP. The MDT is the regimen of choice for all cases of leprosy. Its advantages are:

- Effective even in cases with primary dapsone resistance.
- Prevents emergence of dapsone resistance.
- Affords quick symptom relief and renders MBL cases noncontagious.
- Reduces total duration of therapy.

Under standard MDT, the PBL cases are treated with dapsone + rifampin for 6 months, while the MBL cases are treated with dapsone + rifampin + clofazimine for 2 years.

Multidrug therapy of leprosy

	Multibacillary leprosy	*Paucibacillary leprosy*
Rifampin	600 mg once a month supervised	600 mg once a month supervised
Dapsone	100 mg daily self-administered	100 mg daily self-administered
Clofazimine	300 mg once a month supervised +	—
	50 mg daily self-administered	—
Duration	24 months	6 months

Encouraged by the very low relapse rates obtained with 2-year MDT for MBL cases, the WHO has recommended shortening the duration to 1 year for the mass programme. On the other hand, some patients do not achieve disease inactivity after 1 year or even after 2-year MDT. Independent leprologists, therefore, prefer to keep the duration of therapy flexible to a minimum of 2 years or till disease inactivity/skin smear negativity is achieved. Similarly, in case of PBL also, independent leprologists prefer to extend the duration of MDT from 6 to 12 months or longer till disease inactivity is attained.

It may be concluded that, where feasible, treatment till cure of individual patient should be ensured both in MBL and in PBL.

Alternative regimens Many alternative regimens incorporating newer antileprotic drugs have been investigated. However, these are used only in case of rifampin resistance or when it is impossible/inadvisable to employ the standard MDT regimen. Some of these are:

- Cloflazimine 50 mg + any two of ofloxacin 400 mg/minocycline 100 mg/clarithromycin 500 mg daily for 6 month followed by clofazimine 50 mg + any one of ofloxacin 400 mg/minocycline 100 mg daily for additional 18 months.
- In case of refusal to accept clofazimine: ofloxacin 400 mg or minocycline 100 mg daily can be substituted for it in the standard MDT.
- A multicentric trial[@] has shown that PBL cases having few bacteria in the body and only one skin lesion can be treated with a single dose of rifampin 600 mg + ofloxacin 400 mg + minocycline 100 mg (ROM regimen). This regimen has been recommended by the WHO for patients with solitary lesion PBL.

Many other shorter regimens are under evaluation.

Reactions in leprosy

Lepra reaction These occur in LL, usually with institution of chemotherapy and/or intercurrent infection. It is a Jarish Herxheimer (Arthus) type of reaction due to release of antigens from the killed bacilli. It may be mild, severe or life-threatening (erythema nodosum leprosum).

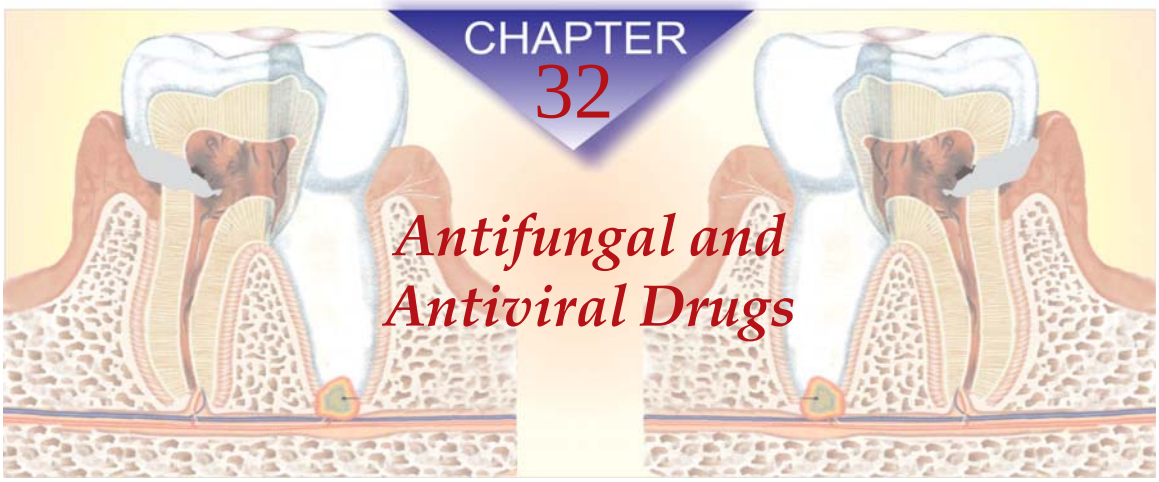
Lepra reaction is of abrupt onset; existing lesions enlarge, become red, swollen and painful; several new lesions may appear. Malaise, fever and other constitutional symptoms may be present and marked.

Clofazimine (200 mg daily) is highly effective in controlling the reaction (except the most severe one) probably because of its antiinflammatory property.

Other drugs used are—analgesics, antipyretics, antibiotics, etc. according to need. Corticosteroids should be used only in severe cases.

Reversal reaction This is seen in TT—is a manifestation of delayed hypersensitivity to *M. leprae* antigens. Cutaneous ulceration, multiple nerve involvement with pain and tenderness occur suddenly even after completion of therapy. It is treated with clofazimine or corticosteroids.

@ Efficacy of single dose MDT for single lesion paucibacillary leprosy. Ind. J. Lepr. (1997) **69,** 127.



CHAPTER 32

Antifungal and Antiviral Drugs

ANTIFUNGAL DRUGS

These are drugs used for superficial and deep (systemic) fungal infections.

A disquietening trend after 1950s has been the emergence of more sinister type of fungal infections which are, to a large extent, iatrogenic. These are associated with the use of anticancer/immunosuppressant drugs, corticosteroids, broad-spectrum antibiotics, dentures, indwelling catheters and implants and emergence of AIDS. As a result of breakdown of host defence mechanisms, saprophytic fungi easily invade living tissue. *Candida albicans* is normally resident in the oral cavity. It invades to cause infection when host defence is impaired or the oral flora is disturbed.

Many topical antifungals have been available since the antiseptic era. Two important antibiotics: amphotericin B and griseofulvin as well as a number of imidazoles and triazoles have been developed for topical and/or systemic use since 1960s.

CLASSIFICATION

1. *Antibiotics*
   - A. *Polyenes:* Amphotericin B (AMB), Nystatin, Hamycin, Natamycin (Pimaricin)
   - B. *Heterocyclic benzofuran*: Griseofulvin
2. *Antimetabolite* Flucytosine (5-FC)
3. *Azoles*
   - A. *Imidazoles* (topical): Clotrimazole, Econazole, Miconazole
     (systemic) : Ketoconazole
   - B. *Triazoles* (systemic): Fluconazole, Itraconazole
4. *Allylamine* Terbinafine
5. *Other topical agents*

Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Sod. thiosulfate.

POLYENE ANTIBIOTICS

The name *polyene* is derived from their highly double-bonded structure.

Amphotericin B (AMB)

It is obtained from *Streptomyces nodosus*.

The polyenes possess a macrocyclic ring, one side of which has several conjugated double bonds and is highly lipophilic, while the other side is hydrophilic with many OH groups. They are all insoluble in water and unstable in aqueous medium.

The polyenes have high affinity for ergosterol present in fungal cell membrane: combine with it, get inserted into the membrane and several molecules together orient themselves in such a way as to form a 'micropore' through which ions,

amino acids and other water-soluble substances move out. Thus, cell permeability is markedly increased.

Cholesterol, present in host cell membranes, closely resembles ergosterol; the polyenes bind to it as well, though with lesser affinity. Thus, the selectivity of action of polyenes is low, and AMB is one of the most toxic systemically used antibiotics. Bacteria do not have sterols and are unaffected by polyenes.

AMB is active against a wide range of yeasts and fungi—*Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis, Torulopsis, Rhodotorula, Aspergillus, Sporothrix*, etc. Dermatophytes are inhibited *in vitro*, but concentrations of AMB attained in infected skin are low and ineffective. It is fungicidal at high and static at low concentrations.

Resistance to AMB is not a problem in the clinical use of the drug. AMB is also active on various species of *Leishmania.*

AMB is not absorbed orally. Administered i.v. as a suspension made with the help of deoxycholate (DOC), it gets widely distributed in the body, but penetration in CSF is poor. It binds to sterols in tissues and to lipoproteins in plasma and stays in the body for long periods. The terminal elimination t½ is 15 days. About 60% of AMB is metabolized in the liver. Excretion occurs slowly both in urine and bile.

Administration and dose Amphotericin B can be administered orally (50–100 mg QID) for intestinal moniliasis; also topically for vaginitis, otomycosis, etc.: FUNGIZONE OTIC 3% ear drops.

For systemic mycosis, it is available as dry powder along with DOC for extemporaneous dispersion before use: FUNGIZONE INTRAVENOUS, MYCOL 50 mg vial. It is diluted to 500 ml with glucose solution and 0.3 mg/kg is infused over 4–8 hours.

Adverse effects The toxicity of AMB is high.

(a) *Acute reaction* This occurs with each infusion and consists of chills, fever, aches and pain all over, nausea, vomiting and dyspnoea lasting for 2–5 hours probably due to release of cytokines (IL, TNFα).

Thrombophlebitis of the injected vein can occur.

(b) *Long-term toxicity* Nephrotoxicity is the most important. It occurs fairly uniformly and is dose related: manifestations are—azotaemia, reduced g.f.r., acidosis, hypokalaemia and inability to concentrate urine.

Table 32.1: Choice of drugs for systemic mycoses

	Disease	*Drugs*	
		1st choice	*2nd choice*
1.	Candidiasis		
	oral/vaginal/cutaneous	FLU/NYS/CLO	ITR
	disseminated	AMB	FLU
2.	Cryptococcosis	AMB ± 5-FC	FLU
3.	Histoplasmosis	ITR/AMB	FLU
4.	Coccidioidomycosis	AMB/FLU	ITR/KTZ
5.	Blastomycosis	ITR/AMB	KTZ/FLU
6.	Sporotrichosis (disseminated)	AMB	ITR
7.	Paracoccidioidomycosis	ITR	AMB—Sulfonamide
8.	Aspergillosis	AMB	ITR
9.	Mucormycosis	AMB	—
10.	Chromomycosis	ITR	KTZ/5-FC

AMB—Amphotericin B; 5-FC—Flucytosine; KTZ—Ketoconazole; FLU—Fluconazole; ITR—Itraconazole; NYS—Nystatin; CLO—Clotrimazole

Most patients develop slowly progressing anaemia due to bone marrow depression.

Uses Amphotericin B can be used topically for oral, vaginal and cutaneous candidiasis and otomycosis.

It is the most effective drug for various types of systemic mycoses and is the gold standard of antifungal therapy. However, because of higher toxicity of AMB, the azole antifungals are now preferred in conditions where their efficacy approaches that of AMB (*see* Table 32.1).

Leishmaniasis: AMB is a reserve drug for resistant cases of kala azar.

Interactions Rifampin and minocycline, though not antifungal in their own right, potentiate AMB action.

Aminoglycosides, vancomycin, cyclosporine and other nephrotoxic drugs enhance the renal impairment caused by AMB.

Nystatin

Obtained from *S. noursei*, it is similar to AMB in antifungal action and other properties. However, because of higher systemic toxicity, it is used only locally.

In dentistry, topically applied nystatin is the 2nd choice drug to clotrimazole for oral thrush, denture stomatitis, antibiotic associated stomatitis and mucocutaneous candidiasis of lips, etc. The 1 lac U (1 mg = 2,000 U) tablet is placed in the mouth to dissolve slowly 4 times a day, or it can be crushed and suspended in glycerine for application on the lesions. A bitter foul taste and nausea are the side effects.

Given orally, it is not absorbed; can be used for monilial diarrhoea. It is effective (but less than azoles) in monilial vaginitis—1 lac U tab inserted twice daily. Similarly, it is used for corneal, conjunctival and cutaneous candidiasis in the form of an ointment. No irritation or other side effect is ordinarily seen.

Candidal resistance to nystatin is not a clinical problem. It is ineffective in dermatophytosis.

Hamycin

It was isolated from *S. pimprina* and developed by Hindustan Antibiotics at Pimpri. It is similar to nystatin, but more water soluble. Use is restricted to topical application for oral thrush, cutaneous candidiasis, monilial and trichomonas vaginitis and otomycosis by *Aspergillus*.

HAMYCIN, IMPRIMA 5 lac U/g oint, 2 lac U/ ml susp for topical use, 4 lac U vaginal ovules.

Natamycin (Pimaricin)

It is similar to nystatin; is non-irritating to the eye and has been used particularly in *Fusarium solani* keratitis. Both monilial and trichomonas vaginitis are amenable to natamycin.

NATAMYCIN 2% cream, 25 mg vaginal tab, PIMAFUSIN VAGINAL 100 mg vaginal tab.

HETEROCYCLIC BENZOFURAN

Griseofulvin

It is active against most dermatophytes, including *Epidermophyton, Trichophyton, Microsporum,* etc., but not against *Candida* and other fungi causing deep mycosis. Bacteria are also insensitive. Griseofulvin interferes with mitosis—multinucleated and stunted fungal hyphae result from its action. It also causes abnormal metaphase configurations.

Pharmacokinetics The absorption of griseofulvin from g.i.t. is somewhat irregular because of its very low water solubility. Absorption is improved by taking it with fats and by microfining the drug particles.

Griseofulvin gets deposited in keratin forming cells of skin, hair and nails; it is specially concentrated and retained in tinea infected cells. Because it is fungistatic and not cidal, the fungus persists in already infected keratin, till it is shed off. Thus, the duration of treatment is dependent upon the site of infection, thickness of infected keratin and its turnover rate.

Griseofulvin is largely metabolized, primarily by methylation, and excreted in urine. Plasma t½ is 24 hrs, but it persists for weeks in skin and keratin.

Adverse effects Toxicity of griseofulvin is low and usually not serious. Headache is the commonest complaint, followed by g.i.t. disturbances. CNS symptoms and peripheral neuritis are occasional.
Rashes, photoallergy may warrant discontinuation.
Transient leukopenia and albuminuria (without renal damage) are infrequent.

Use Griseofulvin is used orally only for dermatophytosis. It is ineffective topically. Systemic azoles and terbenafine are equally or more efficacious; preferred now.

Majority of localized tinea infections are treated with topical agents. Griseofulvin should be reserved for cases with nail, hair or large body surface involvement. It is effective in athletes foot, but not in pityriasis versicolor.
GRISOVIN-FP, DERMONORM 250, 500 mg tabs.

Interactions Griseofulvin induces warfarin metabolism and reduces efficacy of oral contraceptives. Phenobarbitone reduces the oral absorption and induces the metabolism of griseofulvin—failure of therapy may occur.
Griseofulvin can cause intolerance to alcohol.

FLUCYTOSINE (5-FC)

It is a pyrimidine antimetabolite which is inactive as such. It is taken up by fungal cells and converted into 5-fluorouracil and then to 5-fluorodeoxyuridylic acid which is an inhibitor of thymidylate synthesis. Thymidylic acid is a component of DNA.

It is a narrow spectrum fungistatic, active against *Cryptococcus neoformans, Torula, Chromoblastomyces*; and a few strains of *Candida*. Other fungi and bacteria are insensitive.

Flucytosine is not employed as the sole therapy, but only to potentiate AMB. Rapid development of resistance limits its utility in deep mycosis.

IMIDAZOLES AND TRIAZOLES

These are presently the most extensively used antifungal drugs.

Three imidazoles are entirely topical, while ketoconazole is used both orally and topically. Two triazoles fluconazole and itraconazole have largely replaced ketoconazole for systemic mycosis because of greater efficacy, fewer side effects and drug interactions.

The imidazoles and triazoles have broad-spectrum antifungal activity covering dermatophytes, *Candida*, other fungi involved in deep mycosis, *Nocardia*, some gram-positive and anaerobic bacteria, e.g. *Staph. aureus, Strep. faecalis, Bac. fragilis* and *Leishmania*.

The mechanism of action of imidazoles and triazoles is the same. They inhibit the fungal cytochrome P450 enzyme lanosterol 14-demethylase and thus impair ergosterol synthesis leading to a cascade of membrane abnormalities in the fungus. The lower host toxicity of triazoles compared to imidazoles has correlated with their lower affinity for mammalian CYP450 enzyme and lesser propensity to inhibit mammalian sterol synthesis. However, because they are active against certain bacteria as well (which do not have ergosterol), other mechanisms of action also appear to be involved.

Development of fungal resistance to azoles has not so far posed any significant clinical problem.

Clotrimazole It is effective in the topical treatment of tinea infections like ringworm. Athlete's foot, otomycosis and oral, cutaneous, vaginal candidiasis have responded in >80% cases. It is the most commonly used drug for oropharyngeal candidiasis; 10 mg troche of clotrimazole is allowed to dissolve in the mouth 3 to 4 times a day or the lotion/gel is applied/swirled in the mouth for as long as possible. For denture stomatitis, patients are advised to apply clotrimazole lotion/gel to the fitting surface of the denture before wearing it. Also, denture should be kept overnight in sod. hypochlorite/benzalkonium/cetrimide solution, and the denture should be worn only when needed. Topical clotrimazole can be used to treat angular cheilitis that often is a mixed candidal, streptococcal, staphylococcal infection.

Clotrimazole is well tolerated by most patients. Local irritation with stinging and burning sensation occurs in some. No systemic toxicity is seen after topical use.

SURFAZ, CLOTRIN, CLODERM 1% lotion, cream, powder; 100 mg vaginal tab. CANDID 1% cream, gel, lotion, powder.

Econazole It is similar to clotrimazole; and is highly effective in dermatophytosis, otomycosis, oral thrush, but is somewhat inferior to clotrimazole in vaginitis. No adverse effects, except local irritation in few is reported.

ECONAZOLE 1% oint, 150 mg vaginal tab; ECODERM 1% cream.

Miconazole It is an alternative drug to clotrimazole for tinea, pityriasis versicolor, otomycosis, oral, cutaneous and vulvovaginal candidiasis; single application on skin acts for a few days.

Irritation after cutaneous application is infrequent, no systemic adverse effects are seen. However, a higher incidence of vaginal irritation is reported in comparison to clotrimazole; even pelvic cramps have been experienced.

DAKTARIN 2% gel, 2% powder and solution; GYNODAKTARIN 2% vaginal gel; ZOLE 2% oint, lotion, dusting powder and spray, 1% ear drops, 100 mg vaginal ovules.

Ketoconazole (KTZ)

It is the first orally effective broad-spectrum antifungal drug, useful in dermatophytosis, superficial candidiasis as well as in deep mycosis. The oral absorption of KTZ is facilitated by gastric acidity because it is more soluble at lower pH. In the blood it is largely bound to albumin and RBCs. Hepatic metabolism is extensive; metabolites are excreted in urine and faeces. Elimination of KTZ is dose dependent: t½ varies from 1½ to 6 hours. Penetration in CSF is poor. However, therapeutic concentrations are attained in the skin and vaginal fluid.

In spite of relatively short t½, a single daily dose is satisfactory in less severe cases. The usual dose is 200 mg OD or BD.

FUNGICIDE, NIZRAL, FUNAZOLE, KETOVATE 200 mg tab.

FUNGINOC, NIZRAL 2% oint, 2% shampoo (for dandruff), KETOVATE 2% cream.

Adverse effects Ketoconazole is much less toxic than AMB, but more side effects occur than with itraconazole or fluconazole.

The most common side effects are nausea and vomiting; can be reduced by giving the drug with meals. Others are—loss of appetite, headache, paresthesia, rashes and hair loss.

Ketoconazole decreases androgen production from testes and it displaces testosterone from protein binding sites. Gynaecomastia, loss of hair and libido, and oligozoospermia may be the manifestations. Menstrual irregularities occur in some women due to suppression of estradiol synthesis.

