Pharmacology for Physiotherapist

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It is my proud privilege to write a foreword to the Pharmacology for Physiotherapist book authored by my colleagues Dr KV Ramesh and Dr K Ashok Shenoy.

Pharmacology is considered as one of the toughest and ‘difficult to remember’ subjects, whether it is for medical, dental and other specialities like physiotherapy, nursing, etc. Moreover, the objectives and the emphasis are vastly different for different courses. Most often, teachers in pharmacology are at bay when meeting the teaching requirement based on the needs of the students.

I am extremely happy that the authors have made an earnest and genuine attempt in not only understanding the need of the students of physiotherapy but also presenting the required content in a lucid manner which, I am sure, will go a long way in meeting the long-felt need of the students. It is gratifying to note that the content presentation is well organized, concise and easily understandable. By highlighting the main topics and subtopics inside the box, the authors have facilitated easy and quick reference and review which is very essential from the student’s point of view. There is an honest attempt to give the latest development yet scrupulously avoiding irrelevant contents. The classification given is simple and systematic.

There are special topics like drug therapy and exercise, diuretics and exercise, antibiotics and exercise, etc., which are very relevant and necessary for students of physiotherapy. Further, the authors have made an attempt to link the subject to the needs of physiotherapists in every topic. I am sure the schematic representation of the mechanism of action of drugs will be liked by not only physiotherapy students but also dental, nursing and even medical students.

On the whole, the authors have poured in all their teaching experience to distil pharmacology into a simple and useful presentation.

I wish the authors, Dr Ramesh and Dr Ashok Shenoy all the best in their maiden venture. I hope, based on the feedback from their well-wishers and students, they will be able to improve further to make this book all the more useful not only to read but also to understand the subject.

I wish to thank the authors profusely for giving this valuable opportunity to share my feelings through this foreword.

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Preface

This book is written in a simplified and concise way to generate interest among youngsters who wish to learn pharmacology. The main aim of the book is to furnish basic information to the students of bachelor degree course in physiotherapy. Authors are quite aware of the constraints of students of physiotherapy in extracting the lucid information from a large number of voluminous, therapeutics-oriented textbooks of pharmacology. We are sure of the fact that the information studded in this volume is precisely what a beginner needs to learn about the basic concepts of pharmacology without any clinical exposure. We are glad to say that extreme care is taken to provide more authentic and appropriate revelations of the subject. If any improper information is found in this volume, the onus entirely lies in us.

We appeal to all our fellow pharmacologists to give their valuable feedback so that the same may be incorporated in the editions to come. We humbly request the learned men and women of pharmacology not to recommend this book to other than the students of physiotherapy courses.

Finally we express our gratitude and gracefully acknowledge the stress taken by Dr S Gurumadhva Rao, Registrar, Mahe, Manipal to write foreword to this edition. We remain grateful to all kingsmen of Kasturba Medical College, Mangalore and Manipal Academy of Higher Education, Manipal for the unprecedented encouragement given to us. We express our heartfelt gratitude to M/s Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, for having readily accepted the manuscript to bring out this attractive volume. Our sincere thanks to Mrs. Jyothi for her secretarial assistance, without her help, this volume would not have taken a proper shape.

KV Ramesh
K Ashok Shenoy
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Pharmacology is the science of drugs. Like many other subjects, pharmacology had its humble origin thousands of years ago. It is as old as man himself, since, fighting diseases with remedies appear to be an integral part of human life. Search for drugs useful in diseases is a timeless struggle. The rational approach to this struggle is pharmacology. Pharmakon is a Greek term which means “drug” and logos means a systematic study. Modern pharmacology is an ever-expanding discipline of science. With the advent of new techniques of understanding of human physiology and biochemistry, pharmacology is growing at a rapid rate. Further, attempts to reduce adverse effects of drugs have been successful and this has made modern medicine more popular. Method of administration, new drug delivery systems, proven drug efficacy and quality improvement has resulted in increased rate of success in the control of many chronic illnesses. Clinicians, manufacturers of drugs and drug sellers must be aware of the rationale of drug therapy in order to avoid any drug-induced disaster. Physiotherapy is a well-accepted mode of re-equipping the patient back to a normal productive life. A clear knowledge of commonly used drugs is essential for a physiotherapist in view of achieving expected success in the field.

DEFINITIONS

Drug [Drogue (French): dry herb]

The World Health Organization defines drug as “any substance or product that is used or intended to be used to modify or explore physiological system or pathological state for the benefit of the recipient.”

Drug is a substance used in prevention, diagnosis, treatment and cure of diseases. With obvious exceptions, drugs are xenobiotic (xenos: strange, foreign) to human body and hence
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prone to induce allergic reactions in many individuals. This suggests that interaction of drugs and living organisms constitutes the main basis for beneficial or harmful drug effects.

**Pharmacokinetics**

Pharmacokinetics is that branch of pharmacology which deals with the study of absorption, distribution, metabolism and excretion of drugs in a biological system.

**Pharmacodynamics**

Pharmacodynamics deals with the study of the actions and effects of drugs at all levels of interaction in a biological system. This describes the actions and mechanisms of the action of drugs.

**Pharmacotherapeutics**

This correlates the principles of pharmacodynamics with pathologic physiology or microbiological or biochemical aspects of disease. It is the application of concepts of pharmacology to a clinical condition.

**Toxicology**

Toxicology is the science of poisons. It is the study of harmful effects of chemicals as well as occurrence, mechanisms, conditions, management, and treatment of adverse effects.

Environmental toxicology deals with incidental or occupational hazards caused by chemicals of the atmosphere, water and food.

**DRUG NOMENCLATURE**

Drugs used as therapeutic agents are grouped into two broad classes:

1. Over-the-counter drugs (OTC): Non-prescription drugs which are judged safe and for use without medical supervision.
2. Prescription drugs: To be used under medical supervision. Therefore, dispensed only by the order of licensed practitioners, physicians, dentists and veterinarians.

Drugs may also be referred by either chemical or pharmacological relationship among a group of agents. This contributes to their “Generic name”. For example, benzodiazepines, thiazides, opioids, cardiac glycosides, loop diuretics, etc. As a whole, generic name of drugs focus on the pharmacological similarities among the members of a class.

Further, therapeutic agents at least have 3 names. Every drug has a chemical name, a non-proprietary name and a proprietary or trade name or brand name. The non-proprietary name is frequently referred to as the generic name of the drug. By strict definition, this is inappropriate. However, it should be reserved to designate a family relationship among drugs as said above.

Chemical name is the first name of a drug, which indicates the chemical constitution, and arrangements of atoms or atomic groups, for example, 3,4-dihydroxyphenylethylamine—catecholamine—adrenaline. The non-proprietary name of a drug is the name assigned to it when it is said to have demonstrated therapeutic potential, for example, chlordiazepoxide—
which is a benzodiazepine anti-anxiety drug. The non-proprietary name when finally admitted to official compound becomes an approved official name of the drug.

The trade name or brand name is selected by the pharmaceutical company. For example, trade name for chlordiazepoxide–LIBRIUM, diazepam–CALMPOSE, paracetamol–METACIN, CROCIN. As a rule, the proprietary (brand or trade) name is shorter, more euphonic and easier to recall than the non-proprietary name. Now, major countries have a national council for giving adapted names to drugs. A single drug may have many different trade names. Often this brings confusion, which is generally minimized by furnishing non-proprietary name along with the trade name and this ensures accurate recognition of an agent.

A number of compendia at the national and international levels have been published annually at a regular time interval to meet the need of current, critical sources of drug information. There are also several publications, which furnish recent developments in drug therapy and toxicity.

**PHARMACOPOEIA**

Pharmacopoeia is an official compendium containing selected lists of approved drugs with uses, dose, method of administration, toxicities, drug interactions, purity, potency and tests for identification, for example, USP: United States Pharmacopoeia, BP: British Pharmacopoeia, IP: Indian Pharmacopoeia.

**SOURCES OF DRUGS**

Drugs have been obtained from the following sources:

i. plant source
ii. synthetic chemical laboratory
iii. animal source
iv. minerals
v. microbiological source

**Plant Source**

From time immemorial, drugs have been extracted from plants. In fact, the word ‘drug’ took its origin from the French word *drogue* meaning dry herb. Modern medicine now has accepted various herbal medicines in its drug armamentarium. Drugs obtained from plants can be grouped as:

1. **Alkaloids** (alkali-like): Nitrogenous bases which produce marked effects in a living organism. These form water-soluble salts with acid, for example, morphine, atropine, caffeine and quinine.

2. **Glycosides**: Naturally occurring substances, which represent the combination of a non-sugar moiety called ‘aglycone’ with 3 to 4 molecules of sugar. Glycosides on acid hydrolysis liberate reducible sugars, for example, digoxin and digitoxin.

Other plant products include oils, tannins, gums, resins and saponins, which are employed as drugs in various conditions, and are also being used in the drug manufacturing industry.
Animal Source
Various drugs are obtained from animals, for example, insulin, heparin and protamine. Different hormones have been isolated from various animals for the treatment of many endocrinal disorders.

Minerals
Iron, magnesium, iodine, phosphorus, gold and their salts have been used in modern medicine. Gold salts in rheumatoid arthritis and magnesium salts in hyperacidity and acid peptic disease are a few examples for mineral drug use.

Synthetic Drugs
Organic chemical synthetic laboratory is a major source for drugs today. Chemical structure of a drug is intimately associated with the action. Any modification of drug structure results in qualitative changes in the pharmacodynamic as well as kinetic profiles besides toxicity change. Therefore, it is possible to synthesize various structural analogues of established drugs to mitigate adverse effects and increase potency, purity and safety of drugs. By this process, the advent of new drugs is a continuing process since the quest for newer, safer drugs is a timeless, limitless demand. Of late, recombinant DNA technology has revolutionized the art of drug production in the laboratory. More purified forms of human insulin is being produced by this technique. Drugs produced by recombinant DNA technology offer many advantages in the purity, immunogenicity and potency although remain expensive.

Microbiological Source
A wide variety of antibiotics have been isolated from different species of bacteria, for example, penicillins, cephalosporins, tetracyclines. However, semisynthetic derivatives of antibiotics are being produced in the laboratory after the elucidation of the structure of an antibiotic, for example, aminopenicillins.

ROUTES OF DRUG ADMINISTRATION
Drugs are administered by several routes. Each route offers advantages and has limitations. The selection of route of drug administration often demands a thorough consideration of physical and chemical properties of drugs and patient characteristics. At times, the chosen drug dosage form does indicate the route of administration. Hence, the knowledge about the selected route is necessary for both patient and practitioner. This often helps to reduce the cost of drug treatment, for example, oral preparations are comparatively cheaper than parenteral preparations.

The major routes of administration are as follows:

Local
- Application
- Inhalation
- Inunction
- Instillation
- Insufflation
- Iontophoresis
Enteral

- Sublingual
- Oral
- Rectal

Parenteral

- Intradermal
- Intraventricular
- Intraureteral
- Subcutaneous
- Intracardiac
- Intracisternal
- Intramuscular
- Intracoronary
- Intravitreal
- Intravenous
- Intravaginal
- Intralesional
- Intrarterial
- Intra-amniotic
- Intraneural
- Intrathecal
- Intra-bone marrow
- Epidural
- Intraperitoneal
- Intracavernous
- Intrapleural
- Intraarticular

Transdermal

Drugs are applied to skin for systemic action. Transdermal use of drugs minimizes adverse drug reactions and takes away repeated oral consumption of drugs. More importantly, a steady state concentration of drug in plasma is maintained. Scopolamine, clonidine and nitroglycerin are available as transdermal preparations.

Local

Drugs are used locally to produce actions at the site of administration. There are many ways and methods for local use of drugs.

Application

Drugs are applied to mucous membrane or skin to produce local action at the applied site, e.g. surface anesthetics. Anti-inflammatory, antimicrobial and antiallergic drugs are used in the form of ointment, cream, jelly and lotions.

Instillation

Drug solutions are instilled to conjunctival sac or nasal cavity or any other body cavities, for example, eyedrops or nasal drops.

Insufflation

Insufflation is a method of dressing body cavities with powder form of drugs, for example, nebasulpha insufflation.

Inhalation

Various drugs are administered by inhalation to elicit the action at the desired site promptly, for example, salbutamol inhalation for bronchial asthma and insulin nasal spray to reduce postprandial elevation of blood sugar.
Inunction
This is a method of application of drugs on unbroken skin with thorough rubbing or friction. Counter-irritant preparations are applied by inunction to provide relief from pain.

Iontophoresis
A wave of Galvanic current is applied along with the application of drugs on skin to promote dermal absorption. This is a special technique of dermal application of drugs.

Enteral Routes

Sublingual (Buccal)
This route is often employed to produce drug action rapidly within a few seconds to minutes in an ambient patient. Drug is placed beneath the tongue to have prompt action and when the drug action is no longer required, the tablet can be split out. The drug dosage forms meant for sublingual administration are either known as buccal tablets or buccal sprays. Very few drugs are given by this route—nitroglycerin in angina pectoris, buprenorphine for pain relief, nifedipine in hypertensive crisis.

Sublingual administration of drugs produce rapid action and the action of the drug can be terminated at will by spitting out the tablet. Importantly, drugs administered by sublingual route bypass the liver and enter the circulation directly. Therefore, drugs, which undergo extensive first pass metabolism on oral administration, can be conveniently administered by sublingual route.

The major limitations of this route are irritant and unpleasant drugs cannot be given. Significantly, length of time needed for drug administration is limited. Besides, buccal route cannot be employed when the patient is unco-operative, and while doing exercise.

Oral Route (PO: Per oral)
Most commonly drugs are administered by mouth since it offers many advantages. Oral route does not require special purification procedures for drug dosage forms. Method of administration is safe, convenient and economical. Self-medication is possible with oral route. However, irritant substances are not suitable for oral route. This is not the route for emergency situations. Administration of drugs is not possible in an unconscious patient. If the patient is unco-operative, it is better not to employ oral route. Drugs which are destroyed by proteolytic and other enzymes of gastrointestinal tract cannot be given by mouth, for example, insulin and adrenaline. Presence of food, motility of the alimentary tract to a larger extent, alters the route of oral absorption of drugs. For example, an antitubercular drug rifampicin is better absorbed when the stomach is empty, whereas griseofulvin, an antifungal drug is well absorbed after food. Further, drugs which undergo complete metabolism before reaching circulation, cannot be given by oral route, for example, lignocaine. Oral administration is most suitable for long-term drug treatments.

Rectal Administration (PR: Per rectum)
Drugs can be administered by rectal route even when the patient is unconscious. Vomiting does not preclude rectal administration of drugs. In fact, gastric mucosal irritant drugs like
indomethacin are given by rectal route. There are two different types of drug dosage forms meant for rectal administration:

i. Suppository

ii. Enema

A suppository is a cone-shaped solid containing medicaments meant for rectal administration. Suppository, which is in solid state at room temperature, melts at body temperature. These preparations contain greasy or non-greasy bases. Examples of drugs which are available as suppository are bisacodyl (a purgative), diazepam (a sedative-hypnotic), indomethacin (antiinflammatory analgesic), glycerine + senna (a purgative combination).

The liquid meant for rectal administration is known as “enema”. Mainly two types of enema are in use:

i. Retention enema, for example, prednisolone enema used in ulcerative colitis

ii. Evacuant enema, for example, soap water enema commonly given before surgery to evacuate the bowel.

Drugs, which are absorbed from the lowest part of rectum, do escape hepatic metabolism and directly enter circulation. However, drug absorption across rectal mucosa is irregular and incomplete.

Parenteral Routes

Routes other than enteral routes are known as parenteral routes. Drugs administered by parenteral routes require aseptic measures and are often given as injectable solutions. Most commonly, subcutaneous, intramuscular and intravenous parenteral routes are employed. The solid medicament meant for subcutaneous administration is known as pellet. Pellets are implanted subcutaneously to produce action for a few days to months. Steroidal drugs are given as pellets. The quantity of solution given by intramuscular route should not exceed 10 ml at a time.

Intravenous Route of Administration

Intravenous route is the route of emergency. Drugs are introduced directly into the vascular compartment. The mode of intravenous administration of drugs differs according to the need in a given clinical condition. Drugs can be given intravenously either as bolus injection or jet injection or infusion. Bolus injection means that the administration of dose of a drug all at once. Adenosine is given as bolus injection in the treatment of paroxysmal supraventricular tachycardia. Administration of drugs by intravenous route at a required pace is called infusion. Generally, to avoid complications, drugs are infused slowly into the vascular compartment.

Intravenous drug administration offers many advantages—rapid onset of action, any amount of the drug can be given and the rate of administration of a drug can be regulated as required. Since drug is introduced into the circulation, factors that modify absorption of drugs are being circumvented. However, intravenous route is not free from limitations. It requires absolute aseptic measures and skill. Intravenous injectable preparations are expensive. Once the drug is introduced, no retrieval can be done. On intravenous administration of drugs, the individual is more prone for drug toxicity in an unpredictable way. Drugs which are exclusively given by intravenous route are sodium nitroprusside in hypertensive crisis and plasma expanders in hypovolemic shock.
INTRODUCTION

Drugs must move from where they are administered to the site of action. Drugs to reach their locus of action must pass through various cells and tissues that act as barriers to the migration of materials including drugs are called “biological barriers” (i.e. semipermeable cell membranes). Biological barriers are of different types (namely, cell membrane, blood-brain barrier, placental barrier, dermal barrier). Although they differ in their structure, basically, behave as semipermeable barriers. Some biological barriers allow certain chemicals to pass freely, others allow to pass with difficulty and still others restrict the biotransport almost entirely. The solubility of biotransport materials across the anatomical barrier is the consequence of the physico-chemical properties and structural configuration of the barrier as well of the drug molecule.

Pharmacokinetics is that branch of pharmacology, which deals with drug absorption, distribution, metabolism and excretion. The knowledge of drug kinetics in the ailing human body is essential for clinicians to individualize and optimize the drug dosage regimens. Further, how disease affects pharmacokinetics of the given drug in a patient is necessary to avoid complications of drug therapy.
DRUG ABSORPTION
The transport of drugs from the site of administration to systemic circulation is known as drug absorption. The rate of drug absorption determines the intensity and duration of action. Therefore an administered drug must cross various cellular and subcellular structures to reach its site of action. Drugs applied on skin or any surface must cross surface barriers, whereas orally administered drugs have to pass through alimentary tract to reach circulation. Despite the anatomical differences of different absorbing surfaces, transport of drugs across these barriers appears to be remarkably similar.

The permeation of substances across simple biological barrier-plasma membrane occurs by the following processes:
- Simple passive diffusion
- Active transport
- Carrier-mediated transport
  - Facilitated diffusion
  - Exchange diffusion
- Specialized process like
  - Pinocytosis (cell drinking)
  - Phagocytosis (cell eating)

Passive Diffusion
Drug molecules penetrate the biological barriers by passive diffusion along the concentration gradient, through aqueous channels of the cell membrane. Solute molecules are transported from higher concentration to the lower concentration. Passive diffusion of drugs across the cell membrane is a slow process, bi-directional and ceases to operate at the equilibrium phase where solute concentrations remain the same on both sides of the cell membrane. Lipid solubility, area of absorbing membrane and thickness of the membrane are the factors that govern the rate of drug absorption by passive diffusion. Cell membranes are more permeable to unionized lipid-soluble form of drugs.

Active Transport
Active transport of drugs is an energy-dependent rapid process of absorption. This biotransport of drugs occurs against a concentration gradient. Some of the examples of the drugs which are absorbed by active transport are methyldopa, L-dopa, and vitamins. Active transport is one of the basic functions of living cells. Active transport exhibits unique characteristics like selectivity, saturability and energy dependence. The movement of substances across the cell membrane is unidirectional unlike passive diffusion. Many cells prefer fructose to glucose and intestinal epithelial cells absorb sitosterol selectively in the presence of cholesterol. Saturability is a unique feature of active transport wherein active transport ceases to operate when enough concentrations of essential substances/nutrients are achieved. The secretion of H+ into the stomach, iodide trapping process by thyroid and renal absorption of glucose and amino acids are some of the examples of active transport. Cell metabolism inhibitors like dinitrophenol arrest the active transport by depriving energy for the biotransport.
Carrier-mediated Transport

Carrier-mediated transport is a distinct type of biotransport in which the drug attaches to a cell component called “Carrier” which delivers the drug into the cell. This process does not require energy and hence known as “Facilitated Diffusion” and operates along an appropriate concentration gradient unlike active transport, for example, glucose absorption by the red blood cells and nucleoside absorption by the cells. This process is highly selective for specific conformational structure of drugs. Valinomycin is an antibiotic believed to be absorbed by facilitated diffusion.