A dose-dependent decrease in serum hydrocortisone due to synthesis inhibition has also been noted, but without any clinical manifestations in normal individuals. Hepatotoxicity is infrequent.

Interactions H_2 blockers, proton pump inhibitors and antacids decrease the oral absorption of KTZ by reducing gastric acidity.

Rifampin, phenobarbitone, carbamazepine and phenytoin induce KTZ metabolism and reduce its efficacy.

Ketoconazole inhibits cytochrome P450, especially CYP3A4, and raises the blood level of several drugs including warfarin, sulfonylureas, phenytoin, cyclosporine, diazepam, nifedipine, indinavir. A dangerous interaction with terfenadine, astemizole and cisapride has been noted: polymorphic ventricular tachycardia and fatal ventricular fibrillation have occurred due to excessive rise in plasma levels of these drugs.

Use Ketoconazole is rarely used in dental practice. Topically, it has been employed for tinea and other forms of dermal mycosis. Dandruff often responds to KTZ applied as a shampoo. Oral KTZ produces slower response and has a lower efficacy in systemic mycosis than i.v. AMB. However, due to lower toxicity than AMB, it became the preferred drug for less serious forms of systemic mycosis that responded to it. Now, fluconazole and itraconazole have largely replaced it for these indications due to their higher efficacy, fewer side effects and drug interactions. Oral KTZ can be used in dermatophytosis involving large body surface, tinea of nails and

recurrent cases of monilial vaginitis not responding to topical agents.

It has also been tried in dermal leishmaniasis and *kala azar*.

High-dose KTZ has been used in Cushing's syndrome to decrease corticosteroid production.

Fluconazole

It is a newer water- soluble triazole having a wider range of activity than KTZ; indications include cryptococcal meningitis, systemic and mucosal candidiasis in both normal and immunocompromised patients, coccidioidal meningitis and histoplasmosis.

Fluconazole is 94% absorbed; oral bioavailability is not affected by food or gastric pH. It is primarily excreted unchanged in urine with a t½ of 25–30 hours. Fungicidal concentrations are achieved in nails, vagina and saliva; penetration into brain and CSF is good. Dose reduction is needed in renal impairment.

Adverse effects Fluconazole produces few side effects: mostly nausea, vomiting, abdominal pain, rash and headache.

Selectivity for fungal cytochrome P450 is higher; unlike KTZ, it does not inhibit steroid synthesis in man: antiandrogenic and other endocrine side effects have not occurred.

It is not recommended in pregnant and lactating mothers.

Interactions Though fluconazole affects hepatic drug metabolism to a lesser extent than KTZ, increased plasma levels of phenytoin, astemizole, cisapride, cyclosporine, warfarin, zidovudine and sulfonylureas have been observed. A few cases of ventricular tachycardia have been reported when fluconazole was given with cisapride. The same caution as with KTZ or itraconazole needs to be applied in coadministering other drugs.

Use Fluconazole can be administered orally as well as i.v. (in severe infections).

Oral fluconazole 150 mg/day for 2 weeks is highly effective in *Candida* infections of the mouth, but should be given only to patients not responding to topical treatment. A single 150 mg oral dose can cure vaginal candidiasis.

Most tinea infections and cutaneous candidiasis can be treated with 150 mg weekly for 4 weeks, while tinea unguium requires weekly treatment for up to 12 months.

For disseminated candidiasis, cryptococcal/coccidioidal meningitis and other systemic fungal infections the dose is 200–400 mg/day for 4–12 weeks or longer. It is the preferred drug for fungal meningitis.

An eye drop is useful in fungal keratitis.

SYSCAN, ZOCON, FORCAN, FLUZON 50, 100, 150, 200 mg caps, 200 mg/100 ml i.v. infusion.
SYSCAN 0.3% eye drops.

Itraconazole

This newer orally active triazole antifungal has a broader spectrum of activity than KTZ or fluconazole; includes some moulds like *Aspergillus*. It is fungistatic, but effective in immunocompromised patients. Steroid hormone synthesis inhibition and serious hepatotoxicity are absent in itraconazole.

Oral absorption of itraconazole is variable. It is enhanced by food and gastric acid. Itraconazole is highly protein bound, accumulates in vaginal mucosa, skin and nails, but penetration into CSF is poor. It is largely metabolized in liver by CYP3A4; an active metabolite is produced which is excreted in faeces; t½ varies from 30–64 hours.

Itraconazole is well tolerated in doses below 200 mg/day. Gastric intolerance is significant at > 400 mg/day. Dizziness, pruritus, headache and hypokalaemia are the other common side effects. Unsteadiness and impotence are infrequent. Antiandrogenic and other hormonal adverse effects are not seen.

Drug interactions Oral absorption of itraconazole is reduced by antacids, H_2 blockers and proton pump inhibitors.

Rifampin, phenobarbitone, phenytoin and carbamazepine induce itraconazole metabolism and reduce its efficacy.

Itraconazole inhibits CYP3A4; drug interaction profile is similar to KTZ; ventricular arrhythmias

have occurred with terfenadine, astemizole, cisapride and class III antiarrhythmics. Phenytoin, digoxin, sulfonylurea, protease inhibitors, warfarin and cyclosporine levels are also increased.

Uses Itraconazole is preferred over KTZ for most systemic mycosis (*see* Table 32.1) that are not associated with meningitis. It also affords some relief in aspergillosis. It is highly effective in vaginal candidiasis, dermatophytosis and onychomycosis, but use is restricted to cases not amenable to topical therapy. It is seldom used in dentistry for oral candidiasis.

SPORANOX, CANDITRAL, ITASPOR, FLUCOVER 100 mg cap.

TERBINAFINE

This orally and topically active drug against dermatophytes and *Candida* belongs to a new allylamine class of antifungals. In contrast to azoles which are primarily fungistatic, terbinafine is fungicidal: shorter courses of therapy are required and relapse rates are low. It acts as a noncompetitive inhibitor of squalene epoxidase, an early step enzyme in ergosterol biosynthesis by fungi. Accumulation of squalene within fungal cells appears to be responsible for the fungicidal action. The mammalian enzyme is inhibited only by 1000-fold higher concentration of terbinafine.

Side effects of oral terbinafine are gastric upset, rashes, taste disturbance. Some cases of hepatic dysfunction and haematological disorder are reported. Enzyme inducers lower, and enzyme inhibitors raise its steady-state plasma levels. Terbinafine does not inhibit CYP450.

Topical terbinafine can cause erythema, itching, dryness, irritation, urticaria and rashes.

Use Terbinafine applied topically as 1% cream or orally 250 mg OD is indicated in tinea pedis/corporis/cruris/capitis and pityriasis versicolor. Onychomycosis is treated by 3–12 months oral therapy.

It is less effective against cutaneous and mucosal candidiasis: 2–4 weeks oral therapy may be used as an alternative to fluconazole.

LAMISIL, SEBIFIN 250 mg tab, 1% topical cream. EXIFINE 125, 250 mg tabs.

OTHER TOPICAL ANTIFUNGALS

All these drugs are used for dermatophytosis.

1. Tolnaftate It is an effective drug for tinea cruris and tinea corporis—most cases respond in 1–3 weeks. Because of poor penetrability, it is less effective in tinea pedis and other hyperkeratinized lesions. For the same reason, it is ineffective in tinea capitis—involving scalp and tinea unguium—involving nails.

Tolnaftate causes little irritation and is better than many topical agents, but probably inferior to imidazoles. It is not effective in candidiasis or other types of superficial mycosis.

2. Ciclopirox olamine It is a newer drug effective in tinea infections, pityriasis versicolor and dermal candidiasis. Local tolerance without irritation is good. Sensitization occurs occasionally. Also used for vaginal candidiasis.

3. Undecylenic acid It is fungistatic used topically, generally in combination with its zinc salt. It is inferior to the drugs described above, but is still used for tinea pedis, nappy rash and tinea cruris. Irritation and sensitization are infrequent.

4. Benzoic acid It has antifungal and antibacterial property in slightly acidic medium. It is fungistatic—weaker than tolnaftate; eradication of the fungus needs prolonged application till infected keratin is shed.

On hyperkeratotic lesions, it is used in combination with salicylic acid (as Whitfield's ointment: benzoic acid 5%, salicylic acid 3%). Irritation and burning sensation is experienced by many patients.

5. Quiniodochlor By the oral route, it is used as a luminal amoebicide. It also has weak antifungal and antibacterial activity. By external application, it has been used for dermatophytosis, mycosis barbae, seborrhoeic dermatitis, and pityriasis versicolor.

It is also used in vaginal creams for monilial and trichomonas vaginitis.

6. Sodium thiosulfate It is a weak fungistatic, active against *Malassezia furfur*. A 20% solution applied twice daily for 3–4 weeks is effective in pityriasis versicolor.

ANTIVIRAL DRUGS

Viruses are the ultimate expression of parasitism: they not only take nutrition from the host cell but also direct its metabolic machinery to synthesize new virus particles. Viral chemotherapy, therefore, is difficult, as it would require

interference with cellular metabolism in the host. However, virus directed enzymes have been identified in the infected cell and some viruses have a few enzymes of their own which may have higher affinities for some inhibitors than the regular cellular enzymes. Drugs could also target virus specific steps like cell penetration, uncoating, reverse transcription, virus assembly or maturation. Another stumbling block is that in majority of acute infections viral replication is already at its peak when symptoms appear. To be effective, therefore, therapy has to be started in the incubation period, i.e. has to be prophylactic.

The application of antiviral drugs in dentistry is restricted to treatment of oropharyngeal herpes simplex and herpes labialis that occur particularly in immunocompromised patients.

CLASSIFICATION

1. *Anti-Herpes virus*
   Idoxuridine, Acyclovir, Famciclovir, Ganciclovir, Foscarnet
2. *Anti-Retrovirus*

(a) *Nucleoside reverse transcriptase inhibitors (NRTIs):* Zidovudine (AZT), Didanosine, Stavudine, Lamivudine

(b) *Non-nucleoside reverse transcriptase inhibitors (NNRTIs):* Nevirapine, Efavirenz

(c) *Protease inhibitors:* Ritonavir, Indinavir, Nelfinavir,

3. *Anti-Influenza virus*
   Amantadine
4. *Nonselective antiviral drugs*
   Ribavirin, Lamivudine, Interferon α

ANTI-HERPES VIRUS DRUGS

Idoxuridine

It is 5-iodo-2-deoxyuridine (IUDR); acts as a thymidine analogue. It was the first pyrimidine antimetabolite to be used as antiviral drug. It competes with thymidine, gets incorporated in DNA so that faulty DNA is formed which breaks down easily. It is effective only against DNA viruses and clinical utility is limited to *Herpes simplex* keratitis.

The virus selectivity of idoxuridine is low; systemic toxicity (bone marrow depression) is high after i.v. injection.

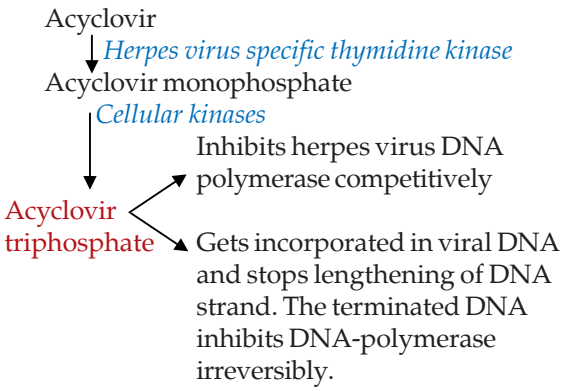
Side effects of idoxuridine eye drops are ocular irritation, edema of lids and photophobia.

Acyclovir is an equally efficacious and better tolerated alternative.

Acyclovir

This deoxiguanosine analogue antiviral drug requires a virus specific enzyme for conversion to the active metabolite that inhibits DNA synthesis and viral replication.

Acyclovir is preferentially taken up by the virus infected cells. Because of selective generation of the active inhibitor in the virus infected cell and its greater inhibitory effect on viral DNA synthesis, acyclovir has low toxicity for host cells: a several hundred-fold chemotherapeutic index has been noted.



Acyclovir is active only against herpes group of viruses; *H. simplex* type I is most sensitive followed by *H. simplex* type II > varicella-zoster virus = Epstein-Barr virus, while cytomegalovirus (CMV) is practically not affected. Both *H. simplex* and *varicella-zoster* virus have been found to develop resistance to acyclovir during therapy; the former primarily due to mutants deficient in thymidine kinase activity and the latter primarily by change in specificity of virus directed enzyme so that its affinity for acyclovir is decreased.

Pharmacokinetics Only about 20% of an oral dose of acyclovir is absorbed. It is little plasma

protein bound and is widely distributed attaining CSF concentration that is 50% of plasma concentration. It penetrates cornea well. Acyclovir is primarily excreted unchanged in urine, plasma t½ is 2–3 hours. Renal impairment necessitates dose reduction.

ZOVIRAX 200 mg tab, 250 mg/vial for i.v. inj; CYCLOVIR 200 mg tab, 5% skin cream; HERPEX 200 mg tab, 3% eye oint, 5% skin cream; OCUVIR 200, 400, 800 mg tab, 3% eye oint, ACIVIR-DT 200, 400, 800 mg tab. ACIVIR EYE 3% oint.

Use Acyclovir is effective in patients with normal as well as deficient immune status.

1. *Mucocutaneous H. simplex* is a type I virus disease, remains localized to lips and gums and does not usually require specific treatment. Started early, 5 times daily application of acyclovir 5% cream may abort or shorten the duration of recurrences in herpes labialis. Prophylactic oral acyclovir 200 mg 3 times a day therapy may prevent sun exposure related recurrences. Symptomatic improvement can occur in acute herpetic gingivostomatitis by acyclovir 200 mg 5 times daily for 10 days. The disease often gets disseminated in immunocompromised individuals and may be treated with oral or i.v. acyclovir (15 mg/kg/day) for 7 days, but recurrences are not prevented.

2. *Genital H. simplex* is generally caused by type II virus, and is treated with topical, oral or parenteral acyclovir depending upon the stage and severity of disease. Symptomatic relief is afforded, but subsequent recurrences are not prevented. Continuous oral medication is advised to ward off recurrences, if they are frequent.

3. *H. simplex encephalitis* (type I virus): Acyclovir is the drug of choice. Treatment is effective only if started early: delay precludes salutary effect on mortality and neurological complications.

4. *H. simplex (type I) keratitis*: Acyclovir is now preferred over idoxuridine.

5. *Herpes zoster*: Acyclovir should be used only in immunodeficient individuals or in severe cases: affords symptomatic relief and faster healing of lesions, but postherpetic neuralgia is not prevented.

6. *Chickenpox*: in patients with immunodeficiency and in neonates calls for acyclovir therapy.

Adverse effects

Topical: stinging and burning sensation after each application.
Oral: The drug is well tolerated; headache, nausea, malaise and some CNS effects are reported.
Intravenous: rashes, sweating, emesis and fall in BP occur only in few patients.
Dose dependent decrease in g.f.r. is the most important toxicity; occurs specially in those with kidney disease; normalises on discontinuation of the drug. Reversible neurological manifestations (tremors, lethargy, disorientation, hallucinations, convulsions and coma) have been ascribed to higher doses.

Famciclovir It is an ester prodrug of a guanine nucleoside analogue *penciclovir*; has good oral bioavailability and prolonged intracellular t½ of the active triphosphate metabolite. Like acyclovir, it needs viral thymidine kinase for generation of active DNA polymerase inhibitor. Famciclovir inhibits *H. simplex* and *H. zoster* but not acyclovir-resistant strains. Some activity against hepatitis B virus (HBV) has been noted. It is used as an alternative to acyclovir for orolabial or genital herpes and herpes zoster.

Dose: Genital herpes (1st episode) 250 mg TDS × 5 days; recurrent cases 250 mg BD for up to 1 year. Herpes zoster and orolabial herpes 500 mg TDS for 7–10 days.
FAMTREX 250, 500 mg tabs.

Famciclovir is a less active alternative to lamivudine in chronic hepatitis B, but not in resistant cases. Side effects are headache, nausea, loose motions, itching, rashes and mental confusion.

Ganciclovir It is an analogue of acyclovir which is active against all herpes viruses including *H. simplex*, *H. zoster*, E-B virus and cytomegalovirus (CMV). It is more active than acyclovir against CMV. The mechanism of action and basis of virus selectivity is similar to acyclovir.

Systemic toxicity of ganciclovir is high (bone marrow depression, rash, fever, vomiting, neuropsychiatric disturbances) and use is restricted to severe CMV infections, especially CMV retinitis, in immunocompromised (AIDS, transplant recipient) patients.

Foscarnet It is a simple straight chain phosphonate unrelated to any nucleic acid precursor which inhibits viral DNA polymerase and reverse transcriptase. It is active against *H. simplex* (including strains resistant to acyclovir), CMV (including ganciclovir resistant ones) and HIV. Viral resistance to foscarnet is minimal. However, viral selectivity of foscarnet is low.

Toxicity of foscarnet is high: damages kidney. Anaemia, phlebitis, tremor, convulsions and other neurological as well as constitutional symptoms due to hypocalcaemia are frequent. Administered by i.v. infusion, foscarnet has been used for:

1. CMV retinitis and other CMV infections in AIDS patients.
2. Acyclovir-resistant mucocutaneous *H. simplex* type II and varicella-zoster infections in AIDS patients.

ANTI-RETROVIRUS DRUGS

These are drugs active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC), but do not cure the infection. The clinical efficacy of antiretrovirus drugs is monitored primarily by plasma HIV-RNA assays and CD4 lymphocyte count carried out at regular intervals.

The first antiretrovirus drug *Zidovudine* was developed in 1987. Over the past 18 years, > 20 drugs belonging to 3 classes have been introduced and a large number of others are under development.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Zidovudine It is a thymidine analogue (azidothymidine, AZT), the prototype NRTI. After phosphorylation in the host cell—zidovudine triphosphate selectively inhibits viral reverse transcriptase (RNA-dependent DNA polymerase) in preference to cellular DNA polymerase.

On the template of single-stranded RNA genome of HIV, a double-stranded DNA copy is produced by viral reverse transcriptase. This DNA translocates to the nucleus and is integrated with chromosomal DNA of the host cell, which then starts transcribing viral genomic RNA as well as mRNA. Under the direction of viral mRNA, viral regulatory and structural proteins are produced. Finally, viral particles are assembled and matured. Zidovudine thus prevents infection of new cells by HIV but has no effect on virus directed DNA that has already integrated into the host chromosome. It is effective only against retroviruses. Zidovudine itself gets incorporated into the growing viral DNA and terminates chain elongation. Resistance to AZT occurs by point mutations which alter reverse transcriptase enzyme. In the past, when AZT was used alone, >50% patients became nonresponsive to AZT within 1–2 years therapy due to growth of resistant mutants.

Pharmacokinetics The oral absorption of AZT is rapid, but bioavailability is ~65%. It is quickly cleared by hepatic glucuronidation (t½ 1 hr); 15–20% of the unchanged drug along with the metabolite is excreted in urine.

Adverse effects Toxicity is mainly due to partial inhibition of cellular DNA polymerase. Anaemia and neutropenia are the most important and dose-related adverse effects.

Nausea, anorexia, abdominal pain, headache, insomnia and myalgia are common at the start of therapy but diminish later.

Myopathy, lactic acidosis, hepatomegaly, convulsions and encephalopathy are infrequent.

Interactions Paracetamol increases AZT toxicity, probably by competing for glucuronidation. Azole antifungals also inhibit AZT metabolism. Stavudine and zidovudine exhibit mutual

antagonism by competing for the same activation pathway.

Use Zidovudine is used in HIV-infected patients only in combination with at least 2 other antiretrovirus drugs. HIV-RNA titer is reduced to undetectable levels and CD4 count increases progressively. Immune status is improved and opportunistic infections become less common. There is a sense of well-being and patients gain weight. The 1 year mortality among AIDS patients is reduced. It has also been shown to slow the progression of HIV infection, including escalation of ARC to full blown AIDS. However, beneficial effects are limited from a few months to a couple of years after which progressively non-responsiveness develops.

Didanosine It is a purine nucleoside analogue which after intracellular conversion to didanosine triphosphate competes with ATP for incorporation in viral DNA, inhibits HIV reverse transcriptase and terminates proviral DNA. Antiretroviral activity of didanosine is equivalent to AZT. Mutational resistance develops, and it is used only in combination regimens.

In contrast to AZT, it does not cause myelosuppression. The prominent dose-related toxicity is pancreatitis and peripheral neuropathy. Diarrhoea, abdominal pain and nausea are the side effects.

Stavudine It is also a thymidine analogue which acts in the same way as AZT. By utilizing the same thymidine kinase for activation, AZT antagonises the effect of stavudine. Resistance to stavudine develops as for other NRTIs.

The anti-HIV efficacy of stavudine is comparable to AZT, and it is used now in combination regimens. The major dose-related toxicity is peripheral neuropathy, but pancreatitis is rare.

Lamivudine This deoxycytidine analogue is phosphorylated intracellularly and inhibits HIV reverse transcriptase as well as hepatitis B virus (HBV) DNA polymerase. Its incorporation into DNA results in chain termination. Most human DNA polymerases are not affected and systemic toxicity of lamivudine is low. Point mutation in HIV-reverse transcriptase and HBV-DNA polymerase gives rise to rapid lamivudine resistance.

Lamivudine is used in combination with other anti-HIV drugs, and appears to be as effective as AZT. It is also frequently used for chronic hepatitis B. HBV-DNA titre is markedly reduced and biochemical as well as histological indices of liver function improve. However, viral titres rise again after discontinuation. Even with continued medication HBV viraemia tends to return after 1 year due to emergence of resistant mutants.

Lamivudine is generally well tolerated. Side effects are headache, fatigue, nausea, anorexia, abdominal pain. Pancreatitis and neuropathy are rare.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Nevirapine and Efavirenz These are nucleoside unrelated compounds which directly inhibit HIV reverse transcriptase without the need for intracellular phosphorylation. Their locus of action on the enzyme is also different. They are more potent than AZT on HIV-1, but do not inhibit HIV-2. Viral resistance to these drugs develops by point mutation and cross resistance is common among different NNRTIs.

The NNRTIs are indicated in combination regimens for HIV, and have succeeded in reducing HIV-RNA levels when an earlier regimen has failed. Rashes, nausea, headache are the usual side effects. Fever and rise in liver enzymes can occur with nevirapine, while efavirenz can cause a variety of neuropsychiatric symptoms.

Retroviral protease inhibitors (PIs)

An aspartic protease enzyme encoded by HIV is involved in the production of structural proteins and enzymes (including reverse transcriptase) of the virus. The large viral polyprotein is broken into various functional components by this enzyme. This protease acts at

a late step in HIV replication, i.e. maturation of the new virus particles when the RNA genome acquires the core proteins and enzymes. The protease inhibitors—*ritonavir, indinavir* and *nelfinavir* bind to the protease molecule and interfere with its cleaving function. They are more effective viral inhibitors than AZT. Because they act at a late step of viral cycle, they are effective in both newly and chronically infected cells. Under their influence, HIV-infected cells produce immature noninfectious viral progeny—hence prevent further rounds of infection.

Oral bioavailability of PIs is variable, and their plasma t½ ranges from 2–5 hours. All are extensively metabolized by CYP3A4 and other CYP isoenzymes. All (especially ritonavir) are inhibitors of CYP3A4—interact with many drugs. Among the drugs used in dentistry whose plasma levels are increased are metronidazole, lignocaine, midazolam and carbamazepine. Nelfinavir and ritonavir induce their own metabolism.

Viral resistance develops against the PIs over months due to selection of resistant mutants in a stepwise manner. Current recommendations are to use a PI in combination with two reverse transcriptase inhibitors. The PI can be combined with two NRTIs or one NRTI + one NNRTI. Boosted protease inhibitor regimens, containing both indinavir and low-dose ritonavir along with NRTIs are also being used.

The most prominent adverse effects of PIs are gastrointestinal intolerance, asthenia, headache, paresthesia, dizziness, rash, abnormal distribution of body fat and exacerbation of diabetes. Indinavir produces crystalluria and increases risk of urinary calculi.

TREATMENT OF HIV INFECTION

The treatment of HIV infection and its complications is complex, prolonged, needs expertise, strong motivation and commitment of the patient, resources and is very expensive. Antiretroviral therapy is < 20 years old, and strategies are still evolving. Initially, anti-HIV drugs were used singly one after the other as each failed in a patient due to emergence of resistance. Understanding the biology of HIV infection and availability of several potent drugs belonging to different classes has mandated 'highly active antiretroviral therapy' (HAART) with combination of 3 or more drugs replace monotherapy.

It has been realized that even with HAART which rapidly kills > 99% virions, a small number survive within the resting CD4 lymphocytes and invariably give rise to relapse. As the disease progresses in the individual (and several anti-HIV drugs are used), the HIV population becomes genetically complex and diverse with respect to susceptibility to drugs. Each failing regimen limits future treatment options.

Since none of the currently available regimens can eradicate HIV from the body of the patient, the goal of therapy is to durably inhibit viral replication so that the patient can attain and maintain effective immune response towards potential microbial pathogens.

Health authorities and professional bodies have framed elaborate guidelines for selecting patients for anti-HIV therapy as well as for devising suitable treatment regimens, details of which are beyond the scope of this text, because dentists do not treat HIV infection.

Briefly, treatment is recommended for all symptomatic HIV disease patients and for asymtomatic cases with CD4 count, < 200/µl. Treatment is not recommended for asymptomatic cases with reasonable immune competence (CD4 cell count > 350/µl), while decision to treat asymptomatic cases with CD4 cell count between 350/µl and 200/µl depends on rate of decline in CD4 count, HIV-RNA level and other factors.

The most commonly employed initial regimens are:

2–NRTIs + 1–PI
2–NRTIs + 1–NNRTI
3–NRTIs

Four-drug regimens have also been tested, but their superiority is not established.

Treatment failures are to be anticipated and occur within the first year or in successive years

with nearly all regimens. Optimally, the regimen should be changed entirely (all 3 drugs changed) to drugs that have not been administered earlier. With repeated failures, it may become more difficult to construct an active combination.

Prophylaxis of HIV infection is recommended for:
(a) Healthcare workers and others who get accidentally exposed to risk of HIV infection by needlestick or similar injury, blood transfusion, etc: zidovudine ± other anti-HIV drugs administered soon after exposure reduce the risk of contacting HIV infection, but do not rule it out completely.
(b) Pregnant HIV positive women: treatment of the mother with zidovudine continued in the neonate for 6 weeks substantially reduces the chances of transmission of HIV to the offspring.

ANTI-INFLUENZA VIRUS DRUGS

Amantadine

Chemically, it is a tricyclic amine unrelated to any nucleic acid precursor, but inhibits replication of influenza A virus (a myxovirus). It appears to act at an early step (possibly uncoating) as well as at a late step (viral assembly) in viral replication. A protein designated 'M2' which acts as an ion channel has been identified as one of its targets of action. Resistance to amantadine develops by mutation causing amino acid substitutions in the M2 protein. Amantadine is well absorbed orally and excreted unchanged in urine over 2–3 days (t½ 16 hr).

Adverse effects Generally well tolerated; nausea, anorexia, insomnia, dizziness, nightmares, lack of mental concentration, hallucinations and postural hypotension have been reported. Ankle edema occurs due to local vasoconstriction.

Uses

1. Prophylaxis of influenza A_2, especially in high risk patients. It is quite virus specific: influenza B is unaffected.
2. Treatment of influenzal (A_2) illness: a modest therapeutic effect (reduction in fever, congestion and cough) occurs if the drug is given quickly after the symptoms appear.
3. Parkinsonism (*see* Ch. 9).

NONSELECTIVE ANTIVIRAL DRUGS

Ribavirin This purine nucleoside analogue has broad-spectrum antiviral activity, including that against influenza A and B, respiratory syncytial virus and many other DNA and double-stranded RNA viruses. Its mono- and triphosphate derivatives generated intracellularly inhibit GTP and viral RNA synthesis and have other sites of action as well. No viral resistance to ribavirin has yet been observed.

Administered orally or i.v. ribavirin has been used in influenza A/B and measles in immunosuppressed patients as well as for herpes virus infections, acute hepatitis and to delay progression of ARC to AIDS, but clinical benefits are uncertain. It has been combined with interferon α in chronic hepatitis C. Nebulized ribavirin has been used for respiratory syncytial virus broncholitis in infants and children with high risk conditions.

Prominent toxic effects are anaemia, haemolysis, CNS and g.i. symptoms. The aerosol can cause irritation of mucosae and bronchospasm.

Interferon α

Interferons are low molecular weight glycoprotein cytokines produced by host cells in response to viral infections and some other inducers. They have nonspecific antiviral as well as other complex effects on immunity and cell proliferation. Interferons bind to specific cell surface receptors and affect viral replication at multiple steps: viral penetration, synthesis of viral mRNA, assembly of viral particles and their release, but the most widespread effect is direct or indirect suppression of viral protein synthesis, i.e. inhibition of translation. Interferon receptors

are tyrosine protein kinase receptors which on activation phosphorylate cellular proteins. These then induce transcription of 'interferon-induced proteins' which exert antiviral effects.

Interferons inhibit many RNA and DNA viruses, but they are host specific: those produced by another species have poor activity in man. Three types of human interferons (α, β and γ) have been produced by recombinant DNA technology. Only interferon α_{2A} and α_{2B} have antiviral activity. Recently, more active pegylated interferons have been produced—but are very expensive.

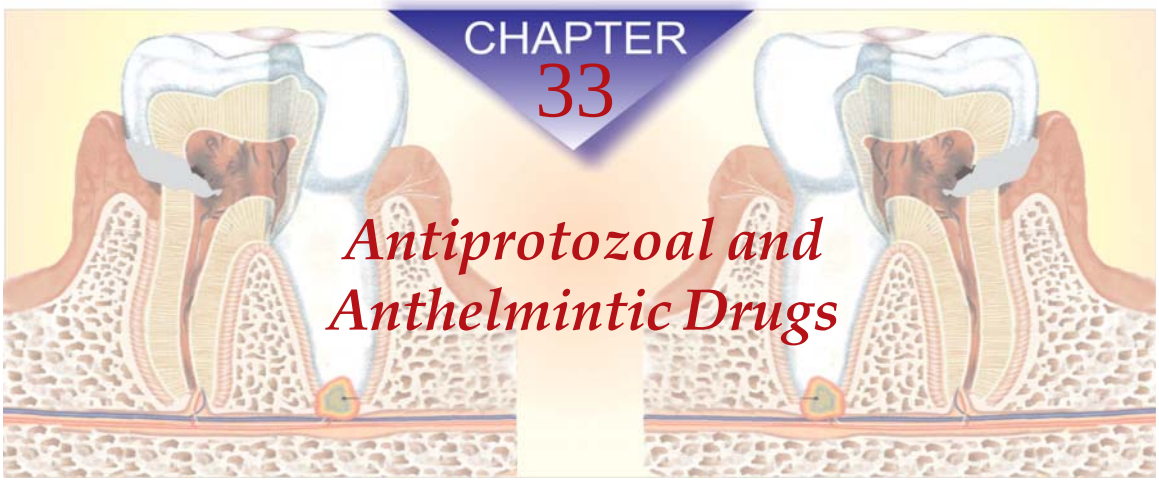
Uses

1. Chronic hepatitis B and C: Interferon causes disappearance of HBV-DNA from plasma and improvement in liver function tests/histology in nearly half of the patients, but relapses do occur.
2. AIDS-related Kaposi's sarcoma (but not to treat HIV as such).
3. Hairy cell leukaemia.
4. Condyloma acuminata caused by papilloma virus refractory to podophyllin.
5. *H. simplex, H. zoster* and CMV infections in immunocompromised patients.
6. Rhinoviral cold: intranasal interferon is prophylactic.

Interferon is not effective orally. Clinical utility of s.c. or i.m. injected interferon is limited by substantial adverse effects.

Adverse effects

Flu-like symptoms—fatigue, aches and pains, malaise, fever, dizziness, anorexia, taste and visual disturbances: develop a few hours after each injection, but become milder later.
Neurotoxicity—numbness, neuropathy, tremor, sleepiness, rarely convulsions.
Myelosuppression (dose limiting)—neutropenia, thrombocytopenia.
Hypotension, transient arrhythmias, alopecia and liver dysfunction.



CHAPTER 33

Antiprotozoal and Anthelmintic Drugs

ANTIMALARIAL DRUGS

These are drugs used for prophylaxis, treatment and prevention of relapses of malaria.

Malaria, caused by 4 species of the protozoal parasite *Plasmodium*, is endemic in most parts of India and other tropical countries. It is one of the major health problems.

CLASSIFICATION

1.	*4-Aminoquinolines*	Chloroquine, Amodiaquine
2.	*Quinoline-methanol*	Mefloquine
3.	*Cinchona alkaloid*	Quinine
4.	*Biguanide*	Proguanil (Chloroguanide)
5.	*Diaminopyrimidine*	Pyrimethamine
6.	*8-Aminoquinolines*	Primaquine, Bulaquine
7.	*Sulfonamides and sulfone*	Sulfadoxine, Sulfamethopyrazine, Dapsone
8.	*Tetracyclines*	Tetracycline, Doxycycline
9.	*Sesquiterpine lactones*	Artesunate, Artemether, Arteether
10.	*Phenanthrene methanol*	Halofantrine, Lumefantrine
11.	*Naphthoquinone*	Atovaquone.

OBJECTIVES AND USE OF ANTIMALARIALS

The aims of using drugs in relation to malarial infection are:

(i) To prevent and treat clinical attack of malaria.
(ii) To completely eradicate the parasite from the patient's body.
(iii) To reduce the human reservoir of infection — cut down transmission to mosquito.

These are achieved by attacking the parasite at its various stages of life cycle in the human host (*see* Fig. 33.1). Antimalarials that act on erythrocytic schizogony are called *erythrocytic schizontocides*, those that act on preerythrocytic as well as exoerythrocytic (*P. vivax)* stages in liver are called *tissue schizontocides*, while those which kill gametocytes in blood are called *gametocides.* Antimalarial drugs exhibit considerable stage selectivity of action (*see* Table 33.1). Antimalarial therapy is given in the following forms.

1. Causal prophylaxis The preerythrocytic phase (in liver), which is the *cause* of malarial infection and clinical attacks, is the target for this purpose. Proguanil is a causal prophylactic primarily for *P. falciparum*, but is not very effective against *P. vivax.* Primaquine is a causal prophylactic for all species of malaria, but has not been used in mass programmes because of its toxic potential.

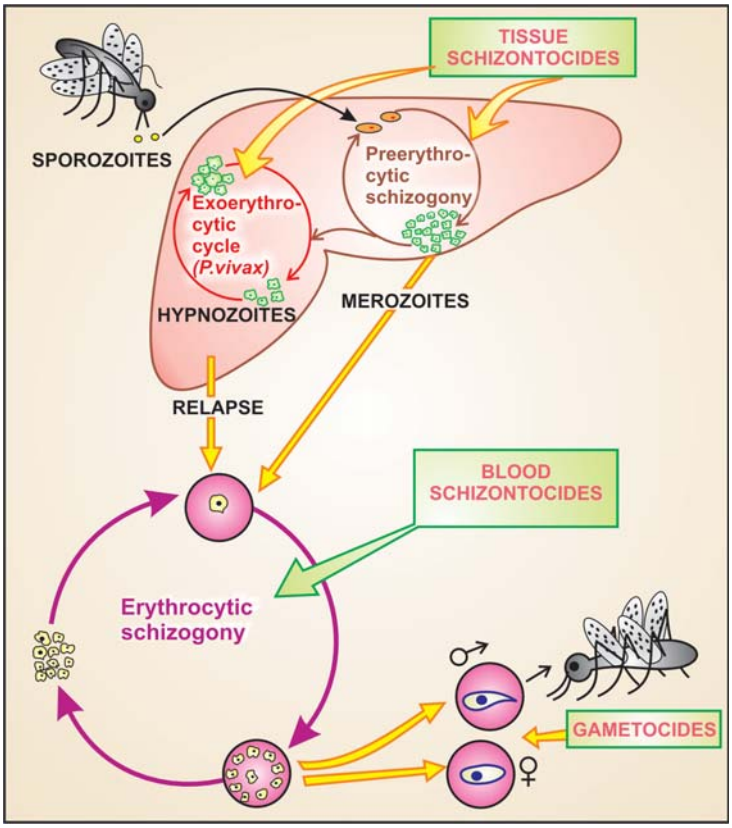


Fig. 33.1: The life cycle of malarial parasite in man. Stages and forms of the parasite at which different types of antimalarial drugs act are indicated

2. Suppressive prophylaxis The schizontocides which suppress the erythrocytic phase and thus attacks of malarial fever can be used as prophylactics. Though the exoerythrocytic phase in case of vivax and other relapsing malarias continues, clinical disease does not appear. Drugs used are chloroquine (300 mg base weekly); in areas with chloroquine-resistant *P. falciparum*: proguanil (200 mg daily along with weekly chloroquine) or mefloquine (250 mg weekly) or doxycycline (100 mg daily).

Chemoprophylaxis of malaria should be limited to short-term use in special risk groups, such as — nonimmune travellers, nonimmune persons living in endemic areas for fixed periods (army units, labour forces) and pregnant women.

3. Clinical cure The erythrocytic schizontocides are used to terminate an episode of malarial fever. These are:

(a) *Fast-acting high-efficacy drugs*: Chloroquine, quinine, mefloquine, halofantrine, atovaquone, artemisinin. They can be used singly to treat attacks of malarial fever.

(b) *Slow-acting low-efficacy drugs*: Proguanil, pyrimethamine, sulfonamides, tetracyclines. They are used only in combination for clinical cure.

The faster acting drugs are preferred. The exoerythrocytic phase of vivax persists which can cause *relapses* subsequently without reinfection. Thus, the above drugs are radical curatives for falciparum but not for relapsing malaria. *Recrudescences* occur in falciparum infection if the

Table 33.1: Comparative properties of antimalarial drugs

Drug	Preerythro.		Erythrocytic Phase			Exo-erythro.	Gametes		Resistance	Toxicity grading
	Fal.	Viv.	Activity	Onset	Duration	Viv.	Fal.	Viv.		
1. Chloroquine	–	–	+	Fast	Long	–	–	+	Slow	±
2. Mefloquine	–	–	+	Int	Long	–	–	–	Minor	++
3. Quinine	–	–	+	Int	Short	–	–	+	Minor	+++
4. Proguanil	+	±	+	Slow	Short	–	*	*	Rapid	±
5. Pyrimethamine	–	–	+	Slow	Long	±	*	*	Rapid	+
6. Primaquine	+	+	–	–	–	+	+	+	Minor	++
7. Sulfonamides	–	–	±	Slow	Long	–	–	–	Minor	+±
8. Tetracyclines	+	–	+	Slow	Short	–	–	–	Nil	+
9. Artemisinin	–	–	+	Fastest	Short	–	+	+	Nil	+
10. Halofantrine	–	–	+	Fast	Int.	–	–	–	Nil	++

*Do not kill gametes but inhibit their development in mosquito.
Preerythro. — Preerythrocytic stage; Exoerythro. — Exoerythrocytic stage
Fal. — *P. falciparum*; Viv — *P. vivax*; Int — Intermediate

blood is not totally cleared of the parasites by the drug. Regimens used are:

- Chloroquine 600 mg *stat* followed by 300 mg after 8 hours and 300 mg daily for next two days is the drug of choice.
- Pyrimethamine 25 mg + a sulfonamide 500 mg tab — 3 tablet single dose; is an alternative, but should be reserved for chloroquine-resistant or chloroquine-intolerant cases.