Exchange diffusion of substances or electrolytes operates in such a way that there will not be any change in osmotic pressure of the cellular and transcellular fluids.

Pinocytosis is otherwise known as “Cell drinking”. Large molecular proteins are transported into the cell by this process, which is commonly observed in cancer cells and also in a wide variety of cells.

Factors that Modify Drug Absorption

Drugs, whether applied locally or administered systemically have to cross cell barriers to produce their action. The rate at which drugs cross biological barriers determines the time of onset of action as well as duration of action. The rate of absorption of drugs is modified by various factors, which include:

- Physicochemical characteristics of drugs
- Drug formulation factors
- Patient factors

Physicochemical Characteristics of Drugs

- Solubility
- Degree of ionisation
- Molecular size and shape
- Concentration

Solubility

Lipid-soluble drugs which are unionised are rapidly absorbed across biological barriers, e.g. thiopentone sodium, organophosphorus compounds. The extent of lipid solubility of a given drug determines the duration of action as well. Thiopentone sodium, an intravenous general anesthetic, acts rapidly because it is highly lipid soluble.

Degree of Ionisation

Most drugs are weak acids or weak bases and have one or more functional groups capable of undergoing ionisation. Biological membranes are permeable to the unionised form of drug molecule, if it is lipid soluble and relatively less permeable to ionised radicals.

The degree of ionisation of an administered drug varies with the pH of the absorbing media. Acids undergo ionisation in alkaline pH and bases ionise readily in acidic pH. Since acidic drugs remain unionised in acidic pH, these are better absorbed from gastric mucosa, e.g. aspirin and barbiturates. At physiological pH (7.4), weak acids and weak bases remain
partly unionised and the absorption is generally proportional to the lipid solubility of the drug.

**Molecular Size and Shape**

If the size of the drug molecule is big, membrane permeability to such drug is rather poor. Aminoglycoside antibiotics (streptomycin) are not absorbed by oral route. The reason is streptomycin, being a large polycation molecule, fails to cross the membrane readily. Therefore, aminoglycosides are always given parenterally in systemic infections. The quaternary ammonium compounds do not cross surface barriers, for example, physostigmine, a tertiary amine is preferred to neostigmine—a quaternary ammonium compound for instillation into eye in glaucoma. However, passive diffusion of quaternary ammonium compounds may occur at high concentration.

**Drug Concentration**

The rate of absorption of a drug is directly proportional to concentration at the site of absorption. The higher the concentration, higher and rapid is the rate of absorption since the concentration gradient across the membrane is high.

**Drug Formulation Characteristics**

Drugs are available in various forms to suit the need of the patient as well as practitioner. The different types of formulations can influence the extent and rate of drug absorption. Drug solutions are readily absorbed than solid dosage forms. This is because solid drug dosage forms must undergo disintegration and dissolution as well. The disintegration rate, i.e. the time required for solid drugs to be converted into fine particles. Whereas, dissolution of the fine particles of an active drug into a solution depends on the drug substance, particle size and the pH of the absorbing site. Thus both the disintegration time and dissolution time determine the rate of absorption of the drug when given orally. In fact, this is the basis for various commercial preparations like enteric-coated tablet, sustained release/controlled release drug formulations. The rate of absorption of these preparations determines the duration of action which is solely due to drug release characteristics. In addition, co-administered solutions and mixtures do play a role in governing the rate of absorption of drugs.

**Patient Factors**

Many patient factors influence the rate of drug absorption, the knowledge of which is necessary for clinicians to achieve the goal of drug therapy. The factors include:

- **Area of absorbing surface**: The greater the area, the higher the rate of absorption.
- **pH of the absorbing area**: Determines the extent of ionisation of the drug.
- **Bile salts pool size**: Bile salts help to absorb more lipid-soluble substances from the gut.
- **Presence and severity of underlying diseases**: Many diseases alter the rate of absorption from gut, e.g. hypermotility disorders.
- **Blood supply to the absorbing area**: The drug absorption is more from highly vascularised areas, e.g. eye, buccal mucosa.
• Structure of the cell membrane: The simpler the structure of the cell membrane, better absorption.
• Body temperature: Hyperthermia usually increases the rate of absorption.
  Besides the above factors, route of administration and presence of other drugs can also modify the rate of drug absorption. Intravenous route of administration can circumvent all the factors that modify drug absorption. Concurrent administration of two or more drugs do influence drug absorption. For example, in the presence of gastric antacids the absorption of tetracycline from the stomach is hindered. Conversely, ascorbic acid facilitates iron absorption.

Methods to Prolong Drug Absorption

Administration of vasoconstrictor: Simultaneous administration of a vasoconstrictor along with the drug reduces the blood supply to the site of drug administration and decreases drug absorption. However, a slow steady rate of drug absorption may be seen by this method, for example, adrenaline and lignocaine. Adrenaline being a vasoconstrictor, reduces the absorption of lignocaine from the site of injection and thus prolong the duration of action of lignocaine at the site of administration.

Application of Tourniquet: Above the site of drug injection, a tourniquet is applied to reduce the blood supply to the site, which decreases the rate of the drug absorption.
  Currently, readymade drug dosage forms have been designed to achieve a steady rate of drug absorption, for example,
  • Slowly disintegrating chemical complexes—procaine penicillin
  • Sustained release/controlled release preparations—L-dopa
  • Transdermal route of administration, e.g. ointments and patches

DRUG DISTRIBUTION

Drug distribution is the transport of a drug to its site of action, storage sites, metabolic sites and to the organs of excretion. Drug distribution determines the efficacy, duration of action, mode of metabolism and rate of excretion. Drugs are promptly distributed to heart, brain, liver, kidney or other highly perfused organs. Drugs reach less rapidly in the muscle and much more slowly in entering fat tissues. Distribution of drug in turn is dependent on two major factors—bioavailability and plasma protein-binding capacity besides other factors like drugs physicochemical characteristics, cardiac output and regional blood flow. The body compartments in which drug accumulates are the potential reservoirs of the drug.

Bioavailability

Bioavailability is the fraction/proportion of unchanged drug that reaches the systemic circulation. This is one of the important pharmacokinetic parameters of the drug that determines the intensity and duration of action.

\[
F = \frac{AUC_{(0-\infty)} \text{ after oral dose}}{AUC_{(0-\infty)} \text{ after i.v. dose}}
\]
where \( F \) = Bioavailability

\[ \text{AUC} = \text{Area under curve} \]

Drug formulation factors, rate of drug absorption, route of administration, dose and frequency of administration, rate of drug metabolism and excretion alter the bioavailability of drugs. Gut diseases do alter oral bioavailability of the drug. Bioavailability can be measured after the administration of the single dose or chronic administration. The concept of **Bioequivalence** is understood when bioavailability of various drug dosage forms of the same drug is compared.

**Volume of Distribution** (\( V_d \))

Volume of distribution of a drug is the quantitative estimate of its tissue localization.

\[ V_d = \frac{\text{Total amount of drug in the body}}{\text{Concentration of drug in the plasma}} \]

\( V_d \) is the volume of fluid in which drug appears to be distributed with a concentration equal to that of plasma. In a 70 kg man, \( V_d \) for aspirin is 11 L, digoxin 440 L and chloroquine 13,000 L. Therefore, \( V_d \) does not denote any real physiological volume. It is important for optimal drug dose response. If a drug has small \( V_{d,0} \) it is easily dialyzable, for example, aspirin whereas drugs with high \( V_d \) like pethidine, cannot be dialysed. Volume of distribution of a drug varies with \( pK_a \), i.e. partition coefficient, protein binding, cardiac output, membrane permeability, tissue perfusion rate, age of the patient, gender and associated diseases.

**Plasma Protein Binding of Drug**

Large numbers of drugs on reaching circulation, bind to plasma proteins, predominantly albumin and to a lesser extent globulin. Plasma albumin exhibits high affinity for acidic drugs. Only free drug can exert pharmacological action and the protein-bound drug is pharmacologically inert. The interaction between drugs and plasma proteins is non-specific, non-selective and reversible. It dissociates rapidly whenever the free concentration of drug in plasma is reduced. Thus, the protein-bound form of the drug acts as **Drug Labile Depot**. Other pharmacological implications of protein binding are:

- The bound drug is not filtered at renal glomerulus.
- Extensive drug binding to plasma proteins means that the action is prolonged, e.g. warfarin—98% of an administered dose is protein bound.
- The bound form of the drug cannot diffuse through the capillary wall.
- Drugs compete each other for protein-binding sites. Consequently, displacement of one drug from binding sites by the other alters the kinetic pattern as well as pharmacodynamics of displaced drug.

Hence, to achieve the desirable therapeutic concentration of drugs in plasma in a given time, the knowledge about the drug protein-binding capacity is helpful to a clinician. Drugs may not always be uniformly distributed—kidneys selectively accumulate mercury, cadmium and lead. Chloroquine is selectively concentrated in liver and eyes. Adipose tissue acts a storage depot for fat-soluble drugs like thiopentone and diazepam.
Drug Reservoirs
An administered drug may be stored in cellular reservoirs like adipose tissue, bone, muscle and liver. Transcellular reservoirs like joint fluids, cerebrospinal fluid, gastrointestinal fluids, aqueous humor and endolymph also concentrate drugs.

Lipid-soluble drugs are commonly stored in neutral fat. Thiopentone, an intravenous anesthetic, is highly lipid soluble and stored in fat tissue. Bone stores tetracyclines, lead and radium. Quinacrine (Mepacrine) is stored in liver. Generally, a stored drug is released slowly from the reservoirs and hence it interferes with action of drugs.

Blood-Brain Barrier
Blood-brain barrier is a permeability barrier interposed between the circulation and the brain parenchyma. This is composed of endothelial cells, astrocytes and their basement membrane. Blood-brain barrier is less permeable to water-soluble substances. However, inflammation and disease alter the permeability of blood-brain barrier. Adrenaline, dopamine, carbidopa, quaternary ammonium compounds and various other drugs do not cross blood-brain barrier. It is believed that drugs like anticonvulsant-phenytoin alter the permeability of the blood-brain barrier.

Placental Transfer of Drugs
The maternal blood sinuses, chorionic villi, fetal membrane capillaries and trophoblast layer with mesenchymal tissue capillary endothelium structurally constitute the placental barrier. Drugs administered to pregnant women can reach fetus and produce unexpected fetotoxicities. Therefore, fetal exposure to such drugs should be avoided by taking all the precautionary measures. Morphine, antithyroid drugs, alcohol, phenytoin, anticancer drugs, oral anticoagulants and oral contraceptives cross the placental barrier and produce malformations in the fetus. Morphine can cause intrauterine fetal death due to respiratory depression. The knowledge about the placental transfer of drugs and their adverse effects on fetus is necessary for the rational use of drugs in pregnancy.

DRUG METABOLISM
The interaction between drugs and living tissues is reciprocal. Drug administration invariably results in biochemical and physiological changes in various organ systems. In turn, body brings about changes in the structure and action of drug. The metabolic transformation of the drugs inside the body is known as Biotransformation. Biotransformation of drugs occurs as a series of interdependent reactions with the product of one reaction becoming substrate for another. Drug metabolism is described to have two phases:

Pathways of Drug Biotransformation
*Phase I (non-synthetic pathways of drug biotransformation)*
- Oxidation
- Reduction
- Hydrolysis
Phase II: Drug conjugations (synthetic pathways of biotransformation)

- Glucuronide conjugation
- Sulfate conjugation
- Acetylation
- Methylation
- Glycine conjugation
- Glutathione conjugation

Generally, biotransformation alters the polarity, solubility, potency and results in rapid excretion of drugs. However, this is not always so. After biotransformation, a drug may become more active than the parent compound. Similarly, biotransformation is not necessary for drug elimination from the body. Many drugs are excreted as unchanged, for example, mannitol, penicillins and aminoglycosides.

Biotransformation of drugs is not the same as detoxification. The process of detoxification is involved in reducing the toxicity of the substance ingested and almost exclusively occurs in liver. A drug may become more toxic after biotransformation, for example, methanol is converted into a toxic metabolite-formaldehyde.

Sites of Drug Metabolism

Biotransformation takes place in the liver, kidney, lungs, intestine and other tissues as well. Metabolic changes of drugs predominantly occur in the liver. However, practically in all tissues drug can undergo biotransformation. Kidneys, intestinal mucosa, intestinal microflora, plasma and lungs are also the sites of drug metabolism.

Liver is the most important organ of drug metabolism. Hepatic microsomal enzyme system extensively catalyses both phase I and phase II reactions of biotransformation. Hepatic microsomal enzyme system consists of a wide variety of group of enzymes. Lipid-soluble drugs readily gain access to hepatic microsomal enzyme system. The enzymatic activity of microsomal enzyme system of liver and other tissues are amenable to the action of drugs. Drugs can stimulate or inhibit the hepatic microsomal enzyme system. Hepatic diseases do alter the drug metabolizing capacity of the liver. Hence, in hepatic diseases, drugs with narrow safety margin are either administered at lowest effective doses or avoided.

Phase I: Non-Synthetic Pathways of Biotransformation

Oxidation

Drugs are extensively metabolized by different oxidative pathways catalysed by several distinct enzymes. The most prominent group of enzymes are mixed function oxidases of liver. These hepatic microsomal enzymes are non-specific in their function. A suprafamily of hemoproteins known as cytochrome P-450 group are the key enzymes, which take part in microsomal electron transfer system with NADPH. Several types of drug oxidases have been described—deamination, aromatic hydroxylation, N-oxidation, S-oxidation, dealkylation and desulfation. Drugs that undergo oxidation include diazepam, phenytoin, chlorpromazine, steroids, antihistamines, and adrenergic agonists.

Drugs can inhibit or stimulate the cytochrome group of enzymes and alter the rate of drug metabolism. As a result of this, various pharmacokinetic drug interactions occur. The implication and clinical significance of these interactions must be known to the physician.
Reduction

Drugs like chloramphenicol, clonazepam undergo nitroreduction in the liver as well as other tissues. Azoreduction, dehalogenation and reduction of N-oxides and S-oxides are other known types of drug reduction pathways.

Hydrolysis

Esters, amides and glycosides are generally metabolised by hydrolysis. Succinylcholine undergoes ester hydrolysis catalysed by pseudocholinesterase present in plasma and liver.

Drug Conjugation

Drug conjugation is a systemic metabolic process involving the incorporation of endogenous radicals or groups to drug molecules or their metabolites. Conjugations take place in the liver and to a limited extent in kidneys. Drug conjugation always results in the loss of pharmacological action.

Glucuronide conjugation is catalysed by glucuronyltransferase enzyme. Morphine is usually excreted as morphine glucuronide. Many drugs including paracetamol and chloramphenicol are excreted as glucuronides.

Drugs which are primary amines generally undergo acetylation catalysed by acetyltransferase in liver, for example, isoniazid.

Adrenaline, histamine, phenols and thiols are the agents for “methylation” whereas acetylsalicylic acid undergoes glycine conjugation. Ethacrynic acid is excreted as glutathione conjugate.

Fate of Drugs after Metabolism

Biotransformation brings changes in pharmacokinetic as well as pharmacodynamics of drugs, which may be beneficial and often harmful. Lipid-soluble drugs are converted into more water-soluble substances. Non-polar compounds will be converted to polar and thus facilitates elimination of drugs. Further, drug metabolism may result in:

A. Change in the Nature of Action

Biotransformation can change the nature of action of the drug, for example,

a. Iproniazid \[\xrightarrow{\text{N-dealkylation}}\] Isoniazid
   (MAO inhibitor, antidepressant) (antitubercular drug)

b. Terfenadine \[\xrightarrow{\text{antihistaminic and arrhythmogenic}}\] Fexofenadine
   (antihistaminic, nonarrhythmogenic)

B. Increased Potency → Activation

Examples:

a. Diazepam → Oxazepam
b. Imipramine → Desmethyliimipramine
c. Talampicillin → Ampicillin
When drug potency is increased after biotransformation due to the release of active metabolites, the concept is regarded to as **activation** of drugs. The parent compound, which is inactive or less active than its metabolite, is known as **prodrug**, for example, dipivefrine and talampicillin.

**C. Increased toxicity**

Many drugs become more toxic after metabolism. Methanol on biotransformation releases formaldehyde, which is neurotoxic. The clinical implication of these metabolic changes, which are observed with drugs, must be known to all. One of the metabolites of cyclophosphamide, an anticancer drug, causes hemorrhagic cystitis.

**Variation in Drug Metabolism**

There are great individual variations in drug metabolism. Frequently, these variations are under genetic control. Physiological factors like age, gender, pregnancy, presence of hepatic disease, environmental factors and stimulation and inhibition of drug metabolising enzymes by drugs cause variation in the rate and types of drug metabolism.

**Enzyme Induction and Enzyme Inhibition**

Many enzymatic metabolic reactions are augmented by drug themselves. This phenomenon is known as **Enzyme Induction**. Drugs that stimulate enzymes are called **Enzyme Inducers** for example, phenobarbitone, rifampicin, phenytoin and alcohol. Certain drugs stimulate their own metabolism by stimulating the metabolising enzyme activity.

The enzyme induction caused by drugs may at times result in clinically significant variation in the efficacy of drug therapy. When a female patient is on oral contraceptive therapy, if rifampicin is prescribed concurrently, oral contraceptive measure may fail resulting in pregnancy. The reason is rifampicin being an enzyme inducer enhances the metabolism of hormonal contraceptive eventually leading to reduced efficacy of the contraceptive.

Conversely, there are drugs that can inhibit hepatic drug metabolising enzyme system, for example, cimetidine, ciprofloxacin and erythromycin. As a result, this causes variation in the efficacy of concurrently administered drug.

**Genetic Variation in Drug Metabolism**

Genetically determined polymodal variation in biotransformation of drugs is common. The metabolism of succinylcholine, isoniazid, primaquine and other drugs show genetically determined variation in their metabolism. Often, this may turn out to be fatal. Therefore, it is important to study the genetic polymorphism in drug metabolism to avoid complications of drug treatment.

Succinylcholine is a skeletal muscle relaxant that undergoes ester hydrolysis in plasma and liver catalysed by pseudocholinesterase. The people of Greece, Israel, Portugal, 2% British and North Africans produce **atypical pseudocholinesterase** which fails to hydrolyse succinylcholine. Administration of succinylcholine to these individuals results in **succinylcholine apnea**, which may lead to paralysis of respiratory muscles and diaphragm.

Isoniazid is a first line antitubercular agent which is metabolised by acetylation. Rate of isoniazid acetylation is genetically determined. The human population can be grouped
into two, based on the rate of isoniazid acetylation—‘slow’ acetylators and ‘rapid’ acetylators. Of late, ‘medium’ acetylators group is being added. It is important to realize that doses of isoniazid have to be titrated depending upon the rate of acetylation in a given patient. This is necessary to avoid any variation in the efficacy and toxicity in a patient.

Genetic factors not only alter the metabolism but also toxicity profile of the drug. Primaquine is an antimalarial innocuous drug. However, if a patient is deficient of glucose-6 phosphate dehydrogenase enzyme, primaquine can cause death causing extensive hemolysis. Pertinently, human genomic research is trying to unleash the details of the relationship between gene and drug kinetics. Till then, clinicians must focus well and be constantly vigilant to avoid drug-induced hazards based on genetic defects in particular.

First Pass Metabolism
The rate of drug metabolism may vary when administrated by different routes. Orally administered drugs can be degraded during their transit before reaching systemic circulation. Drugs like catecholamines, insulin and lignocaine cannot be given by oral route. These drugs are completely destroyed in the gastrointestinal tract and while passing through liver. Drug metabolism that occurs before reaching systemic circulation is described as first pass metabolism.