Relapses of vivax malaria are treated in the same way as the primary attack. Recrudescence in falciparum malaria indicates resistant infection: should be treated with an alternative drug as per local needs. For chloroquine-resistant as well as multiresistant *P. falciparum*, one of the following may be used:

- Mefloquine 15–25 mg/kg (750 mg followed by 500 mg 12 hours later).
- Quinine 600 mg (10 mg/kg) TDS for 7 days, alone or with pyrimethamine 75 mg + sulfonamide 1500 mg.
- Quinine 10 mg/kg TDS along with tetracycline (250 mg QID) or doxycycline 100 mg OD: all for 7 days.
- Artesunate (oral): 100 mg BD (4 mg/kg) on 1st day followed by 100 mg OD (2 mg/kg) for 4 days.
- Artesunate (i.v. or i.m.): 120 mg on 1st day followed by 60 mg daily for 4 days.
- Artemether (i.m.): 80 mg (1.6 mg/kg) BD first day, then OD for 4 days.
- Arteether (i.m.) 150 mg OD for 3 days.

Severe and complicated falciparum malaria This includes *P. falciparum* infection attended by hyperparasitaemia, hyperpyrexia, fluid and electrolyte imbalance, hypoglycaemia, prostration, cardiovascular collapse, pulmonary edema, haemoglobinuria, black water fever, renal failure and cerebral malaria. Parenteral (i.m./i.v.) drugs have to be used; oral drugs may be substituted when the condition improves. Drugs employed are—quinine or artesunate/artemether/arteether or chloroquine (only if parasite is known to be chloroquine sensitive).

4. Radical cure Drugs which attack the exo-erythrocytic stage (hypnozoites) given together with a clinical curative achieve total eradication

of the parasite from the patient's body. A radical curative is needed in relapsing malaria, while in falciparum malaria — adequate treatment of clinical attack leaves no parasite in the body (there is no secondary exoerythrocytic tissue phase).
Drug of choice for radical cure of vivax and ovale malaria is primaquine 15 mg daily for 2 weeks. A shorter course of 5 days is used by NAMP in India.

There is no point in antirelapse treatment in highly endemic areas, because chances of reinfection would be high.

5. Suppressive cure This is a form of radical cure by extended suppressive therapy by:
Chloroquine 300 mg weekly for 10 weeks after leaving endemic area.

6. Gametocidal This refers to elimination of the male and female gametes of *Plasmodia* formed in the patient's blood. Gametocidal action is of no benefit to the patient being treated, but will reduce the transmission to mosquito.

Primaquine is gametocidal to all species of *Plasmodia*, while chloroquine and quinine are active against vivax but not falciparum gametes. Adequate control of clinical attacks will reduce formation of gametes.

- A single 45 mg (0.75 mg/kg) dose of primaquine is employed immediately after clinical cure of falciparum malaria.

CHLOROQUINE

It is a rapidly acting erythrocytic schizontocide against all species of *Plasmodia*; controls most clinical attacks in 1– 2 days with disappearance of parasities from peripheral blood. However, it has no effect on pre- and exoerythrocytic phases of the parasite — does not prevent relapses in vivax malaria.

The mechanism of action of chloroquine is not completely known. It is actively concentrated by sensitive intraerythrocytic plasmodia: higher concentration is found in infected RBCs. By accumulating in the acidic vesicles of the parasite and because of its weakly basic nature, it raises the vesicular pH and thereby interferes with degradation of haemoglobin by parasitic lysosomes. Polymerization of toxic heme to nontoxic parasite pigment hemozoin is inhibited by formation of chloroquine-heme complex. Heme itself or its complex with chloroquine then damages the plasmodial membranes. Clumping of pigment and changes in parasite membranes follow. Other related antimalarials like quinine, mefloquine, appear to act in an analogous manner.

Chloroquine resistance among plasmodia has been slow in developing. However, *P. falciparum* has acquired significant resistance and resistant strains have become prevalent, especially in eastern part of India, South-East Asia, Africa and South America.

Resistance in *P. falciparum* is associated with a decreased ability of the parasite to accumulate chloroquine.

Chloroquine resistance among *P. vivax* has also been detected in some areas, but is not a significant problem yet.

Other actions Chloroquine is active against *Entamoeba histolytica* and *Giardia lamblia* also.
It has antiinflammatory, local irritant and local anaesthetic (on injection), weak smooth muscle relaxant, antihistaminic and antiarrhythmic properties.

Pharmacokinetics Oral absorption of chloroquine is excellent. About 50% gets bound in the plasma. It is concentrated in spleen, kidney, lungs, liver (several hundred-fold), skin, leucocytes and some other tissues. Its selective accumulation in retina is responsible for the ocular toxicity seen with prolonged use.

Chloroquine is partly metabolized by liver and slowly excreted in urine. The plasma t½ varies from 3–10 days or more. Because of tight tissue binding, small amounts persist in the body for months.

Adverse effects Toxicity of chloroquine is low, but side effects are frequent and unpleasant: nausea, vomiting, anorexia, uncontrollable itching, epigastric pain, uneasiness, difficulty in

accomodation and headache. Suppressive doses have been safely given for 3 years.

- Parenteral administration can cause hypotension, cardiac depression, arrhythmias and CNS toxicity including convulsions (more likely in children).
- Prolonged use of high doses (as needed for rheumatoid arthritis, DLE, etc.) may cause loss of vision due to retinal damage.
- Loss of hearing, rashes, photoallergy, mental disturbances, myopathy and graying of hair can occur on long-term use.

Chloroquine can be used for treatment of malaria during pregnancy: no abortifacient or teratogenic effects have been reported.

Chloroquine should not be coadministered with mefloquine, amiodarone and other antiarrhythmics.

Uses

1. Chloroquine is the drug of choice for clinical cure and suppressive prophylaxis of all types of malaria, except that caused by resistant *P. falciparum*.
2. Extraintestinal amoebiasis.
3. Rheumatoid arthritis (Ch. 22).
4. Discoid lupus erythematosus—very effective; less valuable in systemic LE.
5. Lepra reactions.
6. Photogenic reactions.

Amodiaquine It is almost identical to chloroquine in properties and is less unpalatable. It can be used as an alternative to chloroquine for clinical cure of uncomplicated malaria, but is not recommended for prophylaxis because of some reports of fatal hepatitis and agranulocytosis among travelers to Africa in the 1980s.

Side effects of amodiaquine are similar to chloroquine; itching may be less common.

MEFLOQUINE

It is a drug developed to deal with the problem of chloroquine-resistant *P. falciparum*. Mefloquine is a rapidly acting erythrocytic schizontocide, but slower than chloroquine or quinine; effective against chloroquine-sensitive as well as resistant plasmodia. It controls fever and eliminates circulating parasites in infections caused by *P. falciparum* or *P. vivax*. However, like chloroquine, relapses occur subsequently in vivax malaria. It is also an efficacious suppressive prophylactic for multiresistant *P. falciparum* and other types of malaria; continued use achieves suppressive cure. Mefloquine resistance among *P. falciparum* has become common in Thailand, Cambodia and Myanmar, but is not a problem yet in India. Resistance to mefloquine confers cross resistance to quinine and halofantrine.

The mechanism of action of mefloquine is not known, but appears to be similar to that of chloroquine.

Pharmacokinetics Oral absorption of mefloquine is good but quite slow. It is highly plasma protein bound and concentrated in many organs including liver, lung and intestines. Extensive metabolism occurs in liver and it is primarily secreted in bile. Considerable enterohepatic circulation of mefloquine and its tissue binding accounts for the long t½ which is 2–3 weeks.

Adverse effects Mefloquine is bitter in taste; common reaction is dizziness, nausea, vomiting, diarrhoea, abdominal pain and sinus bradycardia. Major concern has been a variety of neuropsychiatric reactions (disturbed sense of balance, ataxia, errors in operating machinery, strange dreams, anxiety, hallucinations, rarely convulsions) occurring in some recipients. Mefloquine appears to be safe during pregnancy, but should be avoided in 1st trimester.

Interactions Halofantrine or quinidine/quinine given to patients who have received mefloquine cause QTc lengthening—cardiac arrests are reported.

Use Mefloquine is an effective drug for multiresistant *P. falciparum.* Because of its potential toxicity, cost and long t½, its use is being restricted to areas where such strains are prevalent. It

cannot be given parenterally and is not used in complicated/cerebral malaria.

Combined use of mefloquine with artesunate is highly effective in chloroquine/multidrug resistant falciparum malaria.

QUININE

Quinine is the levo rotatory alkaloid obtained from cinchona bark. Its *d*-isomer quinidine is used as an antiarrhythmic (and for malaria in some countries).

Quinine is an erythrocytic schizontocide for all species of *Plasmodia*; less effective and more toxic than chloroquine. Resurgence of interest in quinine is due to the fact that most chloroquine and multidrug resistant strains of *P. falciparum* are still sensitive to it. However, even quinine resistance has been described in certain parts of South-East Asia and Brazil. Quinine resistance has not been encountered in India. There is partial cross resistance between quinine and mefloquine, but many mefloquine-resistant cases respond to quinine.

Quinine has no effect on preerythrocytic stage and on hypnozoites of relapsing malaria, but kills vivax gametes. Like chloroquine, it is a weak base: gets concentrated in the acidic vacuoles of the blood schizonts; and inhibits polymerization of heme to hemozoin; free heme or heme-quinine complex damages parasite membranes and kills it.

Quinine has many other actions. It is intensely bitter and irritant: orally causes nausea, vomiting and epigastric discomfort. Gastric secretion is stimulated. Weak analgesic, antipyretic actions, impairment of hearing and vision are produced at higher doses. Cardiodepressant, antiarrhythmic and hypotensive actions are similar to quinidine. Quinine stimulates uterine contractions, but reduces skeletal muscle contractility. Hypoglycaemia can occur on i.v. injection of quinine.

Pharmacokinetics Quinine is rapidly and completely absorbed orally. It is 70% bound to the plasma proteins, especially α_1 acid glycoprotein. Such binding increases during acute malarial infection. CSF concentrations are low. A large fraction of the dose is metabolized in liver by CYP3A4 and excreted in urine with a t½ of 10–12 hours; noncumulative.

Adverse effects Toxicity of quinine is high and dose related; 8–10 g taken in a single dose may be fatal.

Cinchonism Large single doses or higher therapeutic doses taken for a few days produce a syndrome called cinchonism. It consists of ringing in ears, nausea, vomiting, headache, mental confusion, vertigo, difficulty in hearing and visual defects. Diarrhoea, flushing and marked perspiration may also appear.

Poisoning with still higher doses results in delirium, fever, tachypnoea followed by respiratory depression, marked weakness and prostration, hypotension, cardiac arrhythmias.

Few individuals are idiosyncratic/hypersensitive to quinine. Purpura, rashes, itching, angioedema of face and bronchoconstriction may also appear.

Uses

1. Malaria: Quinine is used orally for uncomplicated chloroquine-resistant malaria (alone or in combination with sulfa + pyrimethamine or tetracycline), and i.v. for complicated/cerebral malaria (chloroquine sensitive or resistant), for which it is the drug of choice.
2. Nocturnal muscle cramps.
3. Spermicidal: in vaginal creams.
4. Varicose veins: injected along with urethane, it causes thrombosis and fibrosis of the varicose vein mass.

PROGUANIL (CHLOROGUANIDE)

It is a slow acting erythrocytic schizontocide with causal prophylactic property against *P. falciparum*. Gametocytes exposed to proguanil are

not killed but fail to develop in the mosquito. It is cyclized in the body to a triazine derivative (cycloguanil) which inhibits plasmodial DHFRase in preference to the mammalian enzyme. Resistance to proguanil develops rapidly due to mutational changes in the plasmodial DHFRase enzyme.

Proguanil is slowly but adequately absorbed from the gut, is partly metabolized and excreted in urine; t½ is 16–20 hours; noncumulative. It is very well tolerated; side effects are less compared to chloroquine; mild abdominal upset, vomiting, occasional stomatitis.

Current use of proguanil is restricted to prophylaxis of malaria in combination with chloroquine in areas with low level chloroquine resistance among *P. falciparum*.

PYRIMETHAMINE

It is a directly acting inhibitor of DHFRase (does not require conversion to a cyclic triazine, as is the case with proguanil). It has high affinity for plasmodial enzyme (~2000 times greater than for the mammalian enzyme), which accounts for its selective antimalarial action. In contrast to trimethoprim, it has very poor action on bacterial DHFRase. Under the influence of pyrimethamine, schizogony of malarial parasite in blood gradually stops. At high doses, it inhibits *Toxoplasma gondii*.

Pyrimethamine is a slowly acting erythrocytic schizontocide but does not eliminate the preerythrocytic phase of *P. falciparum.* It is not a radical curative, but by extended treatment, the secondary tissue phase of *P. vivax* may be exhausted. If used alone, resistance develops rather rapidly by mutation in the DHFRase enzyme of the parasite.

Pharmacokinetics Absorption of pyrimethamine from g.i.t. is good but slow. It is concentrated in certain organs like liver, spleen, kidney and lungs. It is metabolized and excreted in urine with a t½ of 4 days. Prophylactic concentrations remain in blood for 2 weeks.

Adverse effects Pyrimethamine is relatively safe. The only side effects are occasional nausea and rashes. Folate deficiency due to pyrimethamine therapy is rare. This can be treated by folinic acid.

Uses Because of its slow action, pyrimethamine alone is not suitable for the treatment of an acute attack of malaria. In combination with a sulfonamide it is used to treat attacks of malaria.

PYRIMETHAMINE-SULFONAMIDE/DAPSONE COMBINATION

Sulfonamides/dapsone are not particularly effective antimalarial drugs in their own right; have some inhibitory influence on the erythrocytic phase, especially of *P. falciparum*. However, they form supra-additive synergistic combination with pyrimethamine due to sequential block. Though both components are slow acting, the combination acts faster, so that it can be employed as a clinical curative, particularly for *P. falciparum*; efficacy against *P. vivax* is rather low. By the addition of sulfonamide, development of resistance to pyrimethamine is retarded. Resistance to sulfa-pyrimethamine combination has become prevalent in South-East Asia, Southern Africa and South America, but is sporadic in India, restricted mainly to northeastern states. There is no cross resistance with other groups of antimalarial drugs.

Sulfadoxine and sulfamethopyrazine are ultra-long acting sulfonamides — attain low blood concentrations, but are able to synergise with pyrimethamine which also has long t½. The combination has the potential to cause serious adverse effects (exfoliative dermatitis, Stevens-Johnson syndrome, etc.) due to the sulfonamide component. Therefore, its use is restricted to single dose treatment of uncomplicated chloroquine-resistant *P. falciparum* malaria or in patients intolerant to chloroquine. Prophylactic use needing multiple unsupervised doses is not recommended.

Pyrimethamine + sulfadiazine combination is the first choice treatment for toxoplasmosis which mainly occurs in immunocompromised patients.

PRIMAQUINE

In contrast to other antimalarial drugs, primaquine is a poor erythrocytic schizontocide: has weak action on *P. vivax*, but blood forms of *P. falciparum* are totally insensitive. On the other hand, it is more active against the preerythrocytic stage of *P. falciparum* than that of *P. vivax*. Primaquine differs from all other available antimalarials in having a marked effect on primary as well as secondary tissue phases of the malarial parasite. It is highly active against gametocytes and hypnozoites.

The mechanism of action of primaquine is not known. However, it is different from that of chloroquine.

Pharmacokinetics Primaquine is readily absorbed after oral ingestion. It is oxidized in liver with a plasma t½ of 3–6 hours and excreted in urine within 24 hours. It is not a cumulative drug.

Adverse effects The usual doses of primaquine produce only abdominal pain, g.i. upset, weakness or uneasiness in chest as side effect. Leucopenia occurs rarely with larger doses.

The most important toxic potential is dose-related haemolysis, methaemoglobinaemia, tachypnoea and cyanosis. These are due to the oxidant property of primaquine. In normal individuals doses < 60 mg (base) produce little haemolysis. Those with G-6-PD deficiency are highly sensitive and haemolytic anaemia can occur with 15–30 mg/day. The incidence of G-6-PD deficiency is low among Indians, except in some tribal people of Jharkhand, Andhra Pradesh, Madhya Pradesh and Assam. Passage of dark urine is an indication of haemolysis; primaquine should be promptly stopped if it occurs. It should be avoided during pregnancy, because foetus is G-6-PD deficient.

Use The primary indication of primaquine is for radical cure of relapsing malaria.

Falciparum malaria: A single 45 mg dose of primaquine is given with the curative dose of chloroquine to kill the gametes and cut down transmission to mosquito.

Bulaquine This congener of primaquine, developed in India, has shown comparable antirelapse activity in vivax malaria when administered for 5 days along with a course of chloroquine. It is partly metabolized in the body to primaquine. Whether the activity is due to bulaquine itself or due to primaquine produced from it is not clear. Precautions and contraindications are the same as for primaquine.

Tetracyclines These antibiotics have slowly acting and weak erythrocytic schizontocidal action against all plasmodial species. In addition, preerythrocytic stage of *P. falciparum* is inhibited. However, they are never used alone to treat malaria. They are used in combination with quinine or pyrimethamine-sulfadoxine for the treatment of chloroquine-resistant falciparum malaria. Doxycycline 200 mg/day has also been combined with artesunate to treat mefloquine/chloroquine/sulfa-pyrimethamine resistant falciparum malaria in Thailand.

Doxycycline 100 mg/day is used as a 2nd line prophylactic for travellers to chloroquine-resistant *P. falciparum* areas.

ARTEMISININ DERIVATIVES

Artemisinin is the active principle of the plant *Artemisia annua* used in Chinese traditional medicine as 'Quinghaosu'. It is a sesquiterpine lactone active against *P. falciparum* resistant to all other antimalarial drugs as well as sensitive strains. Potent and rapid blood schizontocide action is exerted eliciting quicker defervescence and parasitaemia clearance (<48 hr) than chloroquine.

Artemisinin is poorly soluble in water as well as oil. Several derivatives have been produced, of which *Artemether* is soluble in oil, while *Artesunate* (sod.) is water soluble. Another compound *Arteether* has been developed in India. They do not kill hypnozoites but have some action on falciparum gametes. So far no resistance among *P. falciparum* patients to artemisinin has been noted.

Because these are short-acting drugs, monotherapy needs to be extended beyond the disappearance of the parasites to prevent recrudescence. Recrudescence can be totally prevented by combining 3–5 day artesunate with a long-acting drug like mefloquine (15 mg/kg single dose).

Mechanism of action of artemisinin is not definitely known. The endoperoxide bridge in its molecule appears to interact with heme in the parasite. Iron-mediated cleavage of the bridge releases a highly reactive free radical species that binds to membrane proteins, causes lipid peroxidation, damages endoplasmic reticulum, inhibits protein synthesis and ultimately results in lysis of the parasite.

Pharmacokinetics Both artesunate and artemether are prodrugs. They are rapidly absorbed and converted into the active metabolite dihydroartemisinin. The reported t½ of artesunate is <1 hour, while that of artemether is 3–11 hours.

Adverse effects Artesunate/artemether produce few adverse effects; most are mild: nausea, vomiting, abdominal pain, itching and drug fever. Abnormal bleeding, dark urine, S-T segment changes, Q-T prolongation, first degree A-V block, transient reticulopenia and leucopenia have been noted but subside when the patient improves or drug is stopped. Intravenous artesunate is much safer than i.v. quinine.

Interactions Concurrent administration of artemisinin compounds with terfenadine, astemizole, antiarrhythmics, tricyclic antidepressants and phenothiazines may increase risk of cardiac conduction defects.