Lignocaine, propranolol, insulin and catecholamines are a few examples of drugs that undergo extensive first pass metabolism. For this reason, lignocaine is not given orally as an antiarrhythmic agent. However, propranolol can be given by oral route at recommended doses to produce intended action. In fact, on first pass metabolism, an administered drug may be converted into an active metabolite and a rapid action seen. Thus, potency and efficacy of a drug remains same, after first pass metabolism for prodrugs like enalapril.

DRUG EXCRETION
The elimination of drugs and their metabolites occur by several routes. Kidneys, intestine, lungs, and biliary system account for most part of drug excretion. However, renal excretion is by far the major route and to a lesser extent, sweat, salivary and mammary glands in lactating mother also contribute for the elimination of drugs. Generally, water-soluble compounds are more readily eliminated.

Clearance
The time required for complete elimination of administered dose of a drug is called clearance. The total body clearance of a drug is the direct expression of the body’s ability to eliminate drug. In general, the rate of biotransformation to eliminate drug is fairly constant. Nevertheless, drug clearance is dependent upon blood flow to the organs of excretion, protein binding, plasma concentration, hepatic and renal diseases. The principle of clearance is similar to that of renal physiology. Thus, reduction in drug dosages and less frequent administration may be suitable for most drugs in the conditions of renal disease. Therefore, the knowledge about drug clearance is useful in predicting the response in a given condition. The duration of action and plasma concentration are conveniently expressed in terms of half-time.
Many drugs like penicillin, probenecid, digoxin and thiazide diuretics are excreted by active renal tubular secretion. When these drugs are given together, they compete for the renal secretory pathways. Thus, kinetics and dynamics of the affected drug may change. For example, thiazide diuretics compete with uric acid for tubular excretion and uric acid is reabsorbed. The elevated uric acid levels in plasma can precipitate gouty arthritis. Therefore, thiazide diuretics are contraindicated in gout. Physicians need to be aware of drug interactions that occur at the sites of drug excretion.

**Plasma Half-life \( (t_{1/2}) \)**

Plasma half-life of a drug is the time taken for the elimination of half of the plasma concentration of the administered dose. The plasma half-life is an index of plasma concentration and duration of action, which is useful particularly for the optimization of drug dose regimen for chronic treatment. The rate at which drug leaves the body is dependent on volume of distribution and clearance. Hence, plasma half-life of drug expresses the relationship between volume of distribution and dose. Plasma half-life of the drug is an estimate to determine appropriate dosing interval and good indicator of the time required to reach plasma steady state concentration of the drug. As with other pharmacokinetic parameters, plasma half-life of drugs varies with factors like severity of disease, age, protein binding, tissue binding and the rate of absorption.

**Forced Alkaline Diuresis**

The rate of drug excretion can be enhanced by promoting their ionization in plasma, since ionized radicals are rapidly excreted. Acidic drugs undergo ionization in alkaline pH and *vice versa*. Hence, if acidic drugs like barbiturates and salicylates, when ingested in large quantities, their excretion can be enhanced by alkalinization of plasma to reduce toxicity. Further, a diuretic can be used along with sodium bicarbonate to increase the rate of drug elimination. This is known as **forced alkaline diuresis**. Forced alkaline diuresis is commonly employed in acute salicylate and barbiturate poisoning conditions.

**Enterohepatic Circulation**

It means that a drug may be excreted by the liver cells into the bile and eliminated through intestine. From intestine, drug may be absorbed back to reach liver. In this way, drug may be shunted from liver to intestine and intestine to liver. This is referred to as **enterohepatic circulation**. Penicillins, copper, steroid hormones, procainamide, sulfonamides, chloramphenicol, tetracyclines and chlorpromazine are the few examples of drugs that undergo enterohepatic circulation.

**Excretion by other Methods**

**Pulmonary Excretion**

Volatile general anesthetics and paraldehyde are the drugs that are excreted through lungs. Only 2% of the ingested alcohol is excreted through this route since major part of alcohol is metabolised extensively.
Excretion through Hair and Nails
Griseofulvin, an antifungal antibiotic, gets deposited in hair follicles and nails. In fact, this has a clinical advantage. Griseofulvin is the drug of choice to treat fungal infections of hair follicles and nail. Arsenic and mercury are also excreted through hair and nails.

Excretion through Sweat
Quinine, mepacrine, arsenic and mercury are excreted in sweat. Mepacrine produces yellowish discoloration of skin as it gets excreted in the sweat.

Excretion through Saliva
Metronidazole, an antiamoebic drug, gets excreted through saliva producing metallic taste in the mouth. Other examples of drugs that appear in saliva are atropine, clonidine, barbiturates and sulfonamides.

Drugs that are Distributed into Milk
Many drugs are excreted through milk, for example, isoniazid, chloramphenicol, diazepam, oral anticoagulants and antithyroid drugs. When a nursing mother is on drug therapy with agents, which are known to appear in milk, she should be advised not to feed the baby. Otherwise the baby may be exposed to alarming drug toxicity. If the nursing mother on diazepam treatment feeds her baby, the baby may be sedated unduly. Therefore, knowledge about drug excretion in milk is useful for clinicians while prescribing drugs for lactating mothers.

First/Zero Order Kinetics
First Order Kinetics
When the rate of drug administration equals the rate of elimination, the concentration of the drug in plasma remains steady. Drug dose and steady state plasma concentration are directly proportional, i.e. doubling the dose must lead to a two-fold increase in plasma concentration ideally. For many drugs, an exponential time course follows before they disappear from plasma. The relationship between dose and rate of excretion is said to be linear; hence, it is known as first order or linear kinetics.

Zero Order Kinetics
When the drug dose and plasma steady state concentration relationship is non-linear, non-exponential, it is known as zero order kinetics or non-linear or saturation kinetics. Phenytoin, alcohol and heparin are the few examples of drugs that obey zero order kinetics. Drug saturation kinetics bear important clinical consequences. There is likelihood of gradual accumulation of drugs and difficulty to achieve a steady concentration in plasma because of variation in kinetics from individual to individual. This necessitates plasma concentration monitoring to ensure safety. This method is known as therapeutic drug monitoring.
PHARMACODYNAMICS

DEFINITION AND INTRODUCTION

Pharmacodynamics is that branch of pharmacology, which deals with action and mechanism of action of drugs. Drugs produce their action interacting with various cellular mechanisms and events. It is important to recognize that drugs cannot create new functions in the body nor restore the lost functions of any system, which happened due to structural defects. Indeed, drugs can only impart changes in biochemical and physiological processes in the living body to produce their effects.

The action of drugs may be produced by two major ways:
1. Specific action involving a known type of receptors.
2. Actions produced by nonreceptor mechanisms. For example, alcohol-induced action, which does not involve receptors.

DRUG RECEPTORS

Definition of Receptor

A receptor is a macromolecular biophysical unit with which the drug interacts that leads to a sequence of events culminating as a characteristic action of the drug.

A drug, which exhibits both affinity and efficacy on receptor interaction, is called the ‘agonist’ of that particular type of receptor. Affinity of the drug is the tendency to form drug-receptor complex. Efficacy or intrinsic activity of a drug is defined as the ability to induce physico-chemical events, which occur subsequent to the formation of drug receptor complex that results in drug action. Currently, this is referred to as receptor signal transduction pathway.

A drug which has affinity for the receptor but lacks efficacy is known as ‘antagonist’. For example, atropine blocks the muscarinic receptor. It binds with muscarinic receptor but has no intrinsic activity.

An agonist with full receptor occupancy fails to produce maximum effect is known as ‘partial agonist’, for example; buprenorphine is an µ opioid receptor partial agonist. Whereas an agonist on receptor occupation produces opposite effects to that of classical agonist of the same receptor type is known as ‘inverse agonist’, for example, β-carbolines on benzodiazepine receptors.

Many therapeutically useful drugs act either as agonists or antagonists of the known types of receptors. Currently, different types of drug receptors have been studied thoroughly and characterised well by their structure and function. A drug binds to receptors by ionic,
hydrogen, covalent bonds and van der Waals’ force. If a drug establishes covalent bond with a receptor, the interaction is said to be stable and irreversible.

Further, drugs bind to enzymes, carrier molecules and ion channels to produce their action. This evinces that no drug is completely specific in producing actions. However, it is certain that receptors form the sensing elements in the system of chemical communications that co-ordinates drug action as well as cellular function. The precise chain of events occurs following drug receptor interaction which depends upon the particular receptor and the cell. The receptors may be directly linked to ion channels, enzyme kinases, nuclear substances or coupled with G-protein system for signal transduction.

**FACTORS THAT MODIFY DRUG ACTION**

Biological variation in the action of drugs is a natural phenomenon. Many factors cause variation in drug action, which are as follows:

1. **Physical factors**: Body weight and body surface
2. **Physiological factors**: Age, sex, temperature, pregnancy, posture, mental attitude and patient’s compliance
3. **Pathological factors**: Presence of disease and severity of the disease
4. **Pharmacological factors**: Structure of the drug, dose bio-availability, presence of other drugs, route administration, time and frequency of administration and tolerance
5. **Genetical factors**: Species variation and idiosyncrasy
6. **Environmental factors**: ‘CO’-rich air pollution

**Age**

Age is an important factor in determining the response to a given drug. The variability of drug action to an extent is age dependent. At large, the effects of age on the type of quantitative drug response are inseparable. The individuals at the extremes of lifespan are often unusually sensitive to drugs. Apparently, this is due to changes in rates of absorption, distribution, biotransformation and excretion.

In children, liver is ill equipped with enzymes to metabolise drugs. The renal excretion of drugs is also depressed. Further, the volume of blood flowing through the kidney per unit time is smaller in the infant in proportion to the total body water content. Therefore, drug action tends to be intense or prolonged or both. Consequently, effective drug levels persist for longer periods. For example, chloramphenicol is more toxic to infant because the rate of metabolism of this antibiotic is slow and hence produces ‘gray baby syndrome’. Hence, chloramphenicol is contraindicated in neonates.

With aging, there is a normal decline in the integrity of the various organs and systems (homeostenosis). In the elderly people end-organ sensitivity, blood flow to organs and ability to handle drugs are quite different when compared to an adult patient. Hence, geriatric (aged) patients are likely to respond to drugs in quantitatively different ways than the average adult does. For example: it is not unusual to see paradoxical excitement to a sedative hypnotic drug diazepam in an elderly patient. Geriatric patients are readily vulnerable to digoxin toxicity. To avoid complications, drug dose regimens need to be altered for both paediatric and geriatric patients.
Gender
The variation in drug action attributable to gender appears to be of little consequence. However, on the basis of weight, women may need smaller doses of drugs than men. Obviously, sex hormones produce different actions when given to individuals of opposite sex. Estrogens produce feminisation of male and masculinisation trends are seen with androgens in female. Barring these natural differences in drug actions based on gender are infrequent and inconsequential.

Structure of the Drug
The structure of the drug is intimately associated with the action. Any minor/major modification in the structure may alter the kinetic as well as dynamic characteristics of the drug. The study of structure-activity relationship of drugs has been beneficial to produce various congeners of established official drugs. Often, these congeners ensure more potency, efficacy and safety. The knowledge about the structure-activity relationship is of immense value to explore the nature of drug receptor interaction. As a result, it is made possible to synthesize various agonist and antagonist to that particular receptor.

It is not surprising that hardly few changes have been observed in the structure of noradrenaline, adrenaline and dopamine. However, the adrenoceptor activity of these drugs differs substantially. Adrenaline acts on both $\alpha$ and $\beta$ receptors, whereas dopamine receptor agonistic activity is entirely different.

Dose
Dose of a drug is defined as the quantity of the drug that is administered to produce a predictable action in a given clinical condition. Obviously, the dose employed in any clinical circumstances must produce maximal therapeutic benefit and minimal or no toxicities. The action produced by a drug in general is directly proportional to the dose administered. The dose of a drug required to produce 50% of the maximal effect of that drug is described as “drug potency”. The potency of drug is determined by drug affinity and coupling reaction with the receptor. Nonetheless, the selection of the drug is based on its efficacy but not potency. The clinical efficacy of a drug depends on the maximal effect it produces in a patient. Further, the drug efficacy may depend on the route of administration, absorption, distribution and clearance from the site of action. Drug potency is largely determined by the dose to be given for a particular patient. Hence, there is no reason to believe that the more potent drug is clinically preferred as it is being stressed in drug advertisement.

Route of Administration
Route of administration is an important factor in altering the onset, intensity and often the nature of action. Many drugs fail to reach systemic circulation as they undergo complete inactivation when given by mouth, for example, insulin and other protein drugs. A change in the route of drug administration of a drug may result in the production of different pharmacological actions as seen with magnesium sulphate. Orally administered magnesium
sulphate produces purgative action. When given by intravenous route, it acts as central nervous system depressant and on local application induces anaesthetic effect. Thus, often the selection of route of administration is an important therapeutic exercise at least in part, to attain clinical efficacy from the drug treatment.

**Presence of Other Drugs**

Concurrent administration of two or more drugs is a common practice and often a clinical necessity. Multiple drug therapy leads to either beneficial or at times harmful drug interactions. It is well recognised that combination drug therapy results in two types of drug—drug interactions **synergism** and **antagonism** involving both pharmacokinetic and pharmacodynamic mechanisms.

**DRUG SYNERGISM**

Drug synergism is defined as the positive summation of drug effects. In synergism the combined effect of two drugs is greater than the algebraic sum of their individual effects. Often, the term drug potentiation is used as interchangeable word with synergism of drug actions. Therapeutically applied drug combinations for synergistic effects are plenty. Trimethoprim + sulphamethoxazole as antifolate drugs, diuretic with other antihypertensives hydrochlorothiazide + atenolol, organic nitrites with \( \beta \) adrenergic blockers as antianginal drugs, antitubercular—3 or 4 or 5 drug regimens—isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin and co-administration of enzyme inhibitors which inhibit the metabolism of drugs are a few examples for achievable therapeutic synergy for the benefit of the patient.

**DRUG ANTAGONISM**

The negative summation of drug effects is drug antagonism. This is to say that the combined effect of two or more drugs is less than the algebraic sum of the individual effects. Drug antagonism is of different types. Mainly four types have been described:

1. **Physical antagonism**
2. **Chemical antagonism**
3. **Physiological or functional antagonism**
4. **Pharmacological antagonism:**
   a. **Competitive**
   b. **Non-competitive**

**Physical Antagonism**

This type of drug antagonism is mainly due to physical properties of the agents. One drug is inactivated in direct proportion to an extent of opposing physical properties of the other, for example, heparin is a negatively charged macromolecule binds to positively charged proteins like protamine. Thus formed protamine-heparin complex is pharmacologically inactive. For this reason, protamine is used as an antidote in heparin overdose. Nevertheless, protamine is a strong base and heparin is acidic. These properties of drugs also contribute for antagonistic interactions.
Chemical Antagonism
When the chemical reaction that occurs between two drugs form the basis for drug interaction with negative outcome, it is known as chemical antagonism. For example, sodium bicarbonate and hydrochloric acid being acid and alkali neutralise the gastric acid and useful in acid peptic diseases.

Functional or Physiological Antagonism
This is observed when two endogenous substances acting at different sites produce mutually antagonistic effects. Histamine is a powerful bronchoconstrictor and adrenaline counteracts the action of histamine on bronchial smooth muscle. This interaction occurs as a physiological regulatory tissue mechanism hence the name—functional antagonism.

Pharmacological Antagonism
The antagonism observed at receptor level between two drugs on administration of therapeutic/recommended doses is known as pharmacologic antagonism. The cardinal feature of pharmacologic antagonism is as a rule, both the agonist and antagonist act on the same receptor. In many clinical conditions pharmacologic antagonism form the basis for the administration of specific antidotes to save the life of patient. For example, in acute opioid poisoning—naloxone a specific opioid antagonist and atropine in organophosphorous poisoning.

Drug receptor antagonism is of two types:
1. Competitive drug antagonism
2. Non-competitive drug antagonism

Competitive drug antagonism is also known as surmountable or reversible antagonism. In this type of antagonism, the action of an antagonist can be reversed by increasing the dose of agonist by many folds. The agonist administered at high doses displaces the antagonist from the receptor and produces its action on the receptor. Acetylcholine and atropine interaction at muscarinic receptor sites is said to be ‘competitive antagonism’. Atropine action on muscarinic receptor can be reversed by increasing the concentration of acetylcholine at the immediate vicinity of receptors.

In non-competitive (unsurmountable, irreversible) drug antagonism, it is not possible to regain the effect of agonist by increasing its dose. For example, the action of glutamate on its receptor cannot be regained once the receptor is occupied by a non-competitive antagonist memantadine. The interaction between noradrenaline and phenoxybenzamine at stage two establishing covalent bond is also referred to as irreversible antagonism.

Drug Tolerance
Drug tolerance is a state of decreased responsibility to the administered dose of a drug and to achieve the same intensity/degree of response doses needs to be increased. Drug tolerance may involve both kinetic and dynamic mechanisms or alone either. Generally, decreased responsiveness to the given dose of a drug due to variation in absorption is referred to as ‘pseudotolerance’. Whereas, tolerance due to various changes that occur at the target sites of drugs is known as ‘pharmacodynamic tolerance’. Primarily, the mechanisms that are responsible for the development of drug tolerance include increase in the rate of
metabolism, rapid excretion, desensitisation of receptors, which may be associated with
downregulation of receptors and genetic trends also contribute.

The development of drug tolerance may be acute or chronic. The acute tolerance to drug
action is otherwise called ‘tachyphylaxis’. Tachyphylaxis or acute tolerance is defined as
a state of reduced responsibility to the administered dose of a drug given within short
time intervals. The exact mechanisms that give rise to tachyphylaxis remain uncertain. The
development of tachyphylaxis seem to involve:
1. Enhanced drug disposition due to increased rate in biotransformation
2. Rapid elimination
3. Fast adaption of drug site of action to the state of reduced sensitivity—exhaustion of
stored neurotransmitters, downregulation of receptors and desensitisation of receptor.

The common examples of drugs that produce tachyphylaxis include ephedrine, tyramine,
5-hydroxytryptamine and prazosin. Histamine, nitroglycerin, and amphetamine are also known
to provoke tachyphylaxis. The clinical significance of tachyphylaxis is of paramount importance,
especially in chronic drug therapy. The management of high blood pressure is a perennial
exercise; drug used for this must be free from the phenomenon of the development of tolerance
to their action.

Cross-tolerance is seen when a patient develops tolerance to a drug and remains tolerant
to other drugs that belong to the same group. For example, morphine tolerant may show
tolerance to the action of pethidine.

Drug distribution patterns also account for the development of tolerance. Thiopental,
an intravenous general anaesthetic, is a highly lipid-soluble drug. On administration, it reaches
the brain and acts for 11-20 minutes. This ultra short action is due to its redistribution.
After a lapse of brief period of time, the active drug diffuses from brain and reaches adipose
tissue where it is stored. The administered dose of thiopental is very much inside the body
but unavailable at the site of action. Hence, this is known as ‘drug redistribution tolerance’.

DRUG TOXICITY

Drugs produce many actions. All the drug actions may not be required to achieve therapeutic
benefit. The unwanted actions of a drug seen along with the desired main pharmacological
actions are commonly described as ‘adverse drug reactions’. Adverse drug reaction
includes (a) side effects and (b) toxic effect. A side effect appears at therapeutic doses, which
is not wanted and inseparable from the main actions of drugs. For example, morphine is
used for analgesic purposes but causes constipation and respiratory depression as side effects.
Dryness of mouth produced by many drugs is also a classic example for drug-induced side
effect.

All drugs do produce toxicities when administered at supramaximal doses. Toxic effects
of drugs are always due to high abnormal dose administration. Drug-induced toxicities
may be predictable or unpredictable. Predictable toxicity is often an extension of therapeutic
action of drug and related to dose administered. The unpredictable drug toxicity is not always
related to dose and often unintentional. Drug allergic manifestations are regarded
as unpredictable toxicities when observed at first. Drugs can cause structural toxicities like
hepatotoxicity, haematological, renal, pulmonary, gastrointestinal and neurotoxicities besides
mutagenicity, carcinogenicity and teratogenicity.
Iatrogenic Disease
A drug- or physician-induced disease is called ‘iatrogenic disease’. The etiology of iatrogenic disease is not difficult to describe. However, physician’s awareness on drug-induced toxicities can minimise this adversity. Glucocorticoid-induced Cushing’s syndrome and digitalis intoxication are the noted examples for iatrogenic diseases.

Carcinogenicity
The occurrence of cancer inducing agents is abundant in nature. Carcinogenicity has been observed with estrogen and some anticancer drugs like cyclophosphamide. Many environmental chemicals including nicotine cause cancer. Alcohol is regarded to be a procarcinogenic.

Mutagenicity
An agent that causes mutation is known as mutagen. Drugs like dacarbazine, 5-fluorouracil and cytarabine are known to be mutagens. Drug-induced mutagenicity may be one of the reasons for the development of cancer.

Teratogenicity
Drugs that induce malformation of foetus and intrauterine death are regarded as ‘teratogens’. The first trimester of pregnancy is the most vulnerable period for drug-induced foetal deformation, especially at the time of organogenesis. Many drugs are teratogenic, for example, phenytoin, alcohol, warfarin, sodium valproate and thalidomide. Phenytoin causes ‘foetal hydantoin syndrome’, alcohol produces ‘foetal alcohol syndrome’, whereas sodium valproate induces neural tube defect called ‘spina bifida’.

Cumulative Toxicity
Cumulative toxicity produced by drugs is invariably due to frequent administration. Drugs, which have long plasma half-lives like digoxin, boric acid, and emetine, are the common examples known to cause cumulative toxicity. Drugs accumulate in the body in great proportions to produce cumulative toxicity. Optimisation and individualization of drug dose regimen can readily avoid cumulative toxicity.

MEASURE OF DRUG SAFETY
Therapeutic Index
To produce a desired effect, information about the safe use of drugs needs to be furnished with an assessment of margin of drug safety. This measure ought to relate the dose of the drug required to produce an intended action and an undesired action. This is commonly referred to as ‘therapeutic index’. It is the ratio between median lethal dose to median effective dose for animals.

\[
\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}
\]

LD$_{50}$ : Lethal Dose in 50% of the animals used
ED$_{50}$ : Effective Dose in 50% of the animals
If the therapeutic index of a drug is one, that drug is said to be equally toxic. Ideally, therapeutic index should be more than one and preferably a high TD50 to ensure more safety.

The Placebo

The word meaning of this Latin term placebo is ‘I shall please’ or ‘I please’ or ‘I may please’! A placebo resembles the active drug in all respects by appearance. Placebo is a dummy medicament that resembles the active drug in its shape, size, dose, colour and method of administration. Placebos are used as vehicles to cure the ailments by suggestions (not by true actions by any means). Lactose, gelatin and fructose are generally used as placebo medicaments. Tonics are placebos in a true sense except when prescribed for extremely debilitated patients. Not all subjects react to placebo administration. The percentage of placebo reactors is about 40%. Placebo can produce side effects like perspiration, nausea, headache and anorexia. Placebo is mainly employed in the clinical evaluation of drug development studies to avoid human bias. However, deliberate use of placebo is a confession of failure on the part of clinician.

DEVELOPMENT OF NEW DRUGS

The development of a new drug involves time, finance and risk. The procedure is complex (Fig. 1.1) and expensive and extremely arduous. Here the research studies need to be ethically stringent and well designed. Mainly there are two approaches to design a new drug development programme viz.

1. Rational approach in which chemicals are synthesized in the light of detailed knowledge of biological process and tested for efficacy and safety.

2. Random approach aims at conducting a valley of tests for substances and by chance useful activity is found.

Nevertheless, both the approaches must carry out a sequence of experimentation using two/more species of animals. The preclinical testing generally identifies the characteristic activities of a test drug. Both the primary and secondary animal screening of drugs depict activity and selectivity of drugs under study, besides assessing the safety profile. The animal study of the test drug provides evidences for efficacy in relation to safety at the doses employed. These data paves the way for human testing. A well-designed ethical investigation of drugs in human beings for their rational use is called ‘clinical trial’. The clinical trial is a teamwork that comprises healthy normal human volunteers, clinicians, pharmacologists, statisticians and patients. The chief aim of the clinical trial is to reduce a number of variable factors of drug treatment while assuring safety and efficacy.

The clinical trials must be well executed to avoid bias on the part of investigators and patients as well. To avoid human bias, placebo-controlled studies have been the procedures followed in the clinical trials. The clinical trial involves four phases. Phase I study in human volunteers to declare that the test drug is fit for human use or not. In Phase II dosage requirement, dynamic and kinetic profile of the drugs is to be determined with the active participation of limited number of patients. Whereas the long-term safety and efficacy of the test drug is evaluated in phase III employing more number of patients. Phase III study critically evaluates the overall therapeutic value of the test drug. Adverse drug reactions monitoring will invariably continue till the drug is used. This includes the phase IV study
in clinical trial also known as “post-marketing surveillance”. Phase IV examines marketing authorization given to drug developer and drugs may be withdrawn from the market if the agents found them to be more toxic. Post-marketing surveillance also explores new combinations and new methods of administration by gathering pharmacoepidemiological data.
INTRODUCTION

Autonomic nervous system (ANS) is often referred to as visceral or vegetative or involuntary nervous system. The integrating action of autonomic nervous system is of vital importance for the well being of the organism. The functions, which occur without conscious control, are regulated by autonomic nervous system. Respiration, circulation, digestion, body temperature, metabolism, secretion of sweat, saliva and other glandular secretion activities are being controlled by autonomic nervous system to a large extent. The dynamic equilibrium of internal environment, which includes visceral sensation, vasomotor activity and viscerosomatic reflexes, are being regulated by autonomic innervation. In the periphery, the functional unit of autonomic nervous system comprises nerves, plexuses of nerves and ganglia.

Anatomically, physiologically and pharmacologically autonomic nervous system is divided into two major divisions:

a. parasympathetic nervous system
b. sympathetic nervous system

Parasympathetic nervous system is mainly concerned with conservation of energy and maintenance of organ functions like heart, vascular smooth muscle, gastrointestinal

Drugs and Autonomic Nervous System

• INTRODUCTION
• NEUROTRANSMITTER AND SYNAPTIC TRANSMISSION
• CHOLINERGIC RECEPTORS
• CHOLINERGIC DRUGS
• ESTERS OF CHOLINE
• CHOLINOMIMETIC ALKALOIDS
• ANTICHOLINESTERASE AGENTS
• ORGANOPHOSPHORUS POISONING
• DRUGS USED IN GLAUCOMA
• DRUG THERAPY FOR MYASTHENIA GRAVIS
• CHOLINERGIC RECEPTOR ANTAGONISTS
movement and secretions, absorption of nutrients, protection of retina from excessive light and emptying of the bladder and rectum. Sympathetic nervous system is vitally involved in a wide variety of central and peripheral functions. Heart rate and force of contraction, vasomotor tone, blood pressure, bronchial airway tone, carbohydrate and fatty acid metabolism, psychomotor activity and appetite are the major functions of sympathetic nervous system. Drugs acting on ANS have been related to the events that occur during synaptic transmission.

NEUROTRANSMITTER AND SYNAPTIC TRANSMISSION

The nerve impulse is transmitted across synapse or neuroeffector junction by the participation of specific chemical substances. These are synthesized, stored, and released to initiate postsynaptic activity which are known as “neurotransmitters”. Many chemicals may take part in synaptic transmission at a time. However, it is not clearly known that how co-transmission regulates homeostatic mechanisms assigned to an organ system.

The steps involved in synaptic transmission are amenable to the action of drugs, which are as follows:
1. synthesis of neurotransmitter
2. storage
3. release
4. receptor activation
5. processes that terminate the action of neurotransmitter.

Cholinergic Transmission

A few decades ago, acetylcholine was identified as the neurotransmitter of parasympathetic nervous system. Subsequently, specific assays of acetylcholine have been developed to confirm its role in cholinergic nervous system. Of late substances, like substance-P, enkephalin, vasoactive peptide, adenosine, somatostatin and neuropeptide-Y, localization in cholinergic nerves has revealed that these substances may act as co-transmitters. The significance of cholinergic co-transmission at organ level is yet to be elucidated.

Synthesis and Storage

Acetylcholine is synthesized by the acetylation of choline catalyzed by acetyltransferase with acetyl CoA. Immunocytochemical localization and molecular cloning studies have described the structure and release of acetylcholine in detail. Thus, synthesized acetylcholine is stored in vesicle at cholinergic pre-synaptic sites.

Release

In response to a stimulus, acetylcholine release occurs by exocytosis and Ca\(^{2+}\) plays a facilitatory role. Toxins like botulinum and clostridium toxins inhibit the release of acetylcholine. Black widow spider venom, which causes spastic paralysis, promotes massive release of acetylcholine from vesicles.
Metabolism

Acetylcholine after release undergoes hydrolysis catalyzed by two cholinesterases. True acetylcholinesterase is present throughout the parasympathetic nervous system, as well as other parts of the body. Pseudocholinesterase is distributed mainly in plasma and liver. The hydrolysis of acetylcholine occurs at a lightening speed. Hence, even when acetylcholine is given intravenously, it fails to reach active sites and produces no effects. For this reason, acetylcholine is not available as an official drug.

Sites of Action of Acetylcholine

Acetylcholine acts at the following sites:
1. All the preganglionic fibres of autonomic nervous system.
2. All the postganglionic fibres of parasympathetic nervous system.
3. Few of the postganglionic sympathetic nervous systems that supply sweat glands, pancreas and piloerector muscle.
4. Neuromuscular junction (motor end plate).
5. Certain sites in central nervous system.
7. Adrenal medulla.

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Immunological localization studies with molecular cloning have identified different types and subtypes of cholinoreceptors. In fact, Sir Henry Dale in 1915 classified cholinoreceptors into two major types—muscarinic and nicotonic. Since the availability of selective agonist and antagonists, both muscarinic and nicotinic receptors are further subdivided in the following ways:

A. Subtypes of Muscarinic Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>M1 Distribution</th>
<th>M2 Distribution</th>
<th>M3 Distribution</th>
<th>M4 Distribution</th>
<th>M5 Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CNS</td>
<td>CNS myocardium</td>
<td>CNS smooth muscle</td>
<td>CNS smooth muscle</td>
<td>CNS glands</td>
</tr>
<tr>
<td></td>
<td>secretory glands</td>
<td>smooth muscle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ganglia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Nicotinic Receptor Subtypes

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Nn (Nn1+Nn2) Distribution</th>
<th>Nn Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coronary artery, carotid and aortic arch, central nervous system</td>
<td>neuromuscular junction</td>
</tr>
</tbody>
</table>
Actions of Acetylcholine

Acetylcholine produces varied physiological effects at both muscarinic and nicotinic receptors. Muscarinic sites include certain sites in central nervous system, eye, heart, blood vessel, gastrointestinal tract, respiratory system, urinary bladder and exocrine glands. Nicotinic sites are found in neuromuscular junction, ganglia and a few discrete parts of central nervous system.

Effects Produced at Muscarinic Sites

1. **Central nervous system**: The muscarinic activation in central nervous system generally leads to nonspecific stimulation followed by depression.
2. **Eye**: Miosis—pinpoint pupil, contraction of ciliaris muscle, reduction of intra-ocular pressure, increased lacrimation, dilatation of local blood vessels and spasm of accommodation (far and near vision becomes identical)
3. **Heart**: Negative chronotropic, inotropic and dromotropic action, cardiac depression and bradycardia.
4. **Blood vessels**: Acetylcholine is a vasodilator. It relaxes the smooth muscle of vasculature. Acetylcholine releases nitric oxide from the endothelium. In the absence of endothelium acetylcholine causes vasoconstriction.
5. **Gastrointestinal tract**: Motility and secretion increases and relaxation of sphincters
6. **Respiratory system**: Bronchoconstriction, increased secretions and precipitation of an attack of asthma.
7. **Urinary bladder**: Acetylcholine contracts detrusor and relaxes trigone and sphincters: promote micturition by increasing voluntary voiding pressure.
8. **Exocrine glands**: All exocrine glandular secretions are augmented by acetylcholine. Increases lacrimation, salivation and mucous glandular activities.

Effects Produced at Nicotinic Sites

Acetylcholine activates Na⁺ channel-linked nicotinic receptor at neuromuscular junction. Skeletal muscle tone is increased and produces contraction. Acetylcholine-induced stimulation of ganglia is due to nicotinic receptor activation.

CHOLINERGIC DRUGS

(Cholinomimetics, parasympathetics, parasympathomimetics, acetylcholine-like drugs)

Cholinergic or cholinomimetic agents are those that produce actions similar to that of manifestations of stimulation of parasympathetic nerves. These are mainly divided into two groups:

1. **Direct Receptor Agonists**:
   - **Esters of choline**: Acetylcholine, betahanechol (urecholine), carbachol, succinylcholine
   - **Alkaloids**: Pilocarpine, muscarine, arecoline, nicotine
   - **Other synthetic drugs**: Oxotremorine, futrathonium, phenyltrimethylamine (PTMA), dimethylphenylpiperazinium (DMPP)
   - **Central cholinomimetic agents**: Tacrine, rivastigmine

2. **Indirect cholinomimetics**: Anticholinesterase agents
ESTERS OF CHOLINE

Bethanechol (Urecholine)
Bethanechol is a cholinomimetic drug usually given as drug of choice in the management of urinary retention of different etiology. It is administered by mouth as well as subcutaneous injection. Urecholine is also useful in conditions like post-operative abdominal distension, gastric atony and postpartum urinary retention. In chronic hypotonic, myogenic and neurogenic bladder, bethanechol is useful. A sensation of high toneness of urinary bladder is observed on bethanechol therapy as a side effect.

Carbachol
Carbachol is an ester of choline, now rarely used. This is a long-acting cholinergic drug which acts on both muscarinic and nicotinic receptors. Carbachol can be used as miotic in glaucoma as a substitute for pilocarpine if the subjects are resistant to latter. During or after cataract surgery, carbachol is occasionally used.

Esters of choline can produce flushing, sweating, hypotension, belching, difficulty in visual accommodation, headache and salivation as their side effects.

Esters of choline are contraindicated in bronchial asthma, hyperthyroidism, coronary insufficiency and peptic ulcer.

CHOLINOMIMETIC ALKALOIDS
Pilocarpine, muscarine, arecoline, nicotine and physostigmine (an anticholinesterase).

Pilocarpine
Pilocarpine is an alkaloid obtained from the leaves of Pilocarpus microphyllus or jaborandi. It is a miotic (0.5-4% solution) and diaphoretic (promotes sweating). Generally, pilocarpine ophthalmic solution is used in the management of glaucoma. A special drug delivery system of pilocarpine as ocusert is available. Insertion of pilocarpine ocusert in the angle of eye releases the drug slowly and acts up to 7 days. This avoids frequent instillation into the conjunctival sac. In glaucoma, pilocarpine is used along with physostigmine and vasoconstrictors as well as β-blockers, for example, timolol. Pilocarpine can also be used to antagonize mydriasis produced by atropine-like antimuscarinic drugs. In conditions of inflammation of iris, pilocarpine instillation into the eye prevents adhesions between iris and lens.

Pilocarpine long-term use for ophthalmologic purposes can produce local as well as systemic adverse effects. Browache, ocular pain, headache and salivation have been reported. Prolonged use of pilocarpine is known to exacerbate Alzheimer’s disease. However, this requires more confirmatory and convincing evidence.

Mushroom Poisoning
Since centuries, mushroom poisoning is known to man. Various species of mushrooms produce poisoning conditions, which differ in toxin content, clinical features and mode of treatment.
offered. Hence, the severity and strategies of treatment depend on the species of mushroom ingested.

The poisoning due to *Amanita muscaria*, inocybe and clitocybe species, which contain muscarine is easy to treat. These species produce salivation, nausea, vomiting, lacrimation, colic, diarrhoea, bronchospasm, bradycardia, hypotension and shock. The specific antidote for this type of mushroom poisoning is atropine 1-2 mg intramuscularly every 30 minutes with other supportive measures.

Some species of mushrooms like *Amanita phalloides* produce neurotoxicities due to presence of amatoxin and α and β amantin. These toxins inhibit RNA polymerase II. Toxicities caused by *Amanita phalloides* and *Galerina* are of serious nature and there is no antidote. However, thiotic acid is being tried as antidote but in vain.

**ANTICHOLINESTERASE AGENTS**

Drugs that inhibit cholinesterase enzyme are indirect cholinomimetic agents. Anticholinesterases are important from both therapeutic and toxicological significance. Chemical warfare employs anticholinesterase agents and majority of insecticides and herbicides belong to this class.

Cholinesterase hydrolyses acetylcholine at a rapid pace into choline and acetyl moieties. Mainly, two types of cholinesterase have been described: true cholinesterase and pseudocholinesterase. True cholinesterase is present at all sites where acetylcholine acts as neurotransmitter. Pseudocholinesterase is present predominantly in liver and plasma. The inhibition of true cholinesterase leads to functional impairment of parasympathetic nervous system.

**Classification of Anticholinesterase Agents**

Anticholinesterase agents are classified based on their mechanism of action into two major groups:

1. **Reversible anticholinesterases**: Based on source, they subdivided into two subtypes:
   a. Natural: Physostigmine—an alkaloid obtained from *Physostigma venenosum*
   b. Synthetic drugs carbamates:
      i. Short acting—edrophonium
      ii. Intermediate acting—neostigmine
      iii. Long acting—pyridostigmine, ambenonium

2. **Irreversible anticholinesterases**: Example: organophosphorus compounds (3 subgroups)
   a. Therapeutically used:
      i. diisopropylfluorophosphate (DFP)
      ii. echothiophate
      iii. malathion (0.5%) (as anti-lice in shampoo)
   b. War or nerve gases:
      i. soman
      ii. tabun
      iii. sarin
c. Insecticides and pesticides:
   i. diazinon
   ii. parathion
   iii. malathion
   iv. carbaril


**Mechanism of Action**

Anticholinesterases inhibit true cholinesterase and arrest the metabolism of acetylcholine. Thus, augment all the actions of acetylcholine at muscarinic and nicotinic sites. The enzyme cholinesterase has 3 distinct domains for the binding of inhibitory agents.

a. An acyl pocket \(\rightarrow\) these active sites constitute esteratic sites
b. Choline subsite
C. Anionic site

**Reversible inhibition:** edrophonium acts at anionic site only

**Irreversible inhibition:** enzyme-substrate complex

Organophosphorus compounds inhibit enzyme non-competitively, after the formation of enzyme-substrate complex, it undergoes "aging". Aging is a process in which one of the oxygen-phosphate bonds of the inhibited enzyme removes an alkyl group. Thus, the drug-enzyme complex becomes more stable and cannot be split. Aging of phosphorylated enzyme occurs within 6-7 hours after the formation of enzyme-substrate complex. The process of aging has clinical relevance. After aging process, the enzyme cholinesterase cannot be reactivated or freed from the inhibitor, by drugs like pralidoxime. It is pertinent that in organophosphorus poisoning the enzyme reactivator pralidoxime needs to be given before aging process occurs.
**Actions of Anticholinesterase Drugs**

Anticholinesterase agents enhance the actions of acetylcholine at all cholinergic sites. The main actions of therapeutic importance are the following.

**Actions on Eye**

Local instillation of anticholinesterase agents cause miosis, contraction of ciliaris muscle and reduces intra-ocular pressure by facilitating the outflow of aqueous humor.

**Actions on Gastrointestinal Tract**

Neostigmine-like drugs increase acid secretion, peristalsis and motility of the colon. The propulsive movement of intestine is augmented by anticholinesterase agents.

**Exocrine Glands**

All the exocrine secretions are augmented following the administration of anticholinesterase agents. Sweating, salivation, lacrimation, bronchial and mucosal secretions, pancreatic and intestinal secretions are increased by anticholinesterases.