Use In order to protect their powerful antimalarial activity, use of these compounds is restricted to treatment of acute attacks of severe falciparum malaria including cerebral malaria and in chloroquine/multidrug resistant cases. There is no justification in using them for chloroquine/sulfa-pyrimethamine sensitive *P. falciparum* or for malaria due to the other 3 species of plasmodia, for which other effective drugs are available.

Use of artemisinin derivatives for prophylaxis of malaria is irrational and not allowed.

Halofantrine It is a phenanthrene methanol blood schizontocide having activity comparable to mefloquine. It is effective against *P. falciparum* resistant to chloroquine and sulfa-pyrimethamine, as well as against *P. vivax*.

Because of unreliable oral absorption and potential to cause cardiac toxicity, halofantrine should be used only sporadically for multiresistant falciparum malaria when no other effective alternative is available.

Lumefantrine is an orally effective long-acting congener of halofantrine that has not shown cardiotoxicity, and is being combined with artesunate for treatment of falciparum malaria in areas with chloroquine-resistance.

Atovaquone This recently produced synthetic naphthaquinone is a rapidly acting erythrocytic schizontocide for *P. falciparum* and other plasmodia. *P. carinii* and *Toxoplasma gondii* are also susceptible to atovaquone. Proguanil potentiates its antimalarial action and prevents emergence of resistance. A fixed dose oral combination of the two drugs is used for 3 day treatment of uncomplicated chloroquine-resistant *P. falciparum* as well as *P. vivax* malaria in some countries.

Atovaquone is also approved as a second line drug for opportunistic infections with *P. carinii* and *T. gondii* in AIDS patients. It produces few side effects—diarrhoea, vomiting, headache, rashes and fever.

ANTIAMOEBIC DRUGS

These are drugs useful in infection caused by the protozoa *Entamoeba histolytica*.

Amoebiasis has a worldwide distribution, but it is endemic in most parts of India and other developing countries. The disease occurs by faecal contamination of food and water. Amoebic cysts reaching the intestine transform into trophozoites which either live on the surface of colonic mucosa as commensals—form cysts that pass into the stools (luminal cycle) and serve to propagate the disease, or invade the mucosa—form amoebic ulcers (Fig. 33.2) and cause acute dysentery (with blood and mucus in stools) or chronic intestinal amoebiasis (with vague abdominal symptoms, amoeboma).

Occasionally, the trophozoites pass into the bloodstream, reach the liver *via* portal vein and cause amoebic liver abscess. Other organs like lung, spleen, kidney and brain are rarely involved in extraintestinal amoebiasis. In the tissues, only trophozoites are present; cyst formation does not occur. Tissue phase is always secondary to intestinal amoebiasis, which may be asymptomatic. In the colonic lumen, the *Entamoebae* live in symbiotic relationship with bacteria, and a reduction in colonic bacteria reduces the amoebic population.

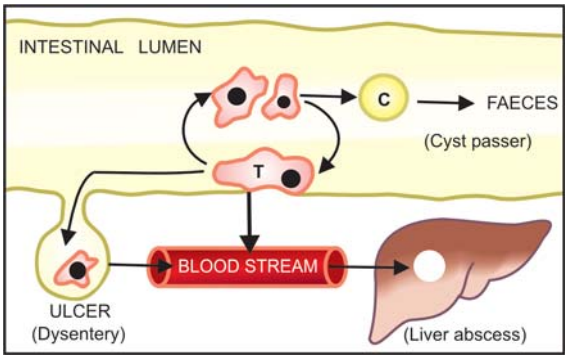


Fig. 33.2: The luminal cycle and invasive forms of amoebiasis. T—trophozoite; C—cysts

CLASSIFICATION

1. *Tissue amoebicides*
   (a) For both intestinal and extraintestinal amoebiasis:
   Nitroimidazoles: Metronidazole, Tinidazole, Secnidazole, Ornidazole, Satranidazole
   Alkaloids: Emetine
   (b) For extraintestinal amoebiasis only: Chloroquine
2. *Luminal amoebicides*
   (a) *Amide* : Diloxanide furoate
   (b) *8-Hydroxyquinolines:* Quiniodochlor (Iodochlorohydroxyquin, Clioquinol), Diiodohydroxyquin (Iodoquinol)
   (c) *Antibiotics*: Tetracyclines

Metronidazole Metronidazole and other nitroimidazoles are the first line drugs for all forms of amoebiasis. They are also active against other protozoa (*Trichomonas vaginalis, Giardia lamblia*) as well as against many anaerobic bacteria, and are described in Ch. 27.

Emetine

It is an alkaloid from *Cephaelis ipecacuanha*. Emetine is a potent and directly acting amoebicide—kills trophozoites but has no effect on cysts. It acts by inhibiting protein synthesis in amoebae by arresting intraribosomal translocation of tRNA-amino acid complex.

The stool in acute dysentery is rapidly cleared of the trophozoites and symptomatic relief occurs in 1–3 days. It is highly efficacious in amoebic liver abscess also.

Emetine cannot be given orally because it will be vomited out. It is administered by s.c. or i.m. injection. Emetine is very slowly excreted in urine taking 1–2 months: can produce cumulative toxicity.

Toxicity of emetine is high, the most prominent of which is nausea, vomiting, abdominal cramps, myocarditis, ECG changes, heart failure, hypotension and myositis. It is now rarely used only in patients not responding to or not tolerating metronidazole.

Chloroquine

Chloroquine kills trophozoites of *E. histolytica* and is highly concentrated in liver. Therefore, it is used in hepatic amoebiasis only. Because it is completely absorbed from the upper intestine and not so highly concentrated in the intestinal wall—it is neither effective in invasive dysentery nor in controlling the luminal cycle (cyst passers).

For amoebic liver abscess, chloroquine is sometimes given along with or immediately after a course of metronidazole to ensure complete eradication of the trophozoites in liver. A luminal amoebicide must always be given with or after chloroquine to abolish the luminal cycle.

Diloxanide furoate

It is a highly effective luminal amoebicide: directly kills trophozoites responsible for production of cysts. The furoate ester is hydrolysed in intestine and the released diloxanide is largely absorbed. Diloxanide is a weaker amoebicide than its furoate ester : no systemic antiamoebic activity is evident despite its absorption. It is primarily metabolized by glucuronidation and is excreted in urine.

Diloxanide furoate exerts no antibacterial action. It is less effective in invasive amoebic dysentery, because of poor tissue amoebicidal action. However, it has produced high cure rates in mild intestinal amoebiasis and in asymptomatic cyst passers.

Diloxanide furoate is very well tolerated; the only side effects are flatulence, occasional nausea, itching and rarely urticaria.

8-Hydroxyquinolines

The 8-hydroxyquinolines were widely employed in the past: have similar properties; are active against *Entamoeba, Giardia, Trichomonas*, some fungi (dermatophytes, *Candida*) and some bacteria. They kill the cyst forming trophozoites in the intestine, but do not have tissue amoebicidal action. Like diloxanide furoate, they are not very effective in acute amoebic dysentery but afford relief in chronic intestinal amoebiasis. Their efficacy in eradicating cysts from asymptomatic carriers is rated lower than that of diloxanide furoate. They are totally valueless in extraintestinal amoebiasis.

8-Hydroxyquinolines are well tolerated: produce few side effects—nausea, transient loose and green stools, pruritus, etc. Goiter has been reported after prolonged medication.

Iodism (furunculosis, inflammation of mucous membranes) may occur due to chronic iodine overload. Individuals sensitive to iodine may experience acute reaction with chills, fever, angioedema and cutaneous haemorrhages.

Prolonged/repeated use of relatively high doses of quiniodochlor caused a neuropathic syndrome called 'subacute myelo-optic neuropathy' (SMON) in Japan in an epidemic form, affecting several thousand people in 1970. However, despite widespread use in the past, only sporadic and unconfirmed cases have been reported from India. These drugs have been banned in Japan and few other countries; but in India, they are banned only for pediatric patients, because their use for chronic diarrhoeas in children has caused blindness. They may be employed in intestinal amoebiasis as alternative to diloxanide furoate.

Other uses are—giardiasis; local treatment of monilial and trichomonas vaginitis, fungal and bacterial skin infections.

Tetracyclines They directly inhibit amoebae only at high concentrations. The older tetracyclines are incompletely absorbed in the small intestine, reach the colon in large amounts and inhibit the bacterial flora with which *Entamoebae* live symbiotically. Thus, they indirectly reduce proliferation of entamoebae in the colon and are specially valuable in chronic, difficult to treat cases with only the luminal cycle and little mucosal invasion. Tetracyclines have an adjuvant role, in conjunction with a directly acting luminal amoebicide. They are not good for acute dysentery and for hepatic amoebiasis.

DRUGS FOR GIARDIASIS

Giardia lamblia is a flagellate protozoon which mostly lives as a commensal in the intestine. It sometimes invades the mucosa and causes diarrhoea requiring treatment. Many drugs useful in amoebiasis are also effective in giardiasis.

Metronidazole and its congeners are the drugs of choice for giardiasis. Quiniodochlor is an alternative. In addition, furazolidone, a nitrofuran compound active against gram-negative bacilli including *Salmonella* and *Shigella* is effective in diarrhoea caused by *Giardia*.

DRUGS FOR TRICHOMONIASIS

Trichomonas vaginalis is another flagellate protozoon which causes vulvovaginitis. A large number and variety of drugs are effective by vaginal application, but may not entirely clear the infection; recurrences are frequent; repeat courses are required.

1. Drugs used orally

Metronidazole 400 mg TDS for 7 days or 2 g single dose, or *Tinidazole* 600 mg daily for 7 days or 2 g single dose or *Secnidazole* 2 g single dose, are the drugs of choice. They produce >90% cure. Additional intravaginal treatment is required only in refractory cases. A hard core of recurrent cases may remain. A repeat course can be given after 6 weeks and additional treatment for nonspecific vaginosis often helps. In some cases recurrences are due to reinfection from the male partner. In such cases, both partners should be treated concurrently to prevent cross infection of each other.

2. Drugs used intravaginally

Drugs that are effective locally in trichomonas vaginitis and are available as vaginal pessaries to be inserted in the vagina every night for 1 – 2 weeks include antiamoebics like quiniodochlor, diiodohydroxyquin, antifungals like clotrimazole, hamycin, natamycin and antiseptic like povidone iodine.

DRUGS FOR LEISHMANIASIS

Visceral leishmaniasis (kala-azar) caused by *Leishmania donovani* occurs in several tropical and subtropical regions of the world. It is endemic in the eastern States of India, particularly Bihar.

Leishmaniasis is transmitted by the bite of the female sandfly phlebotomus. In the fly the parasite exists in the flagellate extracellular (*promastigote*) form, while in man it is found only intracellularly within macrophages in the nonflagellate (*amastigote*) form.

Drugs used in the treatment of leishmaniasis are:

Antimonial	Others
Sodium stibogluconate	Amphotericin B
	Ketoconazole
Diamidine	Miltefosine
Pentamidine	Allopurinol

ANTIMONIAL

Sodium stibogluconate It is a water-soluble pentavalent antimonial and the drug of choice for kala-azar. The mechanism of action and the basis of selective toxicity to the leishmania amastigotes is unclear; probably -SH dependent enzymes are inhibited and bioenergetics of the parasite is interfered with. It has been shown to block glycolytic and fatty acid oxidation pathways.

Sod. stibogluconate is rapidly absorbed from the site of i.m. injection and excreted unchanged in urine within 6–12 hours. A small fraction enters tissues and remains stored for long periods. It is administered in a dose of 20 mg/kg (max. 850 mg) i.m. or i.v. daily for 20–30 days or longer depending on the response. However, 25–40% cases fail to respond due to development of resistance.

Nausea, vomiting, metallic taste, cough, pain abdomen, pain and stiffness of injected muscle, sterile abscesses, and mental symptoms are the side effects. Pancreatitis, liver and kidney damage, myelosuppression, ECG changes are possible, but are seldom severe.

Sod. stibogluconate, nevertheless, is less toxic than pentamidine.

DIAMIDINE

Pentamidine The diamidines are active against *L. donovani*, *Trypanosomes*, *Pneumocystis carinii*, some bacteria and fungi (*Blastomyces*). Their mechanism of action is not properly understood. Pentamidine probably interacts with kinetoplast DNA and inhibits topoisomerase II, or interferes with aerobic glycolysis. That it interferes with the uptake and utilization of polyamines is an attractive proposal.

Dose: 4 mg/kg deep i.m. or slow i.v. injection (over 1 hr) on alternate days for 5–25 weeks till no parasites are demonstrated in two splenic aspirates taken 2 weeks apart.

After absorption from the site of injection, it is rapidly taken up by tissues, especially liver and kidney and stored for months, during which time it is slowly excreted unchanged in urine.

Toxicity of pentamidine is high. Because of its strong basic nature, it causes histamine release which can produce sharp fall in BP, cardiovascular collapse, dyspnoea, palpitation, fainting, vomiting, rigor and fever.

Other adverse effects are rashes, mental confusion, kidney and liver damage, ECG changes.

Pentamidine causes cytolysis of pancreatic β cells: insulin is released initially causing hypoglycaemia. Later on, permanent insulin-dependent diabetes mellitus can result in some cases.

Use

Pentamidine should be used only for antimonial failure cases of kala-azar. Its proper use has

achieved up to 98% cure rate in antimonial unresponsive or relapse cases.

Pneumocystis carinii pneumonia in AIDS patients: Pentamidine is a first line drug along with cotrimoxazole.

OTHER DRUGS

Amphotericin B (AMB) Like fungi, *Leishmania* has high percentage of ergosterol and is susceptible to this antifungal antibiotic. Amphotericin B is highly effective in kala-azar: up to 98% clinical and parasitological cure has been reported in stibogluconate resistant cases. However, high toxicity and need for repeated slow i.v. infusions limit its application as 1st line drug.

Ketoconazole Another antifungal drug found to kill *Leishmania* by inhibiting conversion of lanosterol to ergosterol: membrane function is impaired due to lowered ergosterol content. It is quite effective in dermal leishmaniasis but efficacy in kala-azar is lower.

Miltefosine This newer drug has shown efficacy in kala-azar by oral route, and is being evaluated.

Allopurinol This hypoxanthine analogue and uric acid synthesis inhibitor exerts selective toxic effect on amastigotes. The unique purine salvage pathway present in *Leishmania* metabolizes allopurinol into the corresponding nucleotides which are incorporated in RNA—resulting in interference with protein synthesis.

Because of high failure rate if used alone in kala-azar, allopurinol is employed only as a companion drug to antimonials in resistant cases.

ANTHELMINTIC DRUGS

Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths.

Helminthiasis is prevalent globally (1/3rd of the world's population harbours them), but is more common in developing countries with poorer personal and environmental hygiene. In the human body, g.i.t. is the abode of many helminths, but some also live in tissues, or their larvae migrate into tissues. Helminthiasis is rarely fatal, but is a major cause of ill health.

The common worm infestations and the current drugs of choice for these are listed in Table 33.2.

Mebendazole

This broad-spectrum anthelmintic has produced nearly 100% cure rate/reduction in egg count in roundworm, hookworm (both species), *Enterobius* and *Trichuris* infestations, but is much less active on *Strongyloides*. Up to 75% cure has been reported in tapeworms, but *H. nana* is relatively insensitive. It expels *Trichinella spiralis* from intestines, but efficacy in killing larvae that have migrated to muscles is uncertain. Prolonged treatment has been shown to cause regression of hydatid cysts in the liver. Treatment after resection of the cyst may prevent its regrowth.

The immobilizing and lethal action of mebendazole on worms is rather slow: takes 2–3 days to develop. It acts probably by blocking glucose uptake in the parasite and depletion of its glycogen stores. Intracellular microtubules in the cells of the worm are gradually lost. The site of action of mebendazole appears to be the microtubular protein 'β-tubulin' of the parasite. It binds to β-tubulin of susceptible worms with high affinity and inhibits its polymerization.

Absorption of mebendazole from intestines is minimal.

Mebendazole is well tolerated even by patients in poor health. Diarrhoea, nausea and abdominal pain have attended its use in heavy infestation. Incidents of expulsion of *Ascaris* from mouth or nose have occurred.

Uses

Round worm, Hook worm, *Trichuris*: 100 mg twice a day for 3 consecutive days. No fasting, purging or any other preparation of the patients is needed.

Enterobius: 100 mg single dose, repeated after 2–3 weeks.

Trichinella spiralis: 200 mg BD for 4 days; less effective than albendazole.

Hydatid disease: 200–400 mg BD or TDS for 3–4 weeks; less effective than albendazole.

Albendazole

It is a subsequently introduced congener of mebendazole: retains the broad-spectrum activity

Table 33.2: Choice of drugs for helminthiasis

	Worm	*First choice drugs*	*Alternatives*
1.	**ROUNDWORM** *Ascaris lumbricoides*	Mebendazole, Albendazole, Pyrantel	Piperazine, Levamisole, Ivermectin
2.	**HOOKWORM**		
	Ancylostoma duodenale	Pyrantel, Mebendazole, Albendazole	Levamisole
	Necator americanus	Mebendazole, Albendazole	Pyrantel
3.	**THREADWORM** *Enterobius (Oxyuris) vermicularis*	Pyrantel, Mebendazole, Albendazole	Piperazine
4.	*Strongyloides stercoralis*	Ivermectin	Albendazole
5.	**WHIPWORM**		
	Trichuris trichiura	Mebendazole	Albendazole
6.	*Trichinella spiralis*	Albendazole	Mebendazole
7.	**FILARIA** *Wuchereria bancrofti, Brugia malayi*	Diethyl carbamazine, Ivermectin	Albendazole
8.	**GUINEAWORM** *Dracunculus medinensis*	Metronidazole	
9.	**TAPEWORMS**		
	Taenia saginata	Praziquantel, Niclosamide	Albendazole
	Taenia solium	Praziquantel	Niclosamide, Albendazole
	Hymenolepis nana	Praziquantel	Niclosamide
	Neurocysticercosis	Albendazole	Praziquantel
10.	**HYDATID DISEASE**		
	Echinococcus granulosus, *E. multilocularis*	Albendazole Albendazole	Mebendazole

and excellent tolerability of its predecessor, and has the advantage of single dose treatment in many cases. One dose treatment has produced cure rates in ascariasis, hookworm (both species) and enterobiasis which are comparable to 3-day treatment with mebendazole. Results in trichuriasis have been inferior to mebendazole. In strongyloidosis, it is more effective than mebendazole. Three-day treatment has been found necessary for tapeworms including *H. nana*. Results in hydatid disease and hookworm have been superior to mebendazole.

Absorption of albendazole after oral administration is moderate but inconsistent. The fraction absorbed is converted to its sulfoxide metabolite which is active. Albendazole sulfoxide is widely distributed in the body, enters brain and is excreted in urine with a t½ of 8.5 hours. Thus, albendazole is able to exert antihelmintic activity in tissues as well.

Albendazole is well tolerated; only gastrointestinal side effects have been noted. Prolonged use as in hydatid or in cysticercosis has caused headache, fever, alopecia, jaundice and neutropenia.

No preparation or postdrug fasting/ purging is required.

- *Ascaris,* hookworm, *Enterobius* and *Trichuris:* a single dose of 400 mg.
- Tapeworms and strongyloidosis: 400 mg daily for 3 consecutive days.
- Trichinosis: Three-day treatment expels the adult worm from intestine.

- Neurocysticercosis: One month treatment with 15 mg/kg daily has produced results better than praziquantel. Albendazole is the drug of choice now.
- Hydatid disease: 400 mg BD for 4 weeks, repeat after 2 weeks (if required), up to 3 courses.

Pyrantel pamoate

This polyanthelmintic has high efficacy against *Ascaris, Enterobius* and *Ancylostoma* comparable to that of mebendazole. Lower cure rates (about 60%) have been obtained in case of *Necator* infestation. It is less active against *Strongyloides* and inactive against *Trichuris* or other worms.