**Neuromuscular Junction**

Due to inhibition of metabolism, acetylcholine action on motor end plate does increase. In addition, edrophonium, neostigmine and pyridostigmine have direct action on nicotinic receptors. These agents have decurarizing effects.

Other actions of anticholinesterase drugs are complex. Bradycardia and hypotension at high doses are common. Generally, blood vessels are dilated by anticholinesterases.

**Pharmacokinetics**

Quaternary ammonium anticholinesterases like neostigmine, pyridostigmine and edrophonium are poorly absorbed from the gastrointestinal tract. The oral doses of these drugs are comparatively higher than parenteral dose. Local/surface penetration is poor, whereas organophosphorus compounds being highly lipid soluble are absorbed readily across the skin. This could contribute for toxicity seen as occupational hazards in farmers who are exposed to herbicides and pesticides regularly. Edrophonium is generally administered by intravenous route. Physostigmine being a tertiary amine crosses blood-brain barrier and produces central cholinergic actions. Therefore, it is not preferred in myasthenia gravis. Many anticholinesterase agents cross placental barrier and small amounts are distributed into breast milk.

**Therapeutic Uses**

Anticholinesterases are indicated in many clinical conditions that include:

1. Atony of smooth muscles of intestine and urinary tract
2. Glaucoma
3. Myasthenia gravis
4. Alzheimer’s disease
5. Paralytic ileus.
ORGANOPHOSPHORUS POISONING

Herbicide, insecticide and pesticide poisoning is common. Attempt at suicide and accidental overdosages have been the major causes for organophosphorus poisoning.

Abdominal cramps, diarrhoea, excessive copious exocrine secretions—salivation, lacrimation, sweating and enhanced mucosal secretions, pinpoint pupil, hyperperistalsis, wheezing, bladder incontinence, skeletal muscle weakness, convulsions and respiratory arrest are the major clinical features of anticholinesterase poisoning.

Treatment

Drugs

Atropine is given as specific antidote by intravenous route. The dose of atropine is repeated at every 10-20 minute time intervals and continued till the symptoms of atropinization appear.

Pralidoxime, a cholinesterase reactivator, is also given intravenously before the expiry of 8 hours after the exposure to organophosphorus compounds. Pralidoxime is to be administered before “aging” occurs. Pralidoxime “dephosphorylates” the enzyme-drug complex and thus makes cholinesterase enzyme free.

Emergency Supportive Measures

i. Maintain patent airway: Assist ventilation
   ii. Oxygenation
   iii. Suction the excessive secretions from the airway
   iv. Gastric lavage
   v. Wash the skin repeatedly with soap
   vi. Remove contaminated clothing
   vii. Administer activated charcoal

Drug Interaction

1. Neostigmine + atropine: Given in combination in myasthenia gravis and curare poisoning. Atropine blocks the unwanted muscarinic actions of neostigmine and facilitates the action on nicotinic receptor.
2. The duration of action of ester local anesthetics is prolonged by reversible anticholinesterase agents by competing for enzymatic metabolic pathways.
3. Neostigmine prolongs the motor end plate blockade produced by succinylcholine.

Contraindications

Anticholinesterases are not to be administered in:
1. Intestinal and urinary obstruction
2. Bronchial asthma
3. Parkinsonism
4. Abdominal cramps.
DRUGS USED IN GLAUCOMA

Glaucoma is a complex disease characterized by high persistent increase in intraocular pressure. If left untreated, damage to optic disc, optic nerve and retina can occur. This leads to irreversible blindness. Glaucoma may be primary or secondary or congenital in its origin, primary glaucoma is further classified into narrow angle and wide angle glaucoma based on the configuration of the angle of anterior chamber of the eye.

Drug therapy for glaucoma aims at reducing intraocular pressure. This can be achieved by either decreasing the formation of aqueous humour or enhancing the outflow of aqueous humour or both. Drugs used in glaucoma are as follows:

1. Miotics: Pilocarpine, physostigmine
2. Vasoconstrictors: Adrenaline, dipivefrine
3. Carbonic anhydrase inhibitors: Acetazolamide, dorzolamide, diclorphenamide
4. \( \beta \)-adrenergic receptor blockers: Timolol, levobunolol, betaxolol
5. Osmotic agents: Glycerin, mannitol
6. Latanoprost, apraclonidine

Drugs employed for glaucoma are preferentially administered locally by conjunctival instillation. Miotics instillation enhances the outflow of aqueous humour. Vasoconstrictors act by reducing the formation of aqueous humour. The exact mechanism by which \( \beta \)-blockers reduce intraocular pressure is not known. However, timolol is known to act by dual mechanisms—enhance the outflow and reduce the formation of aqueous humour. The inhibition of carbonic anhydrase enzyme by acetazolamide results in decreased aqueous humour synthesis. Frequent, local instillation of miotics in glaucoma can cause headache, blurred vision, brow pain and congestive iritis. There is a growing concern about the development of specific type of cataract following chronic use of miotics eye drops in glaucoma patients. Early diagnosis and effective prompt treatment are mandatory to save vision in glaucoma. Alternatively, laser trabeculoplasty and iridotomy are also indicated for acute glaucoma, which offers permanent cure.

DRUG THERAPY FOR MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disease, which occurs at all ages. Fatigability, diplopia, ptosis, difficulty in swallowing and increased muscle weakness on activity are the major clinical features of myasthenia gravis. Antinicotinic receptor antibodies have been found in patients of myasthenia gravis. At the motor end plate, decreased number of nicotinic receptors fails to maintain the muscular tone and activity. Receptor-labeling study has revealed that the number of receptors present at neuromuscular junction is only about one-third of the normal in patients with myasthenia gravis. Besides drug therapy, thymectomy and plasmapheresis have been recommended for the management of myasthenia gravis.

Drugs, which are of established clinical value in myasthenia gravis, are:

1. Anticholinesterase agents: Pyridostigmine, edrophonium, neostigmine
2. Immunosuppressants: Cyclosporin, azathioprine, glucocorticoids—prednisolone
3. Monoclonal antibodies and immunoglobulins

It is common to encounter many problems during the management of myasthenia gravis. Particularly, administration of anticholinesterase agents must operate at the optimum dose.
levels. Any minor variation in the individualized anticholinesterase dose administration may result in either cholinergic crisis or myasthenic crisis.

Cholinergic crisis is due to excessive dose of anticholinesterase drug characterized by weakness. Myasthenic crisis is seen with insufficient doses of anticholinesterase, the symptoms of which overlap with cholinergic crisis. To distinguish these crises, edrophonium test is suggested. Edrophonium 2 mg is given intravenously with 0.4-0.6 mg of atropine. If this is not accompanied with lingual fasciculation and the myasthenic condition improves within 45 seconds, they suggest that anticholinesterase dose was inadequate.

CHOLINERGIC RECEPTOR ANTAGONISTS
(Anticholinergics, Muscarinic Receptor Antagonists, Atropine-like Drugs)

Antimuscarinic Drugs
Drugs that block muscarinic receptors competitively are known as antimuscarinic agents. At times, these are referred to as atropinic or atropine-like drugs. Atropine and related drugs have been extensively used in many clinical conditions. Therapeutically used antimuscarinic drugs are classified as:
1. Mydriatics: Tropicamide, cyclopentolate, homatropine, eucotropine
2. Antispasmodics: Atropine methyl nitrate, flavoxate, propantheline, methantheline, oxybutynin, oxyphenonium, dicyclomine (directly acting smooth muscle relaxant)
3. Antiparkinsonian: Benzhexol, benztropine
4. Antisecretory: Atropine sulphate, scopolamine, glycopyrrolate
5. Antiasthmatics: Ipratropium, oxitropium, tiotropium

Mechanism of Action
Atropine-like drugs block the actions of acetylcholine at muscarinic receptors by competitive antagonism. Further, based on selective blockade actions on different types of muscarinic receptors, antimuscarinic drugs are subdivided into:
1. Selective M₁ blockers: Pirenzepine, telenzepine
2. M₁ + M₂ blockers: Atropinic drugs
3. M₂ selective blockers: Methoctramine
4. M₃ selective: Hexahydrosiladifenidol
5. M₄ selective: Himbucine

Though various selective muscarinic receptor-blocking drugs have been synthesized and studied, their clinical efficacy remains uncertain.

It is clear that atropine-like drugs block muscarinic actions of acetylcholine for which atropinic agents are clinically used. Atropine is an alkaloid obtained from Atropa belladonna. Scopolamine is also an alkaloid isolated from the plants Scopolia carniolica and Hyoscyamus niger. Datura stramonium is another plant that yields mainly hyoscine (scopolamine).

Action on Central Nervous System
Antimuscarinic drugs produce antiparkinsonian and antimotion sickness effects on central nervous system. Atropine as such does not cross the blood-brain barrier. However, at toxic dose levels cause delirium, depression, coma and medullary paralysis causing death.
Importantly, atropine derivatives like benzhexol and benztropine have been indicated in drug-induced as well as idiopathic parkinsonism. Here, centrally acting antimuscarinic agents reduce the cholinergic overactivity in basal ganglia. Antimuscarinic-antiparkinsonian drugs, however, have limited value in the management of overt idiopathic parkinsonism. Motion sickness or travel sickness is best prevented since cure is not attainable by drug therapy. Scopolamine is selectively indicated to control motion sickness. Scopolamine transdermal patch is applied behind the external ear 7 to 14 hours before undertaking journey. This drug can also be given orally for seasickness.

**Actions on Eye**

Atropine group of drugs produce mydriasis, cycloplegia, photophobia, increase intraocular pressure and dryness of eye—xerophthalmia. All these actions can be promptly reversed by an anticholinesterase.

Antimuscarinic drugs are passive mydriatics—increase the size of the pupil by blocking the muscarinic receptors of constrictor papillae. Drugs that dilate pupil and paralyse accommodation (cycloplegia) are used extensively by ophthalmologists to examine the eye. Atropine-like drugs produce cycloplegia by causing paralysis of ciliary muscles. The duration of cycloplegia and mydriasis produced by antimuscarinic drugs vary. For atropine, it lasts for 7 to 10 days, homatropine for 3 days, whereas tropicamide has the shortest duration of action. Hence, for regular examination of eye, tropicamide is commonly preferred. Atropine may be used in pediatric patients as resistance is seen to the action of homatropine and others in children.

Antimuscarinic drugs increase intraocular pressure and, therefore, contraindicated in acute angle glaucoma.

**Actions on Gastrointestinal Tract**

Drugs that block muscarinic receptors relax smooth muscles of alimentary tract—antispasmodics. They may thus relieve intestinal spasm and provide relief from spasmodic pain. Since atropine-like drugs are smooth muscle relaxants, they reduce motility of the intestine, useful in hypermotility disorders including irritable bowel syndrome. Other action of atropine on gastrointestinal tract is described as “antisecretory”, inhibits salivation, decreases acid secretion in the stomach. At higher doses, swallowing and talking become difficult.

**Actions on Cardiovascular System**

Atropine reduces the vagal control over the heart and produces tachycardia, therefore, it is useful in the control of different types of bradyarrhythmias. At higher doses, atropinic drugs induce ‘atropine flush’ due to cutaneous vasodilatation. Palpitation is one of the major toxic manifestations of atropinic agents.

**Other Actions**

Atropine arrests the secretion of nose, mouth, pharynx and bronchi. It relaxes the bronchial smooth muscle and reduces laryngospasm caused by general anaesthetics. Dry mouth is one of the common side effects caused by atropine therapy. All exocrine gland secretions
are blocked by antimuscarinic agents except milk. Systemic administration of antimuscarinic drugs may cause urinary retention.

At toxic doses, the skin becomes hot and dry which is described as ‘atropine fever’.

**Routes of Administration**

Atropine-like drugs are generally administered by mouth. These are also given by subcutaneous, intramuscular and intravenous routes. Ipratropium is given by inhalation in bronchial asthma, scopolamine as transdermal patch for motion sickness. For pre-anaesthetic medication, atropine is invariably administered by intramuscular route at least 90 minutes prior to anaesthetic administration.

**Therapeutic Uses**

Antimuscarinic drugs have a wide range of therapeutic uses:

1. **Ophthalmic uses:**
   a. for testing errors of refraction
   b. in the examination of retina and fundus
   c. to break adhesions in iritis and iridocyclitis
   d. choroiditis

2. **Gastrointestinal uses:**
   a. **Peptic ulcer:** Atropine is given with antacids to increase the total acid neutralizing effect since it prolongs the gastric emptying time.
   b. **Diarrhoea:** To reduce the intestinal motility, atropinic drugs are indicated.
   
   Intestinal colicky pain is effectively relieved by antispasmodic antimuscarinics.

3. **Pre-anaesthetic medication:** To reduce the secretion of exocrine glands and the intestinal motility, atropine is used as pre-anaesthetic medicament.

4. **Respiratory conditions:** Ipratropium is useful in relieving bronchoconstriction in bronchitis and emphysema.

5. **Parkinsonism:** Central antimuscarinic drugs, for example, benzhexol is of clinical value in drug-induced parkinsonism in particular.

6. **Drug poisoning:** Atropine is a specific antidote in organophosphorus poisoning as well as rapid type of mushroom poisoning.

**Acute Atropine (belladonna) Poisoning**

Acute antimuscarinic drug poisoning may be the result of accidental overdoses or deliberate attempt at suicide. Children are especially susceptible to atropine toxicity.

Delirium, toxic psychosis, dry mouth, palpitation, mydriasis, hot and dry skin, flushing, hyperpyrexia, anxiety, urgency but difficulty in micturition, cerebral depression and coma are the major signs and symptoms of acute belladonna poisoning.

The treatment of acute atropine poisoning is purely based on symptoms including lifeline supportive modalities.

Intravenous diazepam is necessary to reduce excitement. Artificial respiration, alcohol sponging, gastric lavage and activated charcoal administration have been successfully employed for belladonna poisoning. Oral neostigmine is often recommended. At the same time, intravenous physostigmine administration is not advocated in current practice. Indeed!
in the past, physostigmine was used, as antidote for atropine poisoning generally not recommended now.

**Contraindications**

Antimuscarinic drugs are not to be used/to be used with caution in the following conditions:
1. Prostatic hypertrophy
2. Narrow angle glaucoma
3. Pyloric stenosis
4. Paralytic ileus
5. Oesophageal adhesions
6. Ulcerative colitis
INTRODUCTION
Among many drugs used as adjuvant with general anaesthetics, skeletal muscle relaxants stand first, particularly, to aid intubation. To achieve adequate skeletal muscle relaxation during surgery, skeletal muscle relaxants are extensively employed. A clear understanding of the nature of action, mechanisms, efficacy and adverse effects of drugs that cause muscle relaxation is necessary for physiotherapist. This would pave the way to design exercise programme for subjects who have received skeletal muscle relaxants.

CLASSIFICATION
Currently used skeletal muscle relaxants are classified based on their site of action and/or mechanism of action into the following groups.

Central Skeletal Muscle Relaxants
Diazepam, afloqualone, chlorzoxazone, baclofen, methocarbamol, mephenesin.

Peripheral Skeletal Muscle Relaxants (neuromuscular blockers)
Competitive antagonists
Pancuronium, atracurium, vecuronium, mivacurium, gallamine, d-tubocurarine
Depolarizing blockers
Succinylcholine, decamethonium
Acetylcholine release inhibitor
Botulinum-A toxin

Direct Skeletal Muscle Relaxant
Dantrolene

PERIPHERAL SKELETAL MUSCLE RELAXANTS
(Neuromuscular Junction Blockers, Curare-like Drugs)
Peripheral skeletal muscle relaxants that act by competitive antagonism with acetylcholine at nicotinic receptors are often referred to as ‘myoneural blockers’ or non-depolarizing neuromuscular junction blockers. The first drug to be used as competitive antagonist of acetylcholine at neuromuscular junction was an alkaloid obtained from Chondrodendron tomentosum called d-tubocurarine. Curare is an extract of this plant, which was employed as arrow poison by Red-Indian tribes. Modern medicine now rarely employs d-tubocurarine as skeletal muscle relaxant. Recently, many drugs have been introduced as non-depolarizing...
neuromuscular blockers such as pancuronium, atracurium, alcuronium, vecuronium, rocuronium, doxacurium and mivacurium.

Non-depolarizing neuromuscular blockers compete with acetylcholine for nicotinic receptors at motor end plate. This antagonism can be opposed by increasing acetylcholine concentration at the receptor level by giving an anticholinesterase agent such as neostigmine.

Drugs like pancuronium and atracurium are now being used as skeletal muscle relaxants. These drugs offer more advantages over d-tubocurarine. Pancuronium is more potent, long acting, does not liberate histamine and has no action on ganglia. The duration of action, degree of muscle relaxation, produced by competitive antagonist skeletal muscle relaxants is altered by dehydration, body temperature, hypocalcemia and excess magnesium.

All peripheral skeletal muscle relaxants are administered by intravenous infusion. Rapid intravenous administration may produce haemodynamic changes including hypotension. Not all non-depolarizing skeletal muscle relaxants liberate histamine, which may produce hypotension and headache. Histamine-induced adverse effects can be readily addressed by antihistaminic pre-medication.

Acute curare poisoning is characterized by prolonged apnoea, hypotension, cardiovascular and respiratory failure with hyperkalemia. The specific antidote for curare poisoning is edrophonium or neostigmine given with atropine, which blocks the muscarinic response of the anticholinesterase. Further, vasoconstrictors and H₁ receptor blockers have been used to overcome histamine action.

**Drug Interactions**

1. General anaesthetics like isoflurane, enflurane and ether potentiate the actions of pancuronium-like drugs.
2. Antibiotics like aminoglycoside antibiotics act synergistically with curare-like drugs and there may be danger of diaphragmatic paralysis.
3. Quinidine, local anaesthetics, tetracyclines and calcium channel blockers potentiate the effects of pancuronium-like drugs.
4. Anticholinesterase drugs antagonize the actions of curare-like agents at motor end plate.

**DEPOLARIZING NEUROMUSCULAR JUNCTION BLOCKER—SUCCINYLCHOLINE**

Succinylcholine (suxamethonium) is an ester of choline consisting of two molecules of acetylcholine. Following intravenous administration relaxes the skeletal muscles rapidly within minutes for a brief period of 5 to 10 minutes. To provide muscle relaxation continuously, succinylcholine is infused perisurgically on constant medical supervision.

**Mechanism of Action**

Succinylcholine is a depolarizing neuromuscular junction blocker. The effects of succinylcholine on motor end plate is described to have phase I and phase II blockade.

Phase I neuromuscular blockade is known as ‘depolarizing blockade’ during which the motor end plate is unresponsive to additional stimuli. This is often referred to as physiological block, which causes repetitive excitation of end plate resulting in muscle fasciculation before paralysis.

Phase II block is often called pharmacological blockade of motor end plate ‘desensitization’ blockade.
Adverse Effects
Excess administration of succinylcholine may cause bradycardia, hyperkalemia, muscle pain due to initial fasciculation, increased intraocular pressure and increased gastric pressure leading to aspiration of gastric contents. Hyperkalemia is generally seen in burn and renal failure patients.

Succinylcholine Apnoea
This is an idiosyncratic response to succinylcholine. Succinylcholine is rapidly metabolized by pseudocholinesterase enzyme present in plasma and liver. On account of succinylcholine action is terminated within 5 minutes. However, genetic variation is observed up to 20% in the rate of metabolism of succinylcholine. The presence of atypical pseudocholinesterase fails to metabolize succinylcholine at rapid pace. Thus, prolong the muscle paralysis, which culminates in apnoea. Administration of nitrous oxide with oxygen, transfusion of whole blood and ready sources of pseudocholinesterase preparation has been advocated to combat succinylcholine-induced apnoea.

Malignant Hyperthermia
The combination of succinylcholine and general anaesthetic halothane is known to produce malignant hyperthermia in some patients with a genetic predisposition. Hyperthermia, tachycardia and unstable blood pressure are the major clinical features of this syndrome. Drug treatment should be started as soon as possible after symptoms appear. Rapid intravenous administration of dantrolene with other supportive measures including withdrawal of anesthetic, correction of acidosis, oxygenation and cooling procedures are necessary to avert fatality in malignant hyperthermia.