Pyrantel causes activation of nicotinic cholinergic receptors in the worms resulting in persistent depolarization → slowly developing contracture and spastic paralysis. Worms are then expelled. Because piperazine causes hyperpolarization and flaccid paralysis, it antagonizes the action of pyrantel. Cholinergic receptors in mammalian skeletal muscle have very low affinity for pyrantel. Only 10–15% of an oral dose of pyrantel pamoate is absorbed.

Pyrantel pamoate is remarkably free of side effects: occasional g.i. symptoms, headache and dizziness is reported. Abnormal migration of worms is not provoked.

Use For *Ascaris, Ancylostoma* and *Enterobius*: a single dose of 10 mg/kg is recommended. A 3-day course for *Necator* and for *Strongyloides* has been suggested.

Piperazine

Introduced in 1950, it is a highly active drug against *Ascaris* and *Enterobius*. However, it is now considered a second choice drug even for these worms. Piperazine causes hyperpolarization of *Ascaris* muscle by a GABA agonistic action opening Cl^- channels that cause relaxation and depress responsiveness to contractile action of ACh. Flaccid paralysis occurs and worms are expelled alive. No fasting or patient preparation is required. Piperazine does not excite *Ascaris* to abnormal migration.

A considerable fraction of the oral dose of piperazine is absorbed. It is partly metabolized in liver and excreted in urine.

Piperazine is safe and well tolerated. Nausea, vomiting, abdominal discomfort and urticaria are occasional.

Dizziness and excitement occur at high doses; toxic doses produce convulsions.

Levamisole, Tetramisole

Tetramisole is recemic; its levo isomer (levamisole) was found to be more active and is preferred now. Both are active against many nematodes, but use is restricted to ascariasis and ancylostomiasis, because action on other worms is poor. It stimulates the ganglia in worms, causes tonic paralysis which results in expulsion of live worms.

Uses For *Ascaris* infestation a single dose of levamisole 150 mg for adults is advocated.

Levamisole is a second line drug for *A. duodenale*; 2 doses at 12-hour interval are suggested.

Levamisole is an immunomodulator as well—restores depressed T cell function. It has been tried in aphthous ulcers and recurrent herpes, but repeated doses produce severe reactions; not used now.

One or two doses used in helminthiasis are well tolerated. Incidence of side effects—nausea, abdominal pain, giddiness, fatigue, drowsiness or insomnia is low.

Diethyl carbamazine citrate (DEC)

It is the first drug for filariasis. DEC is absorbed after oral ingestion, distributed all over the body, metabolized in liver and excreted in urine. Excretion is faster in acidic urine. Plasma t½ of usual clinical doses is 4–12 hours.

Diethylcarbamazine has a highly selective effect on microfilariae (Mf). A dose of 2 mg/kg TDS clears Mf of *W. bancrofti* and *B. malayi* from peripheral blood in 7 days. The most important action of DEC appears to be alteration of Mf

membranes so that they are readily phagocytosed by tissue fixed monocytes, but not by circulating phagocytes. It also has an effect on the muscular activity of the Mf and adult worms causing hyperpolarization due to the piperazine moiety, so that they are dislodged. Prolonged treatment may kill adult *B. malayi* and probably *W. bancrofti* worms also.

DEC is active against Mf of *Loa loa* and *Onchocerca volvulus*. The adult worm of *L. loa* but not *O. volvulus* is killed.

Uses

1. *Filariasis*: 2 mg/kg TDS produces rapid symptomatic relief; Mf disappear from blood and patient becomes noninfective to mosquitoes in 7 days. A total dose of 72–126 mg/kg spread over 12 to 21 days may kill adult worms and achieve radical care. Elephantiasis due to chronic lymphatic obstruction is not affected by DEC.

2. *Tropical eosinophilia*: DEC (2–4 mg/kg TDS) for 2–3 weeks produces dramatic improvement in the signs and symptoms of eosinophilic lung or tropical eosinophilia.

Loa loa and *O. volvulus* infections can also be treated with DEC, but ivermectin is preferred.

Adverse effects These are common but generally not serious. Nausea, loss of appetite, headache, weakness and dizziness are the usual complaints.

A febrile reaction with rash, pruritus, enlargement of lymph nodes and fall in BP may occur due to mass destruction of Mf and adult worms. This is usually mild, but may be severe. The reaction can be minimized by starting with a low dose (0.5 mg/kg). Leukocytosis and mild albuminuria are also noted.

Ivermectin

It is an extremely potent semisynthetic derivative of the antinematodal principle obtained from *Streptomyces avermitilis*. Ivermectin is the drug of choice for single dose treatment of onchocerciasis and strongyloidosis, and is comparable to DEC for bancroftian and brugian filaria. It is also highly effective in cutaneous larva migrans and ascariasis, while efficacy against *Enterobius* and *Trichuris* is moderate. Certain insects, notably scabies and head lice are killed by ivermectin.

Nematodes develop tonic paralysis when exposed to ivermectin. It acts through a special type of glutamate gated Cl^- channel found only in invertebrates. Potentiation of GABAergic transmission in the worm has also been observed. The lack of GABA-related actions in man could be due to its low affinity for mammalian GABA receptors and its exclusion from the brain, probably by P-glycoprotein mediated efflux at the blood-brain barrier.

A single 10–15 mg (0.2 mg/kg) oral dose of ivermectin, preferably with 400 mg albendazole, given annually for 5–6 years has been used for filariasis.

Ivermectin is the only drug effective orally in scabies and pediculosis. Single 0.2 mg/kg dose cures most patients.

Ivermectin is well absorbed orally, widely distributed in the body, sequestrated in liver and fat and has a long elimination t½ of 48–60 hours. Side effects have been mild—pruritus, giddiness, nausea, abdominal pain, constipation, lethargy and transient ECG changes, but more important are the reactions due to degeneration products of the Mf.

Niclosamide

It is a highly effective drug against cestodes infesting man—*Taenia saginata*, *T. solium*, *Diphyllobothrium latum* and *Hymenolepis nana*, as well as threadworm. The drug appears to act by inhibiting oxidative phosphorylation in mitochondria and interfering with anaerobic generation of ATP by the tapeworm. Injured by niclosamide, the tapeworms are partly digested in the intestine. In cases of *T. solium*, digestion of the dead segments can be hazardous, because the ova released from them may develop into larvae in the intestine, penetrate its wall and cause visceral cysticercosis.

For tapeworm (*T. saginata*), two doses of niclosamide 1 g each are given 1 hour apart followed by a saline purge after 2 hours to wash off the worm.

For *H. nana,* the 2 g dose is repeated daily for 5 days. This is needed because cysticerci of *H. nana* develop in the jejunal villi of the same host and worms appear in the intestinal lumen after 4 days. Praziquantel is now preferred due to single dose treatment.

Niclosamide is tasteless and nonirritating. It is minimally absorbed from g.i.t.—no systemic toxicity occurs. It is well tolerated; minor abdominal symptoms are produced occasionally.

Praziquantel

This anthelmintic has wide ranging activity against *Schistosomes*, other trematodes, cestodes and their larval forms but not nematodes. It is rapidly taken up by susceptible worms and appears to act by causing leakage of intracellular calcium from the membranes → contracture and paralysis. Praziquantel is active against adult as well as juvenile and larval stages of tapeworms.

At relatively higher concentrations, it causes vacuolization of the tegument and release of the contents of tapeworms and flukes followed by their destruction by the host. This action appears to be more important in cases of schistosomes and flukes.

Pharmacokinetics Praziquantel is rapidly absorbed from intestines and undergoes high first pass metabolism in liver which limits its systemic bioavailability. Phenytoin, carbamazepine and possibly dexamethasone induce praziquantel metabolism and further reduce its bioavailability. Patients of neurocysticercosis are often receiving these drugs—may contribute to therapeutic failure of praziquantel. It crosses blood-brain barrier and attains therapeutic concentrations in the brain and CSF. The plasma t½ is short (1.5 hours). Metabolites are excreted chiefly in urine.

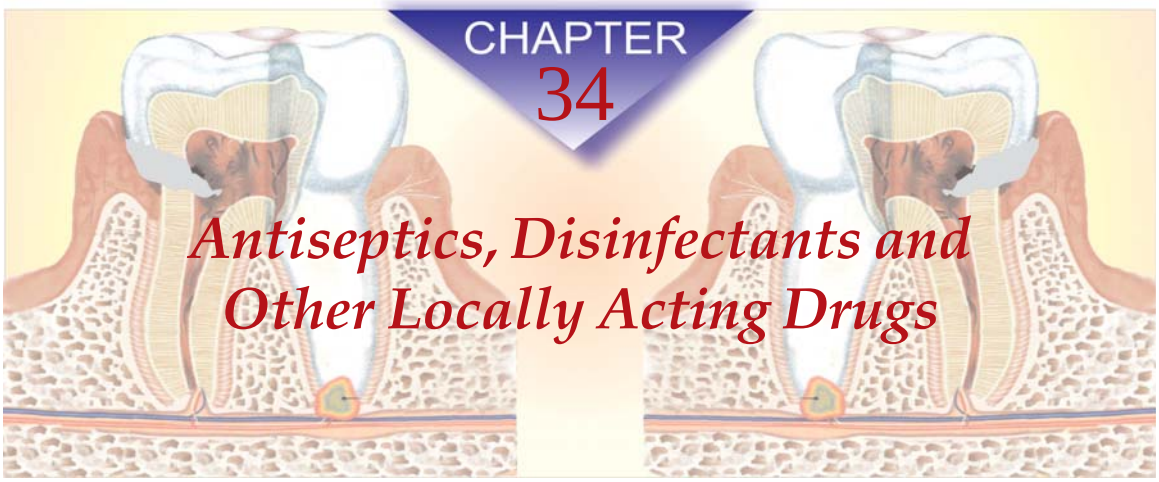
Adverse effects Despite systemic absorption, praziquantel has exhibited no systemic toxicity. It tastes bitter: can produce nausea and abdominal pain. Other side effects are headache, dizziness and sedation. When used for schistosomes and visceral flukes, symptoms like itching, urticaria, rashes, fever and bodyache occur as a reaction to the destroyed parasites.

Uses

1. *Tapeworms*: Praziquantel is the drug of choice for all species of human tapeworms. A single dose achieves > 90% cure rate. Because it also kills tapeworm larvae, there is no risk of cysticercosis in case of *T. solium* and reinfection in case of *H.nana*.

2. *Neurocysticercosis*: Higher dose of praziquantel given daily for 15 days kills tapeworm larvae lodged in brain and other tissues. Inflammatory neurological reactions occur in cerebral cysticercosis needing steroid cover. Now albendazole has been shown to be more consistently effective. It is contraindicated in ocular cysticercosis.

3. *Flukes*: Praziquantel is the drug of choice for all schistosome and fluke infestations except *Fasciola hepatica*.



CHAPTER 34

Antiseptics, Disinfectants and Other Locally Acting Drugs

ANTISEPTICS AND DISINFECTANTS

The terms *antiseptic* and *disinfectant* connote an agent which inhibits or kills microbes on contact. Conventionally, agents used on living surfaces (patient's mouth, dentist's hands, etc.) are called *antiseptics* while those used for inanimate objects (instruments, working surfaces, water supply, privies, etc.) are called *disinfectants*. There is considerable overlap and many agents are used in either way. A practical distinction between the two on the basis of a *growth inhibiting* action on one hand, and a *direct lethal* action on the other is futile because these are often concentration dependent actions. The term *Germicide* covers both category of drugs.

There, however, is difference between 'disinfection' and 'sterilization'. While sterilization means complete killing of all forms of microorganisms, disinfection refers to reduction in the number of viable pathogenic microbes to a level that they do not pose a risk to individuals with normal host defence. Thus, in ordinary usage, disinfectants do not eliminate all microbes.

Antiseptics and disinfectants are used in dentistry to check cross infection as well as to prevent and treat some infective conditions. Many instruments are sterilized by autoclaving, but certain instruments, working surfaces and operating light handles, etc. cannot be autoclaved; have to be sanitized by disinfectants.

The era of antiseptics and disinfectants was heralded by Semmelweiss (washing of hands in chlorinated lime) and Lister (antiseptic surgery by the use of phenol) in the 19th century. These germicides differ from systemically used antimicrobials by their low parasite selectivity—are too toxic for systemic use. However, many systemic antimicrobials are applied topically as well and some antibiotics (bacitracin, neomycin) are restricted to topical use, but are generally not enumerated with the antiseptics. A strict distinction is thus impossible.

A good antiseptic/disinfectant should be:

(i) Chemically stable.
(ii) Cheap.
(iii) Nonstaining with agreeable colour and odour.
(iv) Cidal and not merely static, destroying spores as well.
(v) Active against all pathogens—bacteria, fungi, viruses, protozoa.
(vi) Able to spread through organic films and enter folds and crevices.
(vii) Active even in the presence of blood, pus, exudates and excreta.
(viii) Require brief time of exposure.

A disinfectant in addition should not corrode or rust instruments and be easily washable. An antiseptic in addition should be:

(i) Rapid in action and afford sustained protection.
(ii) Nonirritating to tissues, should not delay healing.

(iii) Nonabsorbable, produce minimum toxicity if absorbed.
(iv) Nonsensitizing (no allergy).
(v) Compatible with soaps and other detergents.

Spectrum of activity of majority of antiseptic-disinfectants is wide, reflecting nonselectivity of action. However, some are rather selective, e.g. hexachlorophene, chlorhexidine, quaternary ammonium antiseptics, gentian violet and acriflavin are more active on gram-positive than gram-negative bacteria; silver nitrate is highly active against gonococci and benzoyl peroxide against *P. acnes*.

Mechanisms of action of germicides are varied, but can be grouped into:
(a) Oxidation of bacterial protoplasm.
(b) Denaturation of bacterial proteins including enzymes.
(c) Detergent like action increasing permeability of bacterial membrane.

Factors which modify the activity of germicides are:
(i) Temperature and pH.
(ii) Period of contact with the microorganism.
(iii) Nature of microbe involved.
(iv) Size of innoculum.
(v) Presence of blood, pus or other organic matter.

Potency of a germicide is generally expressed by its *phenol coefficient* or *Rideal Walker coefficient*, which is the ratio of the minimum concentration of test drug required to kill a 24 hour culture of *B. typhosa* in 7.5 minute at 37.5°C to that of phenol under similar conditions. This test has only limited validity, particularly in relation to antiseptics which have to be tested on living surfaces.

Therapeutic index of an antiseptic is defined by comparing the concentration at which it acts on microorganisms with that which produces local irritation, tissue damage or interference with healing.

CLASSIFICATION

1. *Phenol derivatives*: Phenol, Cresol, Hexylresorcinol, Chloroxylenol, Hexachlorophene.
2. *Oxidizing agents*: Pot. permangnate, Hydrogen peroxide, Benzoyl peroxide.
3. *Halogens*: Iodine, Iodophores, Chlorine, Chlorophores.
4. *Biguanide*: Chlorhexidine.
5. *Quaternary ammonium (Cationic):* Cetrimide, Cetylpyridinium chloride, Benzalkonium chloride, Dequalinium chloride.
6. *Soaps*: of Sod. and Pot.
7. *Alcohols*: Ethanol, Isopropanol.
8. *Aldehydes*: Formaldehyde, Glutaraldehyde.
9. *Acids*: Boric acid.
10. *Metallic salts*: Ammoniated mercury, Phenyl mercuric nitrate, Merbromin, Silver nitrate, Mild silver protein, Zinc sulfate, Calamine, Zinc oxide.
11. *Dyes*: Gentian violet, Acriflavine, Proflavine.
12. *Furan derivatives*: Nitrofurazone.

1. PHENOLS

Phenol (Carbolic acid) It is one of the earliest used antiseptics and still the standard for comparing other germicides. It is a relatively weak agent (static at 0.2%, cidal at >1%, poor action on bacterial spores). It is a general *protoplasmic poison*, injuring microbes and tissue cells alike—at higher concentrations causes skin burns and is a caustic. It acts by denaturing bacterial proteins. Organic matter diminishes its action slightly while alkalies and soaps do so profoundly (carbolic soaps are not more germicidal than soap itself). It is now seldom employed as an antiseptic, but being cheap, it is used to disinfect urine, faeces, pus, sputum of patients and is sometimes included in antipruritic preparations because of its mild local anaesthetic action. When swallowed (for suicidal purpose) it causes buccal, esophageal and gastric burns. Excitation, convulsions, respiratory paralysis and vascular collapse occur on absorption.

Cresol It is methyl-phenol; more active (3–10 times) and less damaging to tissues. Used for disinfection of utensils, excreta and for washing hands.

LYSOL is a 50% soapy emulsion of cresol.

Hexylresorcinol It is a more potent derivative of the phenolic compound resorcinol that is odourless and nonstaining; used as mouthwash, lozenge and as antifungal.

The hydroalcoholic solution of a mixture of phenolic compounds thymol, menthol, eucalyptol along with benzoic acid is a popular mouthwash LISTERINE. It has been found to reduce dental plaque and benefit gingivitis.

Chloroxylenol It has a phenol coefficient of 70; does not coagulate proteins, is noncorrosive, nonirritating to intact skin, but efficacy is reduced by organic matter. It is poorly water soluble; the commercial 4.8% solution (DETTOL) is prepared in 9% terpinol and 13% alcohol; used for surgical antisepsis. A 0.8% skin cream and soap, 1.4% lubricating obstetric cream (for vaginal examination, use on forceps, etc.) and a mouthwash (DETTOLIN 1%) are also available. These preparations lose activity if diluted with water and kept.

Hexachlorophene This potent chlorinated phenol acts by inhibiting bacterial enzymes and (in high concentration) causing bacterial lysis. It is odourless, nonirritating and does not stain. Its activity is reduced by organic matter but not by soap. It is commonly incorporated in soap and other cleansing antiseptics for surgical scrub. It is highly active against gram-positive bacteria but poor against gram-negative organisms (*P. acnes*) and spores. The degerming action is slow but persistent due to deposition on the skin as a fine film that is not removed by rinsing with water.

Use of a 3% solution for baby bath markedly reduced the incidence of staphylococcal infections, but produced brain damage (especially in premature neonates). Around 1970 several fatalities occurred in USA. Since then use of preparations containing > 2% hexachlorophene have been banned. It is a good deodorant and is incorporated in many toilet products.

2. OXIDIZING AGENTS

Potassium permanganate It occurs as purple crystals, highly water soluble, liberates oxygen which oxidizes bacterial protoplasm. The available oxygen and germicidal capacity is used up if much organic matter is present—the solution gets decolourised. A 1:4000 to 1:10,000 solution (condy's lotion) is used for gargling, douching, irrigating cavities, urethra and wounds. The action is rather slow and higher concentrations cause burns and blistering—popularity therefore has declined.

It has also been used to disinfect water (wells, ponds) and for stomach wash in alkaloidal poisoning. It promotes rusting and is not good for surgical instruments.

Hydrogen peroxide It liberates nacent oxygen which oxidizes necrotic matter and bacteria. A 30% solution produces 10 volumes of oxygen, much of which escapes in the molecular form. Catalase present in tissues speeds decomposition resulting in foaming—helps in loosening and removing slough, ear wax, etc. Hydrogen peroxide has poor penetrability and a weak, transient action. It loses potency on keeping. Use therefore is much restricted.

Hydrogen peroxide mouthwash has been employed in acute necrotizing gingivitis because of predominance of anaerobic bacteria in this condition. Though efficacy in reducing plaque formation is marginal, H_2O_2 mouthwash has been advocated in periodontal disease. Frequent use of 3% H_2O_2 rinse can produce oral ulcers.

Benzoyl peroxide It is specifically active against *P. acnes* and used on acne vulgaris.

3. HALOGENS

Iodine It is a rapidly acting, broad spectrum (bacteria, fungi, viruses) microbicidal agent; has been in use for more than a century. Acts by iodinating and oxidizing microbial protoplasm.

A 1 : 20,000 solution kills most vegetative forms within 1 min. Organic matter retards, but does not preclude its germicidal action.

Solid iodine is corrosive, stronger solutions (> 5%) cause burning and blistering of skin. *Tincture iodine* (2% in alcohol) stings on abrasions. It is used on cuts, for degerming skin before surgery, and to treat ring worm. *Mandel's paint* (1.25% iodine dissolved with the help of Pot. iodide forming soluble I_3^--ions) is applied on sore throat. A *nonstaining iodine ointment* (IODEX 4%) is popular as antiseptic and counterirritant. Some individuals are sensitive to iodine—rashes and systemic manifestations occur in them.

Iodophores These are soluble complexes of iodine with large molecular organic compounds that serve as carriers—release free iodine slowly. The most popular—*Povidone (Polyvinyl-pyrrolidone) iodine*: is nonirritating, nontoxic, nonstaining and exerts prolonged germicidal action. Treated areas can be bandaged or occluded without risk of blistering. It is used on boils, furunculosis, burns, otitis externa, ulcers, tinea, monilial/trichomonal/ nonspecific vaginitis and for surgical scrubbing, disinfection of endoscopes and instruments. In dentistry, 1% povidone iodine oral rinse is employed for gingivitis.

BETADINE 5% solution, 5% ointment, 7.5% scrub solution, 200 mg vaginal pessary; PIODIN 10% solution, 10% cream, 1% mouthwash; RANVIDONE AEROSOL 5% spray with freon propellant.

Chlorine A highly reactive element and a rapidly acting, potent germicide, 0.1–0.25 ppm kills most pathogens (but not *M. tuberculosis*) in 30 sec. The degerming action is soon exhausted and it lacks substantivity. It is used to disinfect urban water supplies. Organic matter binds chlorine, so that excess has to be added to obtain free chlorine concentration of 0.2–0.4 ppm. This is known as the 'chlorine demand' of water. Chlorine is more active in acidic or neutral medium.

Chlorophores These are compounds that slowly release hypochlorous acid (HOCl). Because of ease of handling, they are used in preference to gaseous chlorine.

(i) *Chlorinated lime (bleaching powder)* It is obtained by the action of chlorine on lime; resulting in a mixture of calcium chloride and calcium hypochlorite. On exposure, it decomposes releasing 30–35% W/W chlorine. It is used as disinfectant for drinking water, swimming pools and sanitizer for privies, etc.

(ii) *Sodium hypochlorite solution* Contains 4–6% sodium hypochlorite. It is a powerful disinfectant used in dairies for milk cans and other equipment as well as infant feeding bottles. It is unstable and too irritant to be used as antiseptic, except for root canal therapy in dentistry. Irrigation of root canal with 2% sod. hypochlorite solution loosens and dissolves dead tooth pulp in addition to exerting rapid antisepsis.

4. BIGUANIDE

Chlorhexidine A powerful, nonirritating, cationic antiseptic that disrupts bacterial cell membrane. A secondary action is denaturation of intracellular proteins. It is relatively more active against gram positive bacteria. Like hexachlorophene it persists on the skin. Present in SAVLON (*see* below), it is extensively used for surgical scrub, neonatal bath, mouthwash, obstetrics and as general skin antiseptic.

Chlorhexidine is the most widely employed antiseptic in dentistry, mainly in the form of oral rinse (0.12–0.2%) or toothpaste (0.5–1%). It is one of the most effective antiplaque and antigingivitis agents. Good results have been obtained in acute necrotizing gingivitis. It prevents infections following periodontal and other forms of oral surgery. Twice daily chlorhexidine rinse markedly reduces oral infections in immunocompromised patients including those with AIDS. Major disadvantage of intraoral use of chlorhexidine is brownish discolouration of teeth and tongue, an unpleasant after taste, alteration of taste perception and occasionally oral ulceration.

CHLODIN, FLUDENT-CH, HEXIL, REXIDIN 0.2% mouthwash.

5. QUATERNARY AMMONIUM (CATIONIC) ANTISEPTICS

These are detergents; cidal to bacteria, fungi and viruses. However, many gram-negative bacteria (specially *Pseudomonas*) , *M. tuberculosis* and bacterial spores are relatively resistant. They act by altering permeability of cell membranes. Soaps, being anionic, neutralize their action, while alcohol potentiates. They spread through oil and grease, have cleansing and emulgent properties. They are nonirritating and mildly keratolytic. However, the germicidal action is rather slow and bacteria may thrive under a film formed by them on the skin. Pus, debris and porous material like cotton, polyethylene reduce their activity. Occasionally sensitization occurs. These disadvantages not withstanding, they are widely used as sanitizers, antiseptic and disinfectant for surgical instruments, gloves, etc., but should not be considered sterilizing.

Cetrimide A soapy powder with a faint fishy odour; used as 1–3% solution, it has good cleansing action, efficiently removing dirt, grease, tar and congealed blood from road side accident wounds. Alone or in combination with chlorhexidine, it is one of the most popular hospital antiseptic and disinfectant for surgical instruments, utensils, baths, etc.

CETAVLON CONCENTRATE: Cetrimide 20%
SAVLON LIQUID ANTISEPTIC: Chlorhexidine gluconate 1.5% + Cetrimide 3%.
SAVLON/CETAVLEX CREAM: Chlorhexidine HCl 0.1% + Cetrimide 0.5%.
SAVLON HOSPITAL CONCENTRATE: Chlorhexidine gluconate 7.5% + Cetrimide 15%.

Cetylpyridinium chloride It is similar to cetrimide, has been included in mouth washes and lozenges to reduce plaque formation. However, it leaves a bad taste and can cause oral ulceration.

Benzalkonium chloride It is highly soluble in water and alcohol. A 1:1000 solution is used for sterile storage of instruments and 1 in 5000 to 1 in 10,000 for douches, irrigation, etc.

Dequalinium chloride Has been used in gum paints and lozenges.

DEQUADIN 0.25 mg lozenges.

6. SOAPS

Soaps are anionic detergents; weak antiseptics, affect only gram positive bacteria. Their usefulness primarily resides in their cleansing action. Soaps can be medicated by other antiseptics.

7. ALCOHOLS

Ethanol It is an effective antiseptic and cleansing agent at 40–90% concentration. The rapidity of action increases with concentration upto 70% and decreases above 90%. It acts by precipitating bacterial proteins. A cotton swab soaked in 70% ethanol rubbed on the skin kills 90% bacteria in 2 min.; has been used before hypodermic injection and on minor cuts. It is an irritant and should not be applied to mucous membranes or to delicate skin (scrotum), ulcers, etc. On open wounds, it produces a burning sensation, injures the surface and forms a coagulum under which bacteria could grow.

Usefulness of alcohol in dentistry is limited; effective concentrations cannot be applied on gums or oral mucosa. The concentration (5 – 10%) present in many mouth rinses (as solvent for essential oils, etc.) has no antiseptic efficacy. However, it enhances the antiseptic activity of iodine and chlorhexidine when employed as solvent for these. Because alcohol evaporates without leaving any residue and has good cleansing property, it is often employed to sanitize working surfaces in dentistry, but it is a poor disinfectant for instruments—does not kill spores and promotes rusting.

Isopropanol It can be used in place of ethanol.

8. ALDEHYDES

Formaldehyde It is a pungent gas—sometimes used for fumigation. A 37% aqueous solution called *Formalin* is diluted to 4% and used for

hardening and preserving dead tissues. It denatures proteins and is a general protoplasmic poison, but acts slowly. A broad-spectrum germicide, but use as antiseptic is restricted by its irritating nature and pungent odour. It is occasionally employed to disinfect instruments and excreta. Those who handle formalin can develop eczematoid reactions.

Glutaraldehyde It is less volatile, less pungent, less irritating and better sterilizing agent than formalin with broad-spectrum activity against bacteria, viruses and fungi. It is not inactivated by organic matter, and its 2% solution is often used in dentistry as an immersion disinfectant for instruments that cannot be autoclaved, but prolonged contact is needed. It should not be used to disinfect working surfaces because repeated inhalation of its vapours can induce asthma. Repeated application on skin can cause sensitization. The solution has a short shelf-life (2 weeks) unless stablilizing agents are added.

9. ACIDS

Boric acid It is only bacteriostatic and a very weak antiseptic. But being nonirritating even to delicate structures, saturated aqueous solutions (4%) have been used for irrigating eyes, mouthwash, douche, etc. Boroglycerine paint (30%) is used for stomatitis and glossitis. A 10% ointment (BOROCIDE) is available for cuts and abrasion. It is included in prickly heat powders and ear drops. However, boric acid is not innocuous; systemic absorption causes vomiting, abdominal pain, diarrhoea, visual disturbances and kidney damage. Hence its use for irrigating bladder, large wounds, as ointment on extensive burnt areas, liberal use of powder for infants is not recommended.

10. METALLIC SALTS

Mercury compounds They act as bacteriostatic by inactivating SH enzymes. The inhibition is often reversible; bacterial spores survive even after prolonged contact. Though generally considered potent, mercurials are actually poor antiseptics with low therapeutic index.

Phenyl mercuric nitrate has been used in tinea remedies, anorectal, otic and ocular preparations; also used as preservative.

Merbromin is a bright red organic mercurial, non-irritating and less toxic than inorganic salts. A 1–2% solution (MERCUROCHROME) has been traditionally present in the first aid kits for application to skin and eyes, but benefits are more psychological than real.

Silver compounds These are astringent and caustic. They react with SH, COOH, PO_4 and NH_2 groups of proteins.

Water stored in silver vessels is said to become sterile. As the concentration of Ag^+ ions is very low, this has been called '*Oligodynamic action*'. Silver nitrate rapidly kills microbes, action persisting for long periods because of slow release of Ag^+ ions from silver proteinate formed by interaction with tissue proteins. Tissues get stained black due to deposition of reduced silver. Silver nitrate touch is used for hypertrophied tonsillitis and aphthous ulcers. It is highly active against gonococci—1% solution is used for ophthalmia neonatorum.

Zinc salts They are astringent and mild antiseptics.

(i) Zinc sulfate is highly water soluble, 0.1–1% is used for eye wash and in eye/ear drops (Zinc-boric acid drops—in ZINCO-SULFA 0.1% eye drop). Applied to skin, it decreases perspiration. *White lotion* containing 4% each of zinc sulfate and sulfurated potash has been used for acne and impetigo.

(ii) Calamine and zinc oxide are insoluble. In addition to being mildly antiseptic, they are popular dermal protectives and adsorbants.

11. DYES

Gentian violet (crystal violet) A rosaniline dye active against staphylococci, other gram-positive bacteria and fungi, but gram-negative organisms and mycobacteria are insensitive. Aqueous or alcoholic solution (0.5–1%) is used on furuncu-

losis, bed sores, chronic ulcers, infected eczema, thrush, Vincent's angina, ringworm, etc. It has become unpopular due to deep staining.

Acriflavine and Proflavine These are orange-yellow acridine dyes active against gram-positive bacteria and gonococci. Their efficacy is not reduced by organic matter and is enhanced in alkaline medium. Solutions lose efficacy on exposure to light—store in amber bottles. They are nonirritant and do not retard healing—particularly suitable for chronic ulcers and wounds. Bandage impregnated with acriflavine-vaseline is used for burn dressing;

ACRINOL 0.1 % acriflavine cream.

The *triple dye lotion* contains gentian violet 0.25% + brilliant green 0.25% + acriflavine 0.1% (TRIPLE DY), has been used for burns and for dressing umbilical stump in neonates.

12. FURAN DERIVATIVES

Nitrofurazone It is cidal to both gram-positive and negative, aerobic and anaerobic bacteria even in high dilutions, but activity is reduced in the presence of serum. Acts by inhibiting enzymes necessary for carbohydrate metabolism in bacteria. It is highly efficacious in burns and for skin grafting. Its local toxicity is negligible—but sensitization occurs frequently.

FURACIN 0.2% cream, soluble ointment, powder.

Antiseptics and disinfectants in dentistry

Antiseptics and disinfectants are used extensively in dentistry. The main purposes for which they are employed are:

1. Cleaning and disinfection of working surfaces, instrument trays, operating light handles, etc.
2. Cold sterilization of certain instruments and storage of sterilized equipment.
3. Decontamination of the dentist's and assistant's hands.
4. Prevention and treatment of dental plaque and periodontal disease.
5. Treatment of acute necrotizing gingivitis, aphthous ulcers and other infective oral conditions.
6. Root canal therapy.
7. Preoperative preparation of oral mucosa by reducing bacterial load and minimizing local as well as distant infection.
8. As an ingredient of certain dentifrices.

Antiseptics in dental plaque and periodontal disease

Dental plaque is a tenaciously adherent soft deposit on the tooth surface, composed mainly of bacterial aggregates embedded in a matrix of glycoproteins that resists removal by ordinary brushing and rinsing. Plaque is the primary causative factor for both dental caries and periodontal diseases. Bacterial products generated in the plaque irritate gingival margins and produce inflammation. The gums become edematous, swollen and develop subgingival pockets. Periodontal disease can be prevented by inhibiting plaque formation and removing it before it produces inflammatory changes.

Effective therapy of plaque requires that drug applied as mouth rinse, gels or toothpaste remains at the site without being washed away to exert sustained antimicrobial effect. As such, the two most important properties of an antiplaque agent are *antimicrobial spectrum* covering the relevant microbes and '*substantivity*' which refers to persistence of the substance on the surface of teeth/gums due to initial binding and subsequent slow release.

Chlorhexidine It exerts high antiplaque activity largely because of its substantivity in the mouth, rather than due to any unique spectrum of activity on oral microbes, which nevertheless are inhibited. Chlorhexidine binds electrostatically to the acidic groups in the surface proteins affording the substantivity. Though it can also bind to hydroxyapatite of the teeth, this is less important for the antiplaque activity. The amount of chlorhexidine retained on the oral mucosa/

tooth surface depends on the volume as well as concentration of the rinse solution. Lowering the pH of rinse solution markedly decreases retention of chlorhexidine on oral mucosa. Calcium ions inhibit chlorhexidine binding as well as displace already bound drug. Accordingly, toothpastes containing calcium salts reduce substantivity of chlorhexidine if rinsing is done within 30–60 min of brushing with toothpaste. Optimum benefits appear to be obtained by twice daily mouth rinsing for 1–3 min with 10–15 ml of 0.12–0.2% chlorhexidine solution. Such rinsing achieves marked reduction in the number of oral bacteria (85% reduction in 24 hours and 95% reduction after 5 days). With long-term use, bacterial counts tend to increase, but approximately 70% reduction is maintained till rinsing is continued. Resistance to chlorhexidine by bacteria is not clinically significant.

Twice daily oral rinse with 0.2% chlorhexidine consistently reduces dental plaque and prevents onset of gingivitis. Long-term regular use protects against periodontal diseases in susceptible individuals and improves gingival health. However, it should be employed only as adjuvant to other oral hygienic measures and professional care. The main disadvantage of chlorhexidine oral rinse is brown staining of teeth and tongue. Heavy tea/coffee consumption intensifies the staining effect. A lingering bitter aftertaste and occasional mucosal ulceration are the other side effects.

Quaternary ammonium antiseptics such as cetrimide or cetylpyridinium chloride are other effective antiplaque agents, but are inferior to chlorhexidine. Being cationic, they also exhibit considerable substantivity, but their retention on oral mucosa after rinsing is less than that of chlorhexidine. Adverse effects are burning sensation in the mouth, bad taste, discolouration of teeth and oral ulcers. They are alternative antiplaque agents.

Phenolic antiseptics like LISTERINE are another class of germicides that have antiplaque activity, and are employed occasionally. Still other antiseptics have poor efficacy and are practically not used for plaque therapy.

LOCALLY ACTING DRUGS

A variety of drugs applied topically to the skin or mucous membranes produce therapeutic effects localized to the site of application. They act primarily by virtue of their physical/mechanical/chemical/biological attributes.

Demulcents Demulcents are inert substances which sooth inflamed/denuded mucosa or skin by preventing contact with air/irritants in the surroundings. They are, in general, high molecular weight substances and are applied as thick colloidal/viscid solutions in water.

Glycyrrhiza, the sweet tasting root of liquorice, is used to sooth the throat and as flavouring/sweetening agent. Glycerine is a clear, sweet, viscous liquid that is used as vehicle for gum/throat paints and as emollient on dry/cracked lips. Undiluted glycerine is dehydrating and produces a warm sensation in the mouth. It also has mild antiseptic property. Methylcellulose, gum acacia and propylene glycol are other demulcents.

Emollients Emollients are bland oily substances which sooth and soften skin. They form an occlusive film over the skin, preventing evaporation, thus restoring elasticity of cracked and dry skin. Olive oil, arachis oil, hard and soft paraffin, liquid paraffin, wool fat, bees wax and spermaceti are the commonly employed emollients. They are also used as vehicles for topically applied medicaments and as ointment bases.

Adsorbants and protectives Adsorbants are finely powdered, inert and insoluble solids capable of binding to their surface (adsorbing) noxious and irritant substances. They are also called protectives because they afford physical protection to the skin or mucosa. Other protectives form a continuous, adherent and flexible occlusive coating on the skin. Demulcents and emollients also serve as protectives.

Magnesium stearate, zinc stearate, talc, calamine, zinc oxide, starch, collodion, dimethicone and sucralfate are used as protectives.

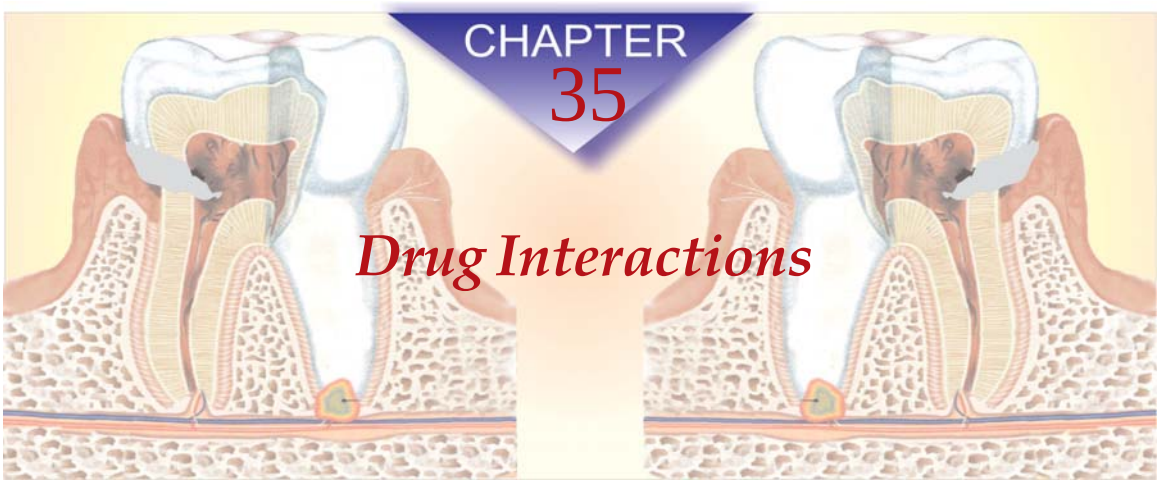
Sucralfate is an aluminium salt of sulfated sucrose that is primarily employed as peptic ulcer protective. It has also been formulated as a topical gel to be applied on aphthous ulcers; serves to facilitate healing by covering the denuded surface. The gel can also be applied on burns, bedsores, excoriated skin, diabetic ulcers, etc.

Astringents Astringents are substances that precipitate proteins, but do not penetrate cells, thus affecting the superficial layer only. They are intended to toughen the surface making it mechanically stronger and decrease exudation.