Therapeutic Uses of Peripheral Skeletal Muscle Relaxants
1. As adjuvants in surgical anaesthesia: Short-acting drugs like succinylcholine and atracurium are widely used than long-acting pancuronium with general anaesthetics.
2. In intensive care where patients requiring mechanical ventilation skeletal muscle relaxants have been employed. Pancuronium is widely used because it has the tendency to increase arterial pressure and the muscle paralysis can be reversed with neostigmine.
3. To prevent trauma in electroshock therapy
4. Refractory convulsions
5. As diagnostic agents: In the detection of pain due to nerve root compression.

DIRECT SKELETAL MUSCLE RELAXANT—DANTROLENE
Dantrolene is a directly acting skeletal muscle relaxant. This drug probably acts by interfering with the release of calcium from the sarcoplasmic reticulum. Dantrolene is given by mouth and intravenously in malignant hyperthermia. Muscle spasticity is another indication for dantrolene. It is also used in neuroleptic malignant syndrome.

Adverse reactions produced by dantrolene are short-lived and often controlled by adjustment of dose. Drowsiness, dizziness, fatigue, muscle weakness and malaise have been reported with dantrolene therapy. Serious diarrhoea necessitates dantrolene withdrawal. Hepatotoxicity, pleural effusion, pericarditis, bleeding and unstable blood pressure are also observed dantrolene toxicities.
Dantrolene should not be used in hepatic diseases. Concurrent administration of dantrolene with calcium channel blockers produces severe myocardial depression. Therefore, dantrolene should not be used with calcium channel blockers.

CENTRAL SKELETAL MUSCLE RELAXANTS

Baclofen, chlorphenesin carbamate, mephenesin, methocarbamol, chlorzoxazone, diazepam

Drugs with central GABA mimetic effects and generally the agents that suppress mono- and polysynaptic pathways in spinal cord produce skeletal muscle relaxation. Principally, central skeletal muscle relaxants are used in painful muscle spasm or spasticity. Diazepam is useful to control neuromuscular manifestations of tetanus and besides reducing patient’s anxiety, produces sedation.

Baclofen

Baclofen is a central skeletal muscle relaxant. It acts mainly by inhibiting mono- and polysynaptic pathways in the spinal cord. Baclofen may act at supraspinal level to produce depression of the central nervous system. Baclofen is used for the symptomatic relief of spasticity of different etiology. Although oral administration of baclofen is common, it is also given by continuous intrathecal infusion in the treatment of spasticity.

The most common side effects of baclofen therapy are drowsiness, dizziness, confusion, fatigue and muscular pain. Overdosage may lead to respiratory depression, muscle dystonia, convulsions and coma.

Baclofen is contraindicated in peptic ulcer and epilepsy.

Botulinum-A Toxin

As the name suggests, botulinum is a neurotoxin produced by Clostridium botulinum. This is a neuromuscular blocker and acts by inhibiting calcium-mediated acetylcholine release at the motor end plate. The effect produced by botulinum-A toxin lasts for 3 to 4 months.

Botulinum toxin is used in several muscular disorders. Local injection of toxin is given in hemifacial spasm, blephoraspasm, spasmodic torticollis, lower limb spasticity and strabismus.

Locally administered botulinum toxin causes burning sensation, muscle weakness and paralysis. Other side effects produced by botulinum toxin are ptosis, lacrimation, reduction in blinking, paralysis of vocal cords, dysphagia and widespread muscle paralysis.

Botulinum toxin should not be given with aminoglycoside antibiotics, tetracyclines, lincosamides, polymyxins and neuromuscular blockers.

IMPLICATIONS TO PHYSIOTHERAPY

It is not possible to go for exercise programme on neuromuscular blocker therapy. The question remains when can exercise programme be prescribed? Soon after succinylcholine administration, exercise programme may cause muscle pain. Obviously, exercise may not be prescribed till the complete recovery is seen. Patients who have received a neuromuscular blocker need assisted respiration until the drug has been inactivated. Care is mandatory before giving an exercise prescription. Patients must be evaluated thoroughly to declare that they are fit for physiotherapy.
INTRODUCTION
Sympathetic nervous system is vitally involved in the homeostatic regulation of a wide variety of central and peripheral functions. This includes heart rate, force of cardiac contraction, vasomotor tone, blood pressure, airway tone, carbohydrate and fatty acid metabolism, psychomotor activity and appetite. Noradrenaline is the neurotransmitter of the adrenergic nervous system. Dopamine is also present in sympathetic nervous system and acts as neurotransmitter in central nervous system in particular. Each step involved in neurohumoral transmission represents as potential target for drug action.

SYNTHESIS OF ADRENERGIC NEUROTRANSMITTER
The synthesis of sympathetic neurotransmitter that occurs at the adrenergic nerve endings is as follows (Fig. 2.1). The major factor that controls the rate of synthesis of noradrenaline and adrenaline is the level of glucocorticoids in blood.

Storage
The synthesized neurotransmitter noradrenaline is stored at the adrenergic nerve terminals by three ways.
1. Mobile pool-I
2. Mobile pool-II
3. Reserve depot.
   The mobile pool-I constitutes cytoplasmic amount of noradrenaline. The mobile pool-II is present in the stored vesicles. Reserve depot of noradrenaline is found in the form of granules, constituted by ATP and chromogranins. Drugs like reserpine and α-methyldopa deplete the stored noradrenaline from the sites of storage and thus reduce the sympathetic control over effector organs.

Release
As a response to the wave of depolarization or any stimuli, the stored noradrenaline is released by exocytosis. Many drugs effect noradrenaline release. Ephedrine and tyramine...
enhance the release, whereas bretylium blocks the release of the neurotransmitter. Similarly, stimulation of presynaptic $\alpha_2$ receptors arrests the release and $\alpha_2$ receptor blockers (yohimbine) promotes the release of noradrenaline.

**Reuptake**

The major process by which the actions of released noradrenaline terminated is by reuptake mechanisms. The neuronal membrane actively reabsorbs a major part of released noradrenaline. There are two types of reuptake processes namely:

1. Neuronal uptake: reuptake-1
2. Non-neuronal uptake: reuptake-2

Drugs like cocaine and tricyclic antidepressants inhibit the reuptake of noradrenaline to produce indirect sympathomimetic effects. Glucocorticoids do block the non-neuronal reuptake of noradrenaline.

**Metabolism**

Monoamine oxidases present in neuronal mitochondria and catechol-o-methyl transferase in plasma catalyse the metabolic reactions of noradrenaline and other sympathomimetics. Dopamine turnover is mainly regulated by monoamine oxidase-B in the brain.

The chief metabolites of adrenaline and noradrenaline that appear in urine are vinyl mandelic acid, MHPG (3-methoxy-4-hydroxyphenylglycol) and phenylglycaldehyde, with
traces of metanephrine. The level of these metabolites would invariably provide an index of catecholamine turnover in the body. For example, in phaeochromocytoma (tumor of adrenal medulla) the urinary level of all these metabolites are elevated.

**ADRENERGIC RECEPTORS**

From the past six decades, adrenergic receptors have been classified mainly into two types—$\alpha$ (alpha) and $\beta$ (beta). Further, each type of adrenergic receptors has been subdivided into different categories based on agonist and antagonist actions of various drugs.

**Alpha-Adrenergic Receptors**

Alpha-adrenergic receptors are further subdivided into $\alpha_2$ and $\alpha_1$. $\alpha_2$ receptors are located at presynaptic in the periphery and postsynaptically in the central nervous system. The main function of $\alpha_2$ receptor appears to be the regulation of neurotransmitter release. Stimulation of presynaptic $\alpha_2$ receptors results in the inhibition of noradrenaline release at the adrenergic nerve terminal. Conversely, $\alpha_2$ receptor antagonist enhances the release of noradrenaline. Postsynaptic central $\alpha_2$ receptors regulate vasomotor tone. The stimulation of central $\alpha_2$ receptors results in fall in blood pressure. Besides, platelets, vascular smooth muscle and islets of Langerhans of pancreas are also endowed with $\alpha_2$ receptors.

$\alpha_1$ receptors are located in vascular smooth muscle, genitourinary tract, intestinal smooth muscle, heart, dilator pupillae and liver. Agonists of $\alpha_1$ receptor induce vasoconstriction and raise the blood pressure. As contrast to this, $\alpha_1$ stimulation relaxes intestinal smooth muscles, predominantly.

**Beta-adrenergic Receptors**

Three subtypes of beta-adrenergic receptors have been identified and their distribution and effects are as follows:

<table>
<thead>
<tr>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>$\beta_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart: increase rate and force of contraction</td>
<td>Relaxes the smooth muscle of Blood vessels&lt;br&gt;Genitourinary tract&lt;br&gt;Gastrointestinal tract&lt;br&gt;Skeletal muscle: tone regulation&lt;br&gt;Liver: metabolic effects</td>
<td>Adipose tissue: known to be involved in lipolysis</td>
</tr>
<tr>
<td>Juxta glomerular apparatus: increase renin level</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GENERAL ADRENERGIC ACTIONS**

Drugs acting on adrenergic receptors produce a wide variety of actions at different sites. Generally, this results in the following effects:

1. **Vasoconstriction**: $\alpha_1$ agonist action—blood vessels of skin and mucous membrane are very much sensitive.
2. **Vasodilator response**: Blood vessels of skeletal muscles are dilated following $\beta_2$ receptor stimulation and increases the blood supply.
3. **Bronchodilatation**: Adrenergic agents that act on $\beta_2$ receptor of bronchial smooth muscle produce bronchodilatation.
4. **Cardiac stimulation:** Sympathetic drugs that act on cardiac β₁ receptor produce positive chronotropic, inotropic and dromotropic actions.

5. **Metabolic actions:** Hyperglycemia secondary to increased glycogenolysis in liver and muscle, and also the release of free fatty acids from adipose tissue are the main action of sympathetic drugs on metabolism.

6. **Central actions:** Respiratory stimulation, reduction in appetite, psychostimulation and increased wakefulness have been described as effects of central sympathetic stimulation.

7. **Endocrine actions:** Adrenergic stimulation modulates the secretion of insulin, enhances the release of renin and to lesser extent pituitary hormones.

Further, sympathetic stimulation results in decreased gastrointestinal motility and immunomodulation. Pertinently, it must be recognised that all adrenergic drugs do not produce all the above actions to the same extent. This is understandably so, since different types of receptors are involved in eliciting sympathetic actions at different sites.

**CLASSIFICATION OF SYMPATHOMIMETICS**

A drug that produces actions similar to that of manifestations of sympathetic nerve stimulation is called “sympathomimetic” or adrenergic agent. Sympathomimetics are classified by three different ways based on their chemistry, mode of action and therapeutic uses.

**Chemical Classification (2 groups)**

1. **Catecholamines**
   - Noradrenaline
   - Adrenaline
   - Dopamine
   - Isoprenaline
   - Dobutamine
   - Isoetharine

2. **Non-catecholamines**
   - Ephedrine
   - Amphetamine
   - Mephentermine
   - Metaraminol
   - Phenylephrine
   - Xylometazoline

**Classification based on Mode of Action (3 groups)**

*Direct Receptor Agonists*

a. **α₂ agonists:** Clonidine, α-methyldopa
b. **α₁ agonists:** Phenylephrine, mephentermine, xylometazoline, oxymetazoline
c. **β₁ agonists:** Dobutamine (predominant)
d. **β₂ agonists:** Salbutamol, terbutaline, salmeterol
e. **Both α and β agonists:** Adrenaline
f. **β₁ + β₂ agonist:** Isoprenaline
Indirectly Acting Sympathomimetics

a. Reuptake inhibitors: Cocaine, tyramine, tricyclic antidepressants
b. Metabolism inhibitors: Monoamine oxidase inhibitors (MAOI), phenelzine, tranylcyromine, selegiline

Both Directly and Indirectly Acting Sympathomimetics
Ephedrine, Amphetamine.

Therapeutic Classification of Sympathomimetics

1. Vasoconstrictors—phenylephrine, mephentermine, midodrine
2. Vasodilators—isoprenaline, oxyfedrine, isoxsuprine
3. Nasal decongestants—xylometazoline, oxymetazoline, pseudophedrine, phenylephrine
4. Bronchodilators—salbutamol, terbutaline, salmeterol
5. Uterine relaxants—ritodrine, terbutaline, salbutamol, isoxsuprine
6. Anorexiants—fenfluuramine, d-amphetamine
7. Cardiac stimulants—noradrenaline, dopamine, isoprenaline, adrenaline, dobutamine
8. Mydriatics—phenylephrine, ephedrine
9. Antiallergic—adrenaline
10. Antihypertensive—clonidine
11. Psychostimulants—d-amphetamine, methamphetamine
12. Antiglaucoma agents—dipivefrine, phenylephrine, adrenaline

CATECHOLAMINES

Adrenaline
Adrenaline is the hormone of adrenal medulla. It is a catecholamine and acts on both α and β receptors. Nevertheless, the effects of adrenaline on β receptors are more persistent than α receptors. In addition, the effect of adrenaline on target organ is complex and dose dependent.

Pharmacodynamics
Adrenaline is a powerful cardiac stimulant, vasoconstrictor of cutaneous and mucosal blood vessels. It produces metabolic actions and antiallergic effects. Adrenaline increases blood pressure in general. However, it produces a characteristic biphasic response on blood pressure. It is also a bronchodilator, relaxant of smooth muscle of gastrointestinal tract and mydriatic.

Cardiac actions: Adrenaline is a direct powerful cardiac stimulant. It produces positive chronotropic, inotropic and dromotropic actions on the heart. It acts on the cardioexcitatory β, receptors. Adrenaline increases the cardiac work in relation to oxygen consumption of the heart. Oxygen consumption of the heart is increased by adrenaline. Consequent to cardiac stimulation produced by adrenaline, cardiac output increases substantially.

Vascular effects: The cutaneous, mucosal and renal blood vessels constrict on adrenaline administration. Blood vessels of skeletal muscles are dilated by adrenaline—a β₂ receptor response.
Adrenaline increases blood flow to skeletal muscles, liver, heart and cerebrum. At the same time, it reduces blood flow to skin and renal tissue.

**Action on blood pressure**: Both systolic and diastolic blood pressure increase on adrenaline administration. The rise in blood pressure is due to:
1. Vasoconstriction
2. Cardiac stimulation
3. Increased pre-capillary resistance.

Vasoconstriction is due to α receptor stimulation. Beta agonistic action on blood vessels decreases blood pressure and causes cardiac excitation, which increases cardiac output. Therefore, adrenaline produces a characteristic biphasic action of blood pressure of anaesthetized laboratory animals. At higher doses, adrenaline may cause cerebral hemorrhage and stroke.

**Metabolic actions**: Adrenaline increases blood glucose level and produces anti-insulin actions. It also increases free fatty acid release and stimulates triglyceride lipase activity.

**Other actions**: Adrenaline acts as a physiological antagonist of histamine. It produces mydriasis and reduces the intraocular pressure by decreasing the formation of aqueous humour. Adrenaline increases sweat secretion particularly in the axilla and palm of hands. On respiratory system adrenaline causes short-lasting apnoea. Adrenaline apnoea is due to its direct and transient reflex inhibition of the respiratory center.

**Pharmacokinetics**
Adrenaline is not effective by oral route. All catecholamines are destroyed in the gastrointestinal tract. Most commonly, adrenaline is given by subcutaneous injection. In emergency conditions like anaphylactic shock, adrenaline is given by intramuscular or intravenous route on monitoring vital parameters. Adrenaline metabolic reactions are catalysed by both monoamine oxidase and catechol-o-methyl transferase enzymes. Metabolites are excreted in urine.

**Therapeutic Uses**
Adrenaline is a life-saving drug in anaphylactic shock, especially caused by penicillin hypersensitivity. Dipivefrine, a prodrug preparation of adrenaline, is indicated in glaucoma. Adrenaline is co-administered with local anesthetic to prolong the action. Adrenaline is a useful topical hemostatic. Cardiac arrest is another indication for adrenaline.

**Contraindications**
Adrenaline administration is contraindicated in angina pectoris, congestive cardiac failure, hyperthyroidism, hypertension, subaortic hypertropic stenosis and emphysema.

**Adverse Reactions**
Most of the adverse reactions of adrenaline are due to excessive stimulation of adrenoceptors. Anxiety, restlessness, tachycardia, sweating, tremor, hyperglycemia, cerebral hemorrhage,
pulmonary edema and difficulty in micturition and ventricular fibrillation are the adrenaline adverse effects.

**Drug Interactions**
1. Adrenaline + lignocaine: Increases the duration of action of lignocaine.
2. Adrenaline + halothane: Cardiac arrhythmias may be seen since halothane sensitizes the myocardium to the excitatory actions of catecholamines.

**Noradrenaline**
Noradrenaline is the neurotransmitter of sympathetic nervous system. It is an endogenous catecholamine with predominant α agonistic action. Noradrenaline is also a cardiac stimulant. Being a vasoconstrictor, it causes rise in blood pressure and increases peripheral resistance, thus induces reflex bradycardia. Noradrenaline is now being used in cardiogenic shock although dopamine is preferred.

**Dopamine**
Dopamine is a catecholamine sympathomimetic drug with both direct and indirect effects. Dopamine acts as a neurotransmitter in central nervous system. It differs from adrenaline and noradrenaline in causing renal and mesenteric blood vessels dilatation and increasing urine output. Dopamine is also a myocardial stimulant. The inotropic action of dopamine is associated with lower incidence of cardiac arrhythmia unlike adrenaline and other sympathomimetic cardiotonic drugs. Dopamine is an inhibitor of prolactin release from the anterior pituitary.

Dopamine is always given by slow intravenous infusion. The plasma half-life of dopamine is 2 minutes. Dopamine is used in acute heart failure as occurs in cardiogenic shock and myocardial infarction. It is also a valuable drug in renal failure, cardiac surgery and in septic shock.

Dopamine should not be used in hyperthyroidism and ventricular fibrillation. Hypovolemia should be corrected before dopamine infusion.

**Dobutamine**
Dobutamine is a synthetic sympathomimetic with predominant action on β₁ adrenoceptor. It can also activate α and β receptors. Dobutamine is used in myocardial infarction superimposed with congestive cardiac failure. As an alternate to exercise in cardiac stress test, dobutamine is employed.

Tachycardia, hypertension, ectopic beats and chest pain are the principal adverse effects of dobutamine. Dobutamine is contraindicated in idiopathic hypertropic subaortic stenosis.

**NON-CATECHOLAMINES**
**Amphetamines**
- d-amphetamine
- Methamphetamine
- Hydroxyamphetamine
Amphetamines are non-catecholamine sympathomimetics, which differ in their pharmacodynamic actions and therapeutic uses.

Methamphetamine produces central actions predominantly. Hydroxyamphetamine produces actions that are seen selectively on peripheral tissues. d-amphetamine produces both peripheral and central actions. Both methamphetamine and d-amphetamine produce psychostimulant, anorexiant and euphoriant actions. These drugs have addiction liability because of their central actions. The nature of action of amphetamine on central nervous system depends upon dose and mental status of the individual. Amphetamine causes wakefulness, increases alertness, abounds self-confidence, speech becomes more eloquent and produces euphoria. Amphetamine deters fatigue. However, prolonged use induces mental depression. Methamphetamine and d-amphetamine inhibit feeding centre and decrease food intake. Thus, they act as appetite suppressant. Tolerance to central actions develops, which in turn depend on dose and duration of amphetamine administration. Amphetamine is known to produce psychic dependence.

Hydroxyamphetamine is a vasoconstrictor, which may be used along with local anaesthetic and in Horner’s syndrome. It does not have addiction liability.

**Adverse Reactions**

Nervousness, restlessness, irritability, talkativeness, dryness of mouth, anorexia, dizziness, tachycardia, altered libido and psychotic reactions are commonly observed as amphetamine-induced adverse effects.

**Uses**

1. Narcolepsy: To desist irresistible urge to sleep, d-amphetamine is used
2. Obesity
3. Hyperkinetic children: Attention deficit syndrome

**Anorexiants**

d-amphetamine, fenfluramine, phenylpropanolamine, phenmetrazine

Drugs that suppress appetite are anorexiants. These are generally prescribed as drugs for overeating or obesity. However, drug therapy alone for obesity may not be more useful. Recently, leptin analogs are commonly used for the control of obesity. Exercise, dietary restriction and drugs may help to reduce obesity. Sympathomimetic anorexiants are seldom used now.

**Vasoconstrictors**

Noradrenaline, metaraminol, ephedrine, mephentermine, phenylephrine, hydroxyamphetamine

Sympathomimetic vasoconstrictors have been used to elevate blood pressure in hypotensive state. In particular, spinal anesthetic-induced hypotension can be effectively controlled by vasoconstrictors. Vasoconstrictors are used in various shock conditions although controversial. To control hemorrhage and hypotension due to severe hemorrhage, vasoconstrictors are indicated.
Nasal decongestants

Local:  
- Xylometazoline  
- Oxymetazoline

Oral:  
- Pseudoephedrine  
- Phenylephrine

Nasal decongestants are α receptor agonist vasoconstrictors, used to relieve mucosal congestion in the nasal cavity. For allergic rhinitis, acute coryza, sinusitis and hay fever nasal decongestants may be used. Nasal decongestants decrease blood flow to engorged edematous mucosa and promote drainage of the sinuses. By relieving the stuffy feeling, these drugs improve nasal ventilation. Nasal decongestants should not be used on a chronic basis. Prolonged use of nasal decongestants may result in anoxemic tissue necrosis. Topical nasal decongestant invariably cause ‘after congestion’. This is the main disadvantage of vasoconstrictors used as nasal drops.

ALPHA-ADRENERGIC RECEPTOR BLOCKERS

Drugs block α adrenoceptors mainly by competitive antagonism. These drugs have different affinities with subtypes of α receptors. Hence, the classification of α blockers is based on their selective receptor antagonism.

Classification—Based on Receptor Subtype Blockade

1. Selective α₁ receptor blockers:  
   - Prazosin, terazosin, alfazosin, doxazosin, trimazosin, indoramin, tamsulosin
2. Selective α₂ receptor blocker:  
   - Yohimbine
3. Both α₁ and α₂ blockers:  
   - Phenoxybenzamine, phentolamine
4. Alpha and beta blockers:  
   - Labetalol, carvedilol

Pharmacodynamics

Alpha-blockers cause vasodilatation, reduce peripheral resistance, decrease blood pressure and provide relief from pain in benign prostatic hyperplasia. Miosis and nasal stuffiness are observed following alpha-blocker administration. Prazosin is by far commonly used drug for high blood pressure since it does not disturb renin, lipid and glucose levels on chronic administration. Further, prazosin-like drugs do not cause exacerbation of bronchial asthma and control the clinical features, benign prostatic hyperplasia as well. These are also more useful in hypertension and heart failure.

Prazosin is usually given by oral route and can be given intravenously.

Therapeutic Uses of α Blockers

Alpha-blockers are used in the following clinical conditions:

1. Hypertension
2. Peripheral vascular diseases (Raynaud’s syndrome or phenomenon)
3. Benign prostatic hyperplasia
4. Phaeochromocytoma
5. Heart failure
6. Cheese reaction
7. Scorpion sting
8. Muscle cramp

Adverse Reactions
Following the initial dose, postural hypotension and syncope have been observed as 'first
dose effect'. Especially prazosin causes severe syncope. This adverse effect can be avoided
by starting treatment with low dose given preferably at night. Many α blockers produce
dizziness, tachycardia, blurred vision, nausea, vomiting, urinary incontinence, hypotension,
impotence and priapism as their unwanted effects.

Drug Interactions
1. α Blockers + diuretics: Enhancement of hypotensive action
2. α Blockers + calcium channel blockers: Risk of first dose effect is more.

BETA-ADRENERGIC RECEPTOR BLOCKERS
Beta-adrenergic receptor blockers constitute a major group of drugs used in cardiovascular
diseases. These act by competitive antagonism at the receptor sites. Beta-blockers have
different affinities with subtypes of β-adrenoceptors: β₁ and β₂. Based on their relative receptor
selective blocking ability, β blockers are classified mainly into the following subgroups:
1. Selective β blockers
2. Non-selective β blockers
   Selective β blockers either block cardiac β₁ receptor or β₂ receptors at different sites.
1. Selective β blockers
   a. β₁ receptor blockers (cardioselective receptor blockers)
      Atenolol, metoprolol, betaxolol, esmolol, bisoprolol, acebutolol
   b. β₂ selective blocker
      Butoxamine (not therapeutically used)
2. Non-selective β blockers (blocks both β₁ and β₂ receptors)
   Propranolol, nadolol, sotalol, timolol
   It is important to recognize that selective receptor blockade activity of all β blockers
   is only relative and selectivity is lost at higher doses. Generally, β blockers produce different
   pharmacodynamic actions. These drugs differ in their potency in producing membrane-
stabilizing activity and initial intrinsic sympathomimetic effects. Some of the β blockers have
   α receptor blockade activity. Lipid solubility profile does vary among β blockers.

Propranolol
Propranolol is a widely used non-selective β blocker. It blocks both β₁ and β₂ adrenoceptors
by competitive antagonism.

Pharmacodynamics
Propranolol, by virtue of it, β receptor blockade effects produce the actions as mentioned
below.
Cardiac Depressant

Negative chronotropic, inotropic and dromotropic action by blocking cardiac excitatory $\beta_1$ receptor. It reduces heart rate, cardiac output and contractility. Propranolol decreases impulse conduction velocity in A-V node. It prolongs the refractory period of AV node. Beta-receptor blockers reduce oxygen requirement of myocardium. Propranolol reduces blood pressure. Thus, $\beta$ blockers have therapeutic value as antihypertensive, antianginal and anti-arrhythmic agents. In addition to this, $\beta$-blockers produce the following effects:

- $\beta_1$ receptor antagonistic action also results in reduction of plasma renin level.
- Inhibit catecholamine-induced hyperglycemia.
- Cause exacerbation of bronchial asthma by blocking $\beta_2$ receptors of bronchial smooth muscle.
- Mild to moderate local anesthetic action unrelated to $\beta$ receptor blockade.
- Increase very low density lipoproteins (VLDL) level and reduces high density lipoprotein (HDL) level. The pharmacological significance of this effect remains elusive.
- Intravenous administration of $\beta$ blockers do alter insulin level in plasma.

Pharmacokinetics

Usually, propranolol is given by mouth. Intravenous propranolol is indicated in life-threatening cardiac arrhythmias and metoprolol in myocardial infarction. Propranolol undergoes extensive first pass metabolism. It crosses blood-brain barrier, placenta and appears in milk. Plasma half-life of propranolol is 2 hours.

Therapeutic Uses

Propranolol is commonly used in all the major cardiovascular disorders which includes the following:

- Hypertension
- Angina pectoris
- Cardiac arrhythmias
- Myocardial infarction

As antihypertensive drug, propranolol is well accepted and cost effective. As an antianginal drug, propranolol reduces the attack frequency, increases exercise tolerance, reduces mortality rate and in acute myocardial infarction decreases infarct size. Re-infarction is also reduced by propranolol.

Other therapeutic uses of propranolol are:

- Subacute obstructive cardiomyopathy
- Phaeochromocytoma
- Hyperthyroidism—thyroxine causes up-regulation of $\beta_1$ receptors that results in palpitation. Propranolol effectively relieves palpitation.
- In neurological disorders like anxiety, migraine, acute panic syndrome and tremors propranolol is indicated. Propranolol is used as a prophylactic agent for migraine not during attack.
- To reduce portal vein pressure in cirrhosis of liver
- Glaucoma: Generally timolol, beventolol, and betaxolol are instilled into conjunctiva but not propranolol in the management of glaucoma.
Contraindications
Propranolol is contraindicated in:
• Congestive cardiac failure
• Heart block
• Mental depression
• Hypotension
• Bronchial asthma
• Hypothyroidism
• Vasospastic disorders
• Sinus bradycardia

Adverse Effects
Bradycardia, bronchospasm, heart failure, heart block, hypotension, mental depression, fatigue, nausea, vomiting, abdominal cramps and blurred vision have been observed with β blocker therapy as adverse effects. Abrupt withdrawal of β blocker may cause rebound angina pectoris, myocardial infarction, arrhythmia and death.

Drug Interactions
1. Propranolol + insulin: Great caution is required because propranolol masks the early signs of hypoglycemia and the patient may sink into hypoglycemic coma.
2. Propranolol + verapamil: This combination should be avoided since cardiac failure may be the unwanted outcome.
3. β blockers + non-steroidal anti-inflammatory drugs (NSAIDs): Attenuation of antihypertensive action of β blockers occurs.
4. β blockers + diuretics therapeutic synergy
   β blockers + ACE inhibitors as antihypertensives
   β blockers + angiotensin receptor antagonist
5. β blockers + nitrates: Being cardiac depressants, propranolol blunts reflex tachycardia caused by antianginal nitrates. Further, this combination therapy in chronic angina pectoris serves as basal prophylaxis regimen.

Some Basic Properties of Widely used β Blockers

<table>
<thead>
<tr>
<th>β blockers</th>
<th>Type of receptor blocked</th>
<th>Route of administration</th>
<th>Plasma half-life</th>
<th>Major indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>β₁ cardioselective</td>
<td>oral</td>
<td>7 hrs</td>
<td>• Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Angina pectoris</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Cardiac arrhythmias</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β₁</td>
<td>IV</td>
<td>10 min</td>
<td>• Supraventricular arrhythmias</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β₁</td>
<td>oral, IV</td>
<td>3-7 hrs</td>
<td>• Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Angina pectoris</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Migraine</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>β₁</td>
<td>oral, instillation into eye</td>
<td>16-20 hrs</td>
<td>• Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Glaucoma</td>
</tr>
<tr>
<td>Timolol</td>
<td>β₁ + β₂ non-selective</td>
<td>oral, instillation into eye</td>
<td>4 hrs</td>
<td>• Glaucoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Migraine</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>• Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Myocardial infarction</td>
</tr>
<tr>
<td>Sotalol</td>
<td>β₁ + β₂ K⁺ channel blocker</td>
<td>oral intravenous</td>
<td>10-20 hrs</td>
<td>• Cardiac arrhythmias</td>
</tr>
</tbody>
</table>
Labetalol, celiprolol, carvedilol, bucindolol

Drugs that block both alpha and beta adrenoceptors produce therapeutically significant antihypertensive effect with vasodilator action. Obviously, these drugs have been explored for their efficacy in heart failure.

**Labetalol**
Primarily, labetalol is a predominant $\beta$ blocker. However, it has alpha-receptor blocking action and thus reduces peripheral vascular resistance. Labetalol decreases blood pressure more readily than other $\beta$ blockers. It can be administered by oral as well as intravenous route. Labetalol is used in the management of hypertension. Intravenous administration of labetalol is recommended to treat hypertensive emergencies. Phaeochromocytoma is also another indication for labetalol. Tingling of scalp, nasal congestion, tremor and jaundice have been observed with labetalol therapy as adverse effects.

**Carvedilol**
Carvedilol is a both alpha- and beta-adrenoceptor blocker. At higher doses, it is known to block calcium channel. Most common route of administration of carvedilol is oral. Carvedilol is used in the management of hypertension, angina pectoris and heart failure. Beta-blockers are generally contraindicated in heart failure because of their cardiac depressant action. Yet, carvedilol since it causes vasodilatation, which is attributed to its alpha-receptor blocking activity, is used in heart failure. Nevertheless, these drugs are not used in the initial management of heart failure. But, these are considered for second stage management with other effective and prompt measures.

**IMPLICATION TO PHYSIOTHERAPY**
Adrenergic receptor antagonists in particular beta-blockers, improve exercise tolerance in ischemic cardiac disease patients. Care is necessary for beta-blocker administration in persons who suffer from exercise-induced asthma. Cardioselective beta-blockers may be preferred for these individuals. Adrenergic agonists may not affect exercise programme. However, increased heart rate after exercise may be more pronounced with cardiac stimulant adrenergic drugs. This may be seen as infrequent outcome; nevertheless, care has to be taken to avoid anxiety and fear in sensitive individual.
Drugs Acting on Haemopoietic System

ANTIANAEMIC DRUGS

Anaemia is a state associated with significant reduction in red blood cell mass and a corresponding decrease in oxygen-carrying capacity of the blood. There are many causes for anaemia. Excessive blood loss, excessive destruction of red blood cells, decreased red blood cell production, nutritional anaemia or combination of all these may account for anaemia. Anaemia may be due to chronic inflammatory disease, malignancy or drug induced. As with any other disease, a definite diagnosis is essential for the success of antianaemic drug treatment, which addresses the underlying cause.

Iron deficiency anaemia is a symptom and not a disease. Inadequate dietary iron intake and excessive blood loss are the common reasons for iron deficiency anaemia. The main clinical features of iron deficiency anaemia are: weakness, anorexia, pallor, breathlessness on exertion, angular stomatitis, brittle nails with hollow raised border—koilonychia, glossitis and dysphagia. Iron deficiency anaemia can be successfully treated with ‘haematinics’ given over a period for 3 to 6 months.

Haematinics: They are the agents used for the prevention and treatment of anaemia. These drugs promote erythropoiesis, for example, erythropoietin, iron salts, folic acid, cyanocobalamin, haemopoietic growth factors and trace elements like copper, manganese, cobalt with pyridoxine and riboflavin.
Iron Salts

Iron is an essential constituent of body, required for haemoglobin synthesis and oxidative processes. Iron is abundantly present in nature. It is present in all foodstuffs including rice. However, milk is a poor source of iron. Humans absorb only 10% of dietary iron at the rate of 1 mg/day in males and 1.4 to 2 mg/day in females. The absorption of iron may be increased in anaemia and pregnancy.

Iron absorption is by both passive and active processes. Duodenum absorbs iron rapidly in ferrous form. Oral absorption of iron is enhanced by ascorbic acid and reduced by antacids. Gastrointestinal diseases do alter the iron absorption. In the mucosal cell, iron is reoxidised to ferric form, which combines with apoferritin to give a protein complex called ferritin.

Ferritin releases iron in the circulation to a globulin known as transferrin, which carries iron to storage depots, like liver, spleen and bone marrow. The unabsorbed iron is excreted through intestine, bile, urine and in traces through sweat, hairs and nails.

Iron Preparations

Clinically used iron preparations are:

<table>
<thead>
<tr>
<th>Oral iron preparations</th>
<th>Parenteral iron dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulphate</td>
<td>dextran injection</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>Iron dextran injection</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>Iron sorbitol citric acid complex</td>
</tr>
<tr>
<td>Ferrous succinate</td>
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</tbody>
</table>

Ferrous sulphate is a commonly used oral iron preparation since it is cost effective. Usually, ferrous sulphate is given after food. Invariably, the success of iron therapy is seen within 10 weeks. However, the treatment is given up to 3-6 months to replenish the iron stores. Frequent side effect of iron therapy is constipation or diarrhoea. Discolouration of teeth also has been observed as adverse effects of iron salts. Prolonged high doses can cause haemosidrosis. Absorption of iron is impaired when given with tetracyclines or milk. Slow-releasing iron tablets have no advantages over ferrous sulphate. These preparations may release iron in the colon from which iron absorption is poor.

Acute Iron Poisoning in Children

Iron poisoning, even though rare, usually does not occur in adults. However, iron at 72 g level is toxic to children. Nausea, vomiting, abdominal pain, diarrhoea, metabolic acidosis, convulsions, coma, hepatic necrosis, jaundice, renal failure, pulmonary edema and cardiovascular collapse are the symptoms of acute iron poisoning.

Desferrioxamine (desferoxamine, deferoxamine) is the specific antidote for acute iron poisoning. Besides the antidote administration other supportive measures like blocking iron absorption, induction of emesis and gastric lavage have to be undertaken.
Parenteral Iron Therapy

It is always preferable to administer iron salts by oral route. Nevertheless, iron is given by intramuscular injection and very rarely by intravenous administration in the following conditions:
1. Genuine oral iron intolerance
2. For post-gastrectomy patient
3. Chronic bleeding
4. Severe anaemia
5. Chronic inflammatory diseases like ulcerative colitis
6. Crohn’s disease
7. Sprue
8. Celiac disease

Intramuscular iron administration is painful and may produce discoloration of skin at the site injection and local inflammatory changes are not uncommon.

Intravenous iron therapy is not free from complications. Headache, faintness, tachycardia, flushing, bronchospasm, and circulatory collapse have been reported. Anaphylaxis may also be seen. Therefore, with all the precautions, iron should be infused slowly.

Drugs used in Megaloblastic Anaemia

Megaloblastic anaemia, as the name suggests large and irregular-shaped red blood corpuscles are seen with oversized platelets and hypersegmented polymorphs. Patients with megaloblastic anaemia are more prone for haemorrhage and susceptible to infection. Megaloblastic anaemia is almost always due to folic acid and vitamin B₁₂ deficiency. Drugs like phenobarbitone, phenytoin, triamterene, methotrexate and metformin also induce megaloblastic anaemia. Reduced intake, decreased absorption and improper utilization of folic acid and vitamin B₁₂ are the major reasons for megaloblastic anaemia. A form of megaloblastic anaemia known as ‘pernicious anaemia’ is due to lack of gastric parietal cell intrinsic factor, which is necessary for the absorption of vitamin B₁₂. Pernicious anaemia is treated with lifelong parenteral administration of vitamin B₁₂. However, folic acid deficiency is the more common cause for megaloblastic anaemia.

Megaloblastic anaemia is managed with two drugs namely, folic acid and cyanocobalamin (vitamin B₁₂). Folic acid alone is never to be given in pernicious anaemia as it improves haematological picture and neurological complications may be masked which need to be addressed with vitamin B₁₂ administration.

Folic Acid

Folic acid is a member of vitamin B complex group. It is abundantly present in yeast, liver and green vegetables. Human requirement of folic acid is 50 μg/day, whereas dietary requirement is 400 μg/day. Folic acid and vitamin B₁₂ are critical for DNA synthesis. Man cannot synthesize folic acid and solely dependent on natural sources of folic acid. The active form of folic acid is tetrahydrofolate, also known as folicic acid or citrovorum factor. Folic acid is necessary for purine synthesis, conversion of homocysteine to methionine, serine to glycine and histidine metabolism.
Folic acid is used in nutritional megaloblastic anaemia and other types of megaloblastic anaemia. It is also used in some cases of agranulocytosis. Folinic acid is administered as antidote in overdose condition of folic acid antagonists like methotrexate.

*Cyanocobalamin (Vitamin B₁₂)*

Cyanocobalamin is a cobalt-containing component of vitamin B complex group. In man, vitamin B₁₂ is synthesized by the intestinal microflora but fails to reach metabolic pool. The reason is vitamin B₁₂ is not absorbed across colonic mucosa. Hence, man is dependent on exogenous sources of vitamin B₁₂. This includes shellfish, oysters, beef, liver, kidney, heart and nuts. Milk is a very poor source of vitamin B₁₂. Egg yolk and some kinds of cheese also have a moderate amount of cobalmins. Two active forms namely methylcobalamin and deoxycobalamin (adenosyl) are essential for cell growth. Vitamin B₁₂ deficiency is characterised by haemopoietic changes and neurological complications. Defective myelin synthesis, spinal cell death, parasthesias and megaloblastic anaemia are the hallmarks of vitamin B₁₂ deficiency.

Actual human requirement is 100 ng/day, whereas dietary requirement is 3-5 μg/day. Vegetarians are more prone for vitamin B₁₂ deficiency. Gastric parietal cell abnormality, achlorhydria and ileal mucosal damage have been known as reasons for vitamin B₁₂ malabsorption. Lack of intrinsic factor of Castle results in pernicious anaemia. Intrinsic factor of Castle from gastric parietal cell is essential for vitamin B₁₂ absorption. Therefore, in pernicious anaemia cyanocobalamin is given parenterally for life long.

Cyanocobalamin is given along with folic acid in megaloblastic anaemia. Hydroxycobalamin is useful in tobacco amblyopia.

**TOPICAL COAGULANTS**

*Haemostyptics*

Haemostyptics are the drugs that are employed to arrest bleeding. There are various measures to arrest bleeding. Local measures like applying pressure packs, haemostatic forceps, electrocautery and ligation have been in vogue. To avoid serious haemorrhage and for temporary haemostasis, vasoconstrictors like adrenaline and topical adrenochrome solution can be employed. Platelet plugs, microfibrillar collagen, methoxycellulose, thrombin spray, gelatin and fibrin foam are also useful to arrest bleeding. Astringents and styptics are commonly employed to stop bleeding. Styptics and astringents are interchangeable terms referring to different concentration of some drugs.

Most commonly used haemostyptics are tannic acid, the salts of zinc, silver, aluminium and iron. However, iron and aluminium salts produce irritation at the applied site. Haemostyptics advocated for use should not delay wound healing. These agents must be used briefly with copious irrigation and debridement. Otherwise, haemostyptics are known to retard healing of wound.

Botropase, a fractionated snake venom and ethamsylate are systemically administered haemostyptics. Botropase is believed to act directly on fibrinogen and enhance clot formation. The mechanism of action of ethamsylate is not known. However, ethamsylate stabilizes the capillary membrane to reduce bleeding. Antifibrinolytics like epsilon aminocaproic acid can also be supplemented to control bleeding.
Procoagulants
Procoagulants are the drugs, which promote coagulation. Plasma coagulation factors namely factor VIII, factor IX, fibrinogen, thrombin are regarded as procoagulants. The cryoprecipitate of various clotting factors are available and can be used to promote coagulation. It is well recognised that bleeding haemophilic patients require replacement of clotting factors to control haemorrhage. One of the major drawbacks of packed clotting factors is hepatitis. Vitamin K$_1$ is used as procoagulant, especially for warfarin overdosage.

Anticoagulants
Drugs that inhibit the formation of clot are known as anticoagulants. Mainly, these drugs interrupt coagulation cascade and fibrin deposition.

Therapeutically used anticoagulants are grouped into:
1. Natural, parenteral anticoagulants (effective both *in vivo* and *in vitro*)
   - Heparin and low molecular weight heparins, for example, enoxaparin, dalteparin, reviparin, nadroparin
2. Synthetic oral anticoagulants (effective only *in vivo*)
   a. Coumarin derivatives, for example, warfarin, nicoumalone
   b. Indandione derivatives, for example, phenindione, anisindione

The most commonly used anticoagulants are heparin, low molecular weight heparins and warfarin. Indandiones offer no advantages over warfarin. However, they show high frequency of toxicities.

Heparin as Anticoagulant
Heparin is an electronegative acidic glycosaminoglycan—a proteoglycan, abundantly present in the lungs of pig and cow. Human mast cells contain heparin with histamine. Heparin is always given by parenteral route and should not be given intramuscularly because it can cause hematoma at the injection site.

Mechanism of Action
Heparin acts as a ‘catalytic template’ for antithrombin III and thrombin binding. In presence of heparin the interaction between antithrombin III and plasmin increases by thousand folds. Consequently, thrombin is inhibited. Thus, conversion of fibrinogen into fibrin does not take place. Additionally, heparin inactivates factors like IIa, XIIa, Xla, Xa, IXa. Heparin acts immediately and the manifestation of anticoagulant action is seen quickly. The anticoagulant activity of heparin is monitored by activated partial thromboplastin time (aPTT) test.

Other Actions
Besides as anticoagulant, heparin delays wound healing except the healing of burn wounds. It has antiproliferative, anticomplement, antihistaminic and hypolipidemic actions as well.

Adverse Reactions and Antidote
Haemorrhage, acute thrombocytopenia, hypoaldosteronemia, osteoporosis, arthralgia and alopecia are the adverse reactions produced by heparin. Heparin overdosage can be promptly
Pharmacology for Physiotherapist

treated by protamine. Protamine is a strong base and electropositive molecule interacts with heparin strongly and inactivation is complete. Protamine is obtained from gonads and sperm of fishes belonging to the family of solominidae. One mg of protamine neutralises 100 IU of heparin.

**Low Molecular Weight Heparins (Heparinoids)**

Low molecular weight heparins are poor inhibitors of thrombin unlike heparin *per se*. These are long acting, less toxic, less thrombocytopenic and less antilipemic, and partial thromboplastin time is much sensitive to low molecular weight heparins.

**Warfarin**

Warfarin is an oral anticoagulant. It acts by antagonising vitamin K effects *in vivo*. Warfarin inhibits the vitamin K-dependent hepatic synthesis of clotting factors namely factors II, VII, IX and X and proteins C and S. Warfarin induces functional deficiency of vitamin K. Although oral anticoagulants act immediately and inhibit clotting factor synthesis, the effects of warfarin is seen only after 16-70 hours after administration.

![Fig. 3.1: Warfarin mechanism of action: vitamin K antagonism](image)

The observed latency period after oral anticoagulant therapy is due to the presence of preformed clotting factors in plasma. Unless the clotting factors reserve is not exhausted, warfarin action is not seen. Therefore, for immediate anticoagulant response, heparin is given and not warfarin. Once the patient is stabilized, oral anticoagulant therapy may be instituted.

Warfarin therapy is always defined in terms of an international normalised ratio (INR) to avoid haemorrhage. The INR is prothrombin time ratio (test/control) obtained using thromboplastin made from human brain rather than rabbit brain thromboplastin. If the INR>4, no surgery is performed until it is reduced to 3 (<4).
**Adverse Effects**

Bleeding, skin necrosis, urticaria and purple toe syndrome are commonly observed with warfarin administration. Warfarin is a teratogen and can cause neonatal haemorrhage. Therefore, warfarin should not be used in pregnancy. The selective antidote used in warfarin overdosage is vitamin K, preparation namely phytonadione.

**Drug Interactions with Warfarin**

Several drugs interact with warfarin. This list of drugs, which interact with warfarin, is ever increasing. Hence, the patient must report additional drug therapy to avoid hazardous drug interactions. The clinically significant warfarin drug interactions involve both pharmacokinetic and pharmacodynamic mechanisms as mentioned below:

1. Drugs that increase metabolism of warfarin and decrease the efficacy: Rifampicin, phenobarbitone, phenytoin, chronic alcoholism, oral contraceptives, griseofulvin, diuretics.
2. Drugs that decrease warfarin metabolism and increase the toxicity: Metronidazole, sulphonamides, cephalosporins, allopurinol, clofibrate.
3. Warfarin should not be used with aspirin. Both the drugs compete for plasma protein-binding sites. Aspirin is antithrombotic, hypoprothrombinemic and gastric irritant, hence, produces gastrointestinal haemorrhage. Warfarin augments aspirin-induced haemorrhage and aspirin potentiates the toxicities produced by anticoagulants. Therefore, aspirin and warfarin should not be used together, particularly in coronary thrombosis.

**Therapeutic Uses of Anticoagulants**

Anticoagulants are extensively used in thromboembolic disorders like venous thrombosis, pulmonary embolism, arterial thrombosis and cerebral embolism. Other uses of anticoagulants include myocardial infarction, atrial fibrillation, valvular heart diseases, prosthetic heart valves, cardiomyopathy and haemodialysis. Heparin is used in extracorporeal services, for example, to prevent clotting of blood while transferring a specimen of blood to the laboratory.

**Contraindications for Anticoagulants**

Anticoagulants should not be used in conditions of haemorrhage and also in haemophilia, hypoprothrombinemia, hypertension, active tuberculosis lesion, peptic ulcer, severe wounds and subacute bacterial endocarditis. In pregnancy the anticoagulants are not being given. In conditions like renal and hepatic insufficiencies, anticoagulants are to be used with caution.

**Fibrinolytics (Thrombolytics)**

Drugs that promote clot dissolution by the degradation of fibrin are known as fibrinolytics or thrombolytics. Streptokinase, urokinase and recombinant tissue plasminogen activator (tPA) are the commonly used fibrinolytics. Fibrinolytics are given intravenously in myocardial infarction, pulmonary embolism, valvular heart embolism and other thromboembolic diseases.

Streptokinase is derived from streptococci and rapidly combines with plasminogen activator to activate fibrin degradation. Streptokinase being a bacterial product can produce high fever, fall in blood pressure and haemorrhage. Streptokinase should be avoided in
conditions of active internal bleeding, after recent surgery, parturition, trauma and cerebral neoplasm.

Urokinase is isolated from human urine and hence the name. It also directly stimulates plasminogen activator. Urokinase can be used to promote the lysis of intraocular clot. Urokinase may also be used in myocardial infarction, catheter obstructed by blood clot and many other thrombotic conditions. Unlike streptokinase, hypersensitivity reactions are rare to urokinase. However, haemorrhage is the main adverse effect observed with urokinase.

The fibrinolytic agents are effective in reducing ischemic heart disease-induced necrosis, if given within 30-60 minutes after the onset of chest pain.

**Antifibrinolytics**

Antifibrinolytics are the drugs that competitively inhibit both plasminogen and plasminogen activator from binding to fibrin. These drugs are of immense value in the treatment of haemorrhage due to excessive fibrinolysis or overdosage of thrombolytics. Antifibrinolytics can also be used in the prophylaxis of haemorrhage.

The commonly used antifibrinolytics are epsilon-aminocaproic acid (EACA) and tranexaemic acid. These are usually administered by intravenous route. Oral administration of antifibrinolytics is also possible. Tranexaemic acid is more potent and well tolerated than epsilon-aminocaproic acid. Conjunctival congestion, muscle damage, renal failure, and convulsions are the few adverse effects reported with epsilon-aminocaproic acid.
INTRODUCTION

The major physiological role of kidney is the regulation of body fluids and electrolytes that determine arterial pressure level. At the normal physiological circumstances, kidneys excrete a volume of urine equivalent to the daily fluid intake. The amount of Na⁺ excreted is adjusted to equal the amount ingested. The most abundant cation present in extracellular fluid is Na⁺. Sodium is 90% osmotically active solute in plasma and interstitial fluid. More importantly, the arterial pressure regulation has been directly linked with electrolyte balance and fluid volume. The salt retention increases plasma volume leading to perpetual rise in blood pressure. Kidneys have an overriding role in the control of blood pressure. Obviously, kidneys are the common target organs for drug action to modulate the mechanisms of urine formation aiming at reducing the blood volume to regulate arterial pressure. Hence, it is important to understand the renal mechanisms of urine formation before embarking on the pharmacology of drugs that affect renal functions.

PHYSIOLOGY OF URINE FORMATION: A BRIEF ACCOUNT

The basic urine-forming unit of the kidney is nephron, which consists of filtering apparatus, proximal tubule, loop of Henle, distal convoluted tubule and collecting duct. The processes
that determine the volume and composition of urine are glomerular filtration, tubular reabsorption and active tubular secretion.

**Glomerular Filtration**
Every day kidneys filter 180-200 litres of blood. The glomerular filtration rate is 125 ml/minute. If the filtration rate is increased by improved renal blood flow, the rate of urine formation also goes up.

**Tubular Reabsorption**
Throughout the length of nephron, reabsorption of solutes and water occurs by different ways. Sodium bicarbonate, amino acids, glucose, calcium, potassium and magnesium get reabsorbed in the proximal convoluted tubule. This is important for maintenance of salt and water balance. The electrolyte (solute) transport is either by uniport, symport and antiport. Uniport is a carrier-mediated transport or facilitated diffusion. Symport is the co-transport of solute species in the same direction. The transport of solute species is countered in opposite direction which is called antiport. For example, Cl⁻ antiport with formate in proximal tubule.

**Loop of Henle**
Divalent cation K⁺-Na⁺-Cl⁻ symport occurs in thick ascending limb. The thin descending limb is permeable to water and increases the osmolarity of tubular fluid.
**Diuretics**

**Distal Convoluted Tube**
Sodium chloride symport is also a major reabsorption process which operates in distal tubule. Calcium absorption is facilitated by parathyroid hormone. K⁺ secretion also occurs here. Distal tubule is impermeable to water.

**Collecting Tubule**
Mineralocorticoid-regulated Na⁺ reabsorption occurs in collecting tubule. K⁺ and H⁺ ions are secreted in exchange with sodium. Antidiuretic hormone-facilitated water absorption determines the volume of urine output.

**DEFINITION**
Diuretics are the drugs that increase the volume of urine. These agents promote salt and water elimination from the body. A drug that enhances Na⁺ excretion is called ‘natriuretic’ and potassium excretion promoter is known as ‘kaliuretic’. Likewise, chloruretic and calciuretic terms have been in vogue to denote excretion of chloride and calcium respectively. Conversely, the drug that decreases urine output is called ‘antidiuretic’. Antidiuretics are mainly indicated in diabetes insipidus, for example, chlorpropamide and antidiuretic hormone and its analogues.

**CLASSIFICATION (Based on Site and Mechanism of Action)**

<table>
<thead>
<tr>
<th>Extrarenal diuretics</th>
<th>Renal diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>(act by improving haemodynamics, ↑ GFR)</td>
<td>(act directly on renal mechanism of urine formation)</td>
</tr>
<tr>
<td>• Xanthine alkaloid: Caffeine</td>
<td></td>
</tr>
<tr>
<td>• Cardiac glycosides: Digoxin</td>
<td></td>
</tr>
<tr>
<td>• Dopamine</td>
<td></td>
</tr>
<tr>
<td>• Colloids</td>
<td></td>
</tr>
</tbody>
</table>

**Renal Diuretics**

1. **Osmotic diuretics**
   - Mannitol, isosorbide, urea, glycerin
2. **Carbonic anhydrase inhibitors**
   - Acetazolamide, dorzolamide, dichlorphenamide
3. **Loop diuretics**
   - Na⁺-K⁺-2Cl⁻ symport inhibitors:
     - Frusemide, torsemide, bumetanide, piretanide, ethacrynic acid
4. **Thiazides:**
   - Na⁺-Cl⁻ symport inhibitors:
     - Hydrochlorothiazide, polythiazide, cyclothiazide, benflumethiazide
   - Thiazide-like drugs:
     - Chlorthalidone, xipamide, metolazone, clopamide, mefruside
5. **K⁺-sparing diuretics**
   - Spironolactone, amiloride, triamterene
6. **Uricosuric diuretics**
   - Ticrynafen, indacrynic acid

7. **Miscellaneous:**
   - Indapamide, sodium polystyrene sulphonate, water, alcohol, angiotensin-converting enzyme inhibitors.

**OSMOTIC DIURETICS**

**Mannitol**

The commonly used osmotic diuretic is mannitol. Mannitol is a polyhydric alcohol freely filtered at renal glomeruli and relatively pharmacologically inert. At larger doses, it increases osmolarity of plasma and tubular fluid. By changing the osmolarity of the tubular fluid, mannitol increases Na⁺, K⁺, Ca²⁺, Mg²⁺, HCO₃⁻, H₂O and chloride excretion. Water extraction from the descending limb of loop of Henle is reduced by mannitol.

Mannitol is used in acute renal failure. Before and after surgery to reduce cerebral edema, mannitol is indicated by intravenous infusion. To reduce intraocular pressure in glaucoma, osmotic diuretics are helpful. Mannitol is used to increase osmolarity of extracellular fluid in dialysis disequilibrium syndrome. In acute drug poisoning condition mannitol is infused to increase the rate of drug excretion. Particularly, in salicylate and barbiturate poisoning along with alkaline substances, mannitol is indicated for forced alkaline diuresis.

**Adverse Effects**

Pulmonary edema, hyponatremia and pain on extravasation.

**Contraindications for Mannitol**

1. Congestive cardiac failure
2. Acute cranial bleeding
3. Hypertension
4. Anuria

**LOOP DIURETICS**

Loop diuretics are so called because these act on loop of Henle. Loop diuretics are also known as high ceiling diuretics or high efficacy diuretics. Currently, furosemide (frusemide), torsemide, pirenemide, bumetanide, and etharynic acid are commonly used loop diuretics.

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Bioavailability</th>
<th>Half-life</th>
<th>Major site of action</th>
<th>Transport protein inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frusemide</td>
<td>Up to 90%</td>
<td>3-3.4 hrs</td>
<td>Loop of Henle</td>
<td>Na⁺K⁺-Cl symport</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>60 to 70%</td>
<td>5-15 hrs</td>
<td>Cortical segmental part of the distal tubule</td>
<td>Reabsorption of sodium</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Up to 90%</td>
<td>-</td>
<td>Distal portion of tubule</td>
<td>Sodium (K⁺ sparing)</td>
</tr>
</tbody>
</table>
Furosemide (Frusemide)

Furosemide is a loop diuretic. It acts by inhibiting sodium-potassium-chloride symport. Generally, increases renal blood flow, which may involve prostaglandin role since non-steroidal anti-inflammatory drugs attenuate this effect of furosemide. Furosemide also increases the systemic venous capacitance and decreases left ventricular filling pressure which is secondary to decrease blood volume.

Furosemide is well absorbed from the gastrointestinal tract. It binds up to 99% to plasma albumin and mainly excreted in the urine and also appears in breast milk. Except in emergency conditions, furosemide is given by mouth.

Adverse Effects

The most common side effect associated with frusemide therapy is fluid and electrolyte imbalance including hyponatremia. Overzealous use causes extracellular volume depletion, hypotension and circulatory collapse. Besides, hypokalemia, hypomagnesemia, hyperglycemia, hyperuricemia, hyperlipidemia, hypercalcemia, tinnitus, vertigo, sense of fullness in the ears, fatigue and skin rashes are produced by furosemide.

Therapeutic Uses

Furosemide is used in the following conditions:
1. Acute pulmonary edema: Administration of frusemide intravenously produces brisk natriuresis and increases rapid systemic venous capacitance. As a result, left ventricular filling pressure is reduced, which provides therapeutic benefit.
2. Congestive cardiac failure
3. Acute renal failure
4. High blood pressure
5. Ascites
6. Forced alkaline diuresis in acute drug poisoning
7. Refractory edema of nephrotic syndrome

Drug Interactions

1. Frusemide + aminoglycoside antibiotics: Increased ototoxicity
2. Frusemide + cisplatin: Augmented ototoxicity
3. Frusemide + NSAIDs: Blunts diuretic effect
4. Frusemide + lithium: Increased lithium plasma level may aggravate toxicity

THIAZIDES

A wide number of thiazide diuretics and their structural derivatives have been used in various types of edema and non-edematous clinical conditions. Thiazides act by various mechanisms to induce diuresis.
1. Inhibit Na⁺-Cl⁻ symport
2. Increase K⁺, HCO₃⁻ excretion
3. Reduce the excretion of Ca²⁺ by a direct action on Ca⁺ reabsorption at distal convoluted tubule
4. Enhance Mg²⁺ excretion
Adverse Effects
Besides gastrointestinal disturbances like nausea, vomiting, anorexia, constipation and diarrhoea, thiazides cause a number of metabolic disturbances. Hyperglycemia—hyperuricemia—precipitates gouty arthritis, hypokalemia, hyponatremia, hyperlipidemia, hypotension, metabolic alkalosis and hypersensitivity reactions, especially in the sulphonamide sensitive individuals. Impotence may be seen in hypertensive patients on thiazide administration.

Therapeutic Uses
1. Thiazides are extensively used in the management of congestive cardiac failure
2. Oral thiazides are in fact, commonly used in mild to moderate hypertensive patients
3. Cirrhosis of liver
4. Nephrotic syndrome and chronic renal failure
5. Edema caused by steroids
6. Drug-induced edema and renal failure
7. Calcium nephrolithiasis
8. Bromide intoxication
9. May be used in osteoporosis
10. As antidiuretic in nephrogenic diabetes insipidus.

Contraindications
1. Acute gouty arthritis
2. Hypercalcemia
3. Severe diabetes mellitus
4. Hepatic encephalopathy

Drug Interactions
1. Thiazides + NSAIDs: Antagonism of diuretic effects by NSAIDs.
2. Thiazides + quinidine: Prolongation of Q-T interval in ECG and lethal arrhythmias have been reported.
3. Thiazides + K⁺-sparing diuretics: Maintains K⁺ balance in the body—therapeutic synergy. This is a beneficial interaction, hence, combination is preferred to avoid