Tannic acid obtained from nutgalls and tannins found in tea, catechu, betelnut are vegetable astringents. Glycerine of tannic acid (30%) and mouthwashes/gum paints containing tannic acid (1–5%) are used to strengthen gums and to check bleeding from them. Efficacy however, is dubious. Heavy metal salts have astringent property. Zinc chloride, zinc sulfate, aluminium chloride, ferric chloride, strontium chloride are included in several mouthwashes and dental gels to afford symptomatic relief and promote healing of oral lesions, as well as to reduce gum bleeding, but benefit is uncertain. Alcohol is a potent astringent, but is unsuitable for use in mouth. It is rubbed on skin to prevent bedsores. Other uses of astringents are in bleeding piles and as antiperspirant/deodorant.

Caustics These are corrosive chemicals that cause local tissue destruction and sloughing. Concentrated solutions of silver nitrate, zinc chloride, phenol, trichloroacetic acid and podophyllum resin are caustic and have been used to remove moles, warts, papillomas and necrotic material. They are to be applied carefully on the lesions only so as to avoid ulceration of normal mucosa/skin.

The use of caustics in dentistry is very limited; occasionally applied on aphthous ulcers. Silver nitrate painted on exposed necks of teeth can reduce dentine sensitivity, but is not favoured because of black staining. Carefully applied trichloracetic acid can reduce pain of pericoronitis.



CHAPTER 35

Drug Interactions

Drug interaction refers to modification of response to one drug by another when they are administered simultaneously or in quick succession. The modification is mostly quantitative, i.e. the response is either increased or decreased in intensity, but sometimes it is qualitative, i.e. an abnormal or a different type of response is produced. The possibility of drug interaction arises whenever a patient concurrently receives more than one drug, and the chances increase with the number of drugs taken.

Many medical/dental conditions are treated with a combination of drugs. The components of the combination are so selected that they complement each other's action, e.g. an antibiotic is used along with an analgesic to treat a painful infective condition; adrenaline is combined with lignocaine for dental anaesthesia; mixed aerobic-anaerobic bacterial infections, including many orodental infections, are treated with a combination of antimicrobials. More commonly, multiple drugs are used to treat a patient who is suffering from two or more diseases at the same time. The chances of unintended/adverse drug interactions are greater in this later situation because an assortment of different drugs may be administered to a patient depending on his/her diseases/symptoms.

Several drug interactions are desirable and deliberately employed in therapeutics, e.g. the synergistic action of ACE inhibitors + diuretics to treat hypertension or sulfamethoxazole + trimethoprim to treat bacterial infection or furosemide + amiloride to prevent hypokalaemia. These are well-recognized interactions and do not pose any undue risk to the patient. The focus of attention in this chapter are drug interactions which may interfere with the therapeutic outcome, be responsible for adverse effects, or may even be fatal (bleeding due to excessive anticoagulant action).

The severity of drug interactions in most cases is highly unpredictable. Because the dentist prescribes and administers certain drugs, he/she must know which drugs are not to be prescribed

Regular medication drugs

(Likely to be involved in drug interactions)

1. Antidiabetics
2. Antihypertensives
3. Antianginal drugs
4. Antiarthritic drugs
5. Antiepileptic drugs
6. Oral contraceptives
7. Anticoagulants
8. Antiasthmatics
9. Psychopharmacological agents
10. Antipeptic ulcer drugs
11. Corticosteroids
12. Antitubercular drugs

concurrently. More importantly, a large section of dental patients are elderly, who are specially likely to be receiving one or several drugs for their chronic medical conditions like hypertension, diabetes, arthritis, etc. (*see* box for regular medication drug classes employed commonly). The dentist may prescribe certain drugs which may interact with those already being taken by the patient and result in adverse consequences. It is, therefore, imperative for the dentist to elicit a detailed medical history of the patient and record all the medication that he/she is currently on. The list of potential adverse drug interactions is already quite long and constantly growing. It is practically impossible for anyone to know/remember all possible drug interactions. Fortunately, the clinically important and common drug interactions that may be encountered in dental practice are relatively few. These are listed in Table 35.1. More exhaustive compilations and documentation are available in specialized books, monographs, review articles and computer database on the subject, but these also need constant updating.

Certain types of drugs (*see* box) can be identified that are most likely to be involved in clinically important drug interactions. The dentist may take special care and pay attention to the possibility of drug interactions when the patient is receiving one or more of such medications or when he/she intends to prescribe any of such drugs. Consultation with the physician treating the medical condition is advised.

Drugs most likely to be involved in clinically important drug interactions

- Drugs with narrow safety margin, e.g. aminoglycoside antibiotics, digoxin, lithium
- Drugs affecting closely regulated body functions, e.g. antihypertensives, antidiabetics, anticoagulants
- Highly plasma protein bound drugs like NSAIDs, oral anticoagulants, sulfonylureas
- Drugs metabolized by saturation kinetics, e.g. phenytoin, theophylline

MECHANISMS OF DRUG INTERACTIONS

Drug interactions can be broadly divided into *pharmacokinetic* and *pharmacodynamic* interactions. In certain cases, however, the mechanisms are complex and may not be well understood. Few interactions take place even outside the body when drug solutions are mixed before administration.

Pharmacokinetic interactions

These interactions alter the concentration of the object drug at its site of action (and consequently the intensity of response) by affecting its absorption, distribution, metabolism or excretion.

Pharmacokinetic interactions

- Alteration of absorption or first-pass metabolism
- Displacement of plasma protein bound drug
- Alteration of drug binding to tissues affecting volume of distribution and clearance
- Inhibition/induction of metabolism
- Alteration of excretion

Absorption Absorption of an orally administered drug can be affected by other concurrently ingested drugs. This is mostly due to formation of insoluble and poorly absorbed complexes in the gut lumen, as occurs between tetracyclines and calcium/iron salts, antacids or sucralfate. Phenytoin absorption is also decreased by sucralfate due to binding in the g.i. lumen. Such interactions can be minimized by adminstering the two drugs with a gap of 2 – 3 hours so that they do not come in contact with each other in the g.i.t. Antibiotics like ampicillin, tetracyclines, cotrimoxazole markedly reduce gut flora that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronides and permits their enterohepatic circulation. Several instances of contraceptive failure have been reported with concurrent use of these antibiotics due to lowering of the contraceptive blood levels. Alteration of gut motility by atropinic drugs, tricyclic antidepressants, opioids and prokinetic drugs like

metoclopramide or cisapride can also affect drug absorption.

Distribution Interactions involving drug distribution are primarily due to displacement of one drug from its binding sites on plasma proteins by another drug. Drugs highly bound to plasma proteins that have a relatively small volume of distribution like oral anticoagulants, sulfonylureas, certain NSAIDs and antiepileptics are particularly liable to displacement interactions. Another requirement is that the displacing drug should bind to the same sites on the plasma proteins with higher affinity. Displacement of bound drug will initially raise the concentration of the free and active form of the drug in plasma that may result in toxicity. However, such effects are usually brief because the free form rapidly gets distributed, metabolized and excreted so that steady-state levels are only marginally elevated. The clinical outcome of displacement interactions is generally significant only when displacement extends to tissue binding sites as well or is accompanied by inhibition of metabolism and/or excretion. Quinidine has been shown to reduce the binding of digoxin to tissue proteins as well as its renal and biliary clearance resulting in nearly doubling of digoxin blood levels and toxicity.

Metabolism Certain drugs reduce or enhance the rate of metabolism of other drugs. They may thus affect the bioavailability (if the drug undergoes extensive first pass metabolism in liver) and the plasma half-life of the drug (if the drug is primarily eliminated by metabolism).Inhibition of drug metabolism may be due to competition for the same CYP 450 isoenzyme or cofactor, and attains clinical significance mostly for drugs that are metabolized by saturation kinetics. Macrolide antibiotics, azole antifungals, chloramphenicol, omeprazole, cimetidine, ciprofloxacin and metronidazole are some important inhibitors of metabolism of multiple drugs. Because lignocaine metabolism is dependent on hepatic blood flow, propranolol has been found to prolong its t½ by reducing blood flow to the liver.

A number of drugs induce microsomal drug metabolizing enzymes and enhance biotransformation of several drugs (including their own in many cases). Induction involves gene mediated increased synthesis of certain CYP450 isoenzymes; takes 1 – 2 weeks of medication with the inducer to produce maximal effect (contrast inhibition of metabolism which develops quickly) and regresses gradually over 1 – 3 weeks after discontinuation of the inducer. Barbiturates, phenytoin, carbamazepine, rifampin, cigarette smoking, chronic alcoholism and certain pollutants are important microsomal enzyme inducers. Instances of failure of antimicrobial therapy with metronidazole, doxycycline or chloramphenicol have occurred in patients who are on long-term medication with an inducing drug. Contraceptive failure and loss of therapeutic effect of many other drugs have occurred due to enzyme induction. On the other hand, the toxic dose of paracetamol is lower in chronic alcoholics and in those on enzyme inducing medication because one of the metabolites of paracetamol is responsible for its overdose hepatotoxicity.

Excretion Interaction involving excretion are important mostly in case of drugs actively secreted by tubular transport mechanisms, e.g. probenecid inhibits tubular secretion of penicillins and cephalosporins and prolongs their plasma t½. This is particularly utilized in the single dose treatment of gonorrhoea. Aspirin blocks the uricosuric action of probenecid and decreases tubular secretion of methotrexate. Change in the pH of urine can also affect excretion of weakly acidic or weakly basic drugs. This has been utilized in the treatment of poisonings. Diuretics and to some extent tetracyclines, ACE inhibitors and certain NSAIDs have been found to raise steady-state blood levels of lithium by promoting its tubular reabsorption.

Pharmacodynamic interactions

These interactions derive from modification of the action of one drug at the target site by another drug independent of a change in its concentration. This may result in an enhanced response (synergism),

Table 35.1: Clinically important drug interactions in dentistry

	*Precipitant drug**	*Object drug£*	*Likely interaction and comments*
1.	Ampicillin Amoxicillin	Oral contraceptives	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception
		Oral anticoagulants	Inhibition of gut flora → decreased vit K production in gut → risk of bleeding; Monitor INR and reduce anticoagulant dose if needed.
2.	Probenecid	Penicillin Ampicillin Cephalosporins	Inhibition of tubular secretion → prolongation of antibiotic action; Desirable interaction utilized for single dose therapy.
3.	Allopurinol	Ampicillin	Increased incidence of rashes; Avoid concurrent use.
4.	Carbenicillin Ticarcillin	Aspirin and other antiplatelet drugs	Perturbation of surface receptors on platelets → additive platelet inhibition → risk of bleeding; Avoid concurrent use
5.	Ceftriaxone Cefoperazone	Oral anticoagulants	Additive hypoprothrombinaemia → bleeding; Monitor INR and reduce dose of anticoagulant.
6.	Sulfonamides Cotrimoxazole	Phenytoin	Displacement$ + inhibition of metabolism → phenytoin toxicity; Avoid concurrent use
		Warfarin	Displacement + inhibition of metabolism + decreased production of vit K in gut → risk of bleeding; Monitor INR and reduce dose of warfarin
		Sulfonylureas	Displacement + inhibition of metabolism → hypoglycaemia; Avoid concurrent use
		Thiazide diuretics	Increased incidence of thrombocytopenia; Avoid concurrent use
		Oral contraceptives	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception
7.	Metronidazole Tinidazole Cefoperazone	Alcohol	Accumulation of acetaldehyde → disulfiram-like or bizarre reactions; warn the patient not to drink alcohol
8.	Metronidazole Tinidazole	Lithium salts	Decreased excretion → Li^+ toxicity; Monitor Li^+ level and reduce lithium dose
		Warfarin	Inhibition of metabolism → risk of bleeding; Avoid concurrent use
9.	Ciprofloxacin Norfloxacin Pefloxacin	Theophylline Warfarin	Inhibition of metabolism → toxicity of object drug; Monitor and reduce dose of object drug
10.	Erythromycin Clarithromycin Ketoconazole Itraconazole Fluconazole	Terfenadine Astemizole Cisapride	Inhibition of metabolism by CYP3A4 → rise in blood level of object drug → dangerous ventricular arrhythmia; Concurrent use contraindicated
		Phenytoin Carbamazepine Warfarin Sulfonylureas Diazepam Theophylline Cyclosporine HIV protease inhibitors	Inhibition of metabolism by CYP3A4 → toxicity of object drug; Avoid concurrent use or readjust dose of object drug

Contd...

* Precipitant drug is the drug, which alters action/pharmacokinetics of the other drug
£ Object drug is the drug whose action/pharmacokinetics is altered
$ Displacement of plasma protein bound drug

Contd...

Precipitant drug	*Object drug*	*Likely interaction and comments*
11. Tetracyclines	Oral contraceptives	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception
	Lithium salts	Rise in plasma Li^+ level due to decreased excretion; Avoid use of tetracycline or monitor and reduce dose of lithium
12. Iron salts Calcium salts Antacids Sucralfate	Tetracyclines Fluoroquinolones	Decreased absorption due to formation of complexes in g.i.t. → failure of antibiotic therapy; stager drug administration by 2–3 hours
13. Furosemide	Minocycline	Enhanced vestibular toxicity; Avoid concurrent use
	Aminoglycoside antibiotics	Additive ototoxicity and nephrotoxicity; Avoid concurrent use
14. Diuretics	Tetracycline	Antianabolic effect of tetracycline increases urea production which is retained by the diuretic; Avoid concurrent use
15. Tetracyclines Chloramphenicol Macrolide antibiotics Clindamycin	Penicillins Cephalosporins	Bactericidal action of penicillins and cephalosporins may be antagonized by the bacteriostatic antibiotics; Avoid concurrent use, consult the physician
16. Clindamycin	Erythromycin Clarithromycin Azithromycin Chloramphenicol	Mutual antagonism of antibacterial action due to proximal binding sites on bacterial ribosomes; Avoid concurrent use
17. Phenobarbitone Phenytoin Carbamazepine Rifampin	Metronidazole Doxycycline Chloramphenicol	Induction of metabolism → failure of antimicrobial therapy; Avoid concurrent use or increase antibiotic dose with monitoring
18. Chloramphenicol	Warfarin Phenytoin Sulfonylureas	Inhibition of metabolism → toxicity of the object drug; Avoid concurrent use or monitor and reduce dose of object drug
19. NSAIDs	Ciprofloxacin and other fluoroquinolones	Enhanced CNS toxicity, seizures; Avoid concurrent use
20. Aspirin and other NSAIDs	Sulfonylureas Phenytoin Valproate Methotrexate	Displacement and/or reduced elimination → toxicity of object drug; Avoid concurrent use/substitute NSAID with paracetamol
	Warfarin Heparin	Enhanced risk of bleeding due to antiplatelet action and gastric mucosal damage; Avoid concurrent use
	ACE inhibitors β blockers Thiazide diuretics	Reduced antihypertensive effect due to inhibition of renal PG synthesis; Avoid concurrent use
	Furosemide	Reduced diuretic action due to PG synthesis inhibition in kidney; Avoid concurrent use
	Alcohol Corticosteroids	Increased risk of gastric mucosal damage and gastric bleeding; Concurrent use contraindicated
21. Aspirin	Spironolactone	Reduced K^+ conserving action due to decreased tubular secretion of canrenone (active metabolite of spironolactone); Avoid concurrent use
22. Chronic alcoholism	Paracetamol	Hepatotoxic dose of paracetamol is reduced; doses < 3 g/day are safe
23. Chlorpromazine Imipramine and other TCAs	Morphine Pethidine Codeine	Enhanced CNS and respiratory depression; Avoid concurrent use

Contd...

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Precipitant drug	*Object drug*	*Likely interaction and comments*
24. TCAs	Adrenaline (added to local anaesthetic)	Potentiation due to neuronal uptake inhibition → rise in BP; Use plain local anaesthetic solution
25. Promethazine Alcohol Opioids Antipsychotics	Diazepam and other benzodiazepines	Additive CNS and respiratory depression, motor impairment; Avoid concurrent use
26. Cimetidine Isoniazid	Diazepam and other benzodiazepines	Inhibition of metabolism → exaggerated CNS depression; Avoid concurrent use or reduce benzodiazepine dose
27. Propranolol	Adrenaline (injected with local anaesthetic)	Rise in BP due to blockade of vasodilator action of adrenaline that enters systemic circulation; Avoid adrenaline containing local anaesthetic or limit volume of injected local anaesthetic solution
	Lignocaine	Reduced hepatic clearance of lignocaine; amount used in dental anaesthesia safe, but ceiling dose is reduced
28. Lignocaine	β-blockers	Enhanced bradycardia and hypotension; Avoid concurrent use
	Quinidine and other antiarrhythmic drugs	Exaggerated cardiac depression, precipitation of arrhythmias; Avoid concurrent use

NSAIDs: Nonsteroidal antiinflammatory drugs
TCAs: Tricyclic antidepressants

an attenuated response (antagonism) or an abnormal response. The phenomena of synergism and antagonism are described in Chapter 3, and are deliberately utilized in therapeutics for various purposes. Of clinical significance are the inadvertent concurrent administration of synergistic or antagonistic pair of drugs with adverse consequences. Some examples are:

1. Excessive sedation, respiratory depression, motor incoordination due to concurrent administration of a benzodiazepine (diazepam), a sedating antihistaminic (promethazine), a neuroleptic (chlorpromazine), an opioid (morphine) or drinking alcoholic beverage while taking any of the above drugs.
2. Excessive fall in BP and fainting due to concurrent administration of α_1 adrenergic blockers, vasodilators, ACE inhibitors, high ceiling diuretics and cardiac depressants.
3. Additive prolongation of prothrombin time and bleeding by administration of ceftriaxone or cefoperazone to a patient on oral anticoagulants.
4. Excessive platelet inhibition resulting in bleeding due to simultaneous use of aspirin/ticlopidine/clopidogrel and carbenicillin.
5. Additive ototoxicity due to use of an aminoglycoside antibiotic in a patient receiving furosemide.
6. Antagonism of bactericidal action of β-lactam antibiotic by combining it with a bacteriostatic drug like tetracycline, erythromycin or clindamycin.
7. Mutual antagonism of antibacterial action of macrolides, clindamycin and chloramphenicol due to interference with each other's binding to the bacterial 50S ribosome.
8. Attenuation of antihypertensive effect of ACE inhibitors/β blockers/diuretics by NSAIDs due to inhibition of renal PG synthesis.
9. Blockade of antiparkinsonian action of levodopa by neuroleptics and metoclopramide having antidopaminergic action.

Abnormal responses sometimes result from pharmacodynamic interaction between certain drugs, e.g. metronidazole and cefoperazone inhibit the enzyme aldehyde dehydrogenase resulting in bizarre distressing symptoms if the patient drinks alcohol. The basis of certain interactions is not explained, e.g. ampicillin has produced high incidence of skin rashes in patients treated with allopurinol.

Drug interactions before administration

Certain drugs react with each other and get inactivated if their solutions are mixed before administration. In combined oral or parenteral formulations the manufacturers take care that such incompatibilities do not take place. In practice situations these *in vitro* interactions occur when injectable drugs are mixed in the same syringe or infusion bottle. Some examples are:

- Penicillin G or ampicillin mixed with gentamicin or another aminoglycoside antibiotic.
- Thiopentone sodium when mixed with succinylcholine or morphine.
- Heparin when mixed with penicillin/gentamicin/hydrocortisone.
- Noradrenaline when added to sodium bicarbonate solution.

In general, it is advisable to avoid mixing of any two or more parenteral drugs before injecting.

Comment Not all patients taking interacting drugs experience adverse consequences, but it is advisable to take due precautions to avoid mishaps in all cases where interactions are possible. That two drugs have the potential to interact does not necessarily contraindicate their concurrent use. In many cases, knowledge of the nature and mechanism of the possible interaction may permit their concurrent use provided appropriate dose adjustments are made or other corrective measures are taken. A list of clinically significant and common drug interactions that may be encountered in dental practice is given in Table 35.1, along with the suggested corrective measure. However, it is a good practice to consider the possibility of drug interaction whenever two or more drugs are prescribed to a patient, or any drug is added to what the patient is already taking.

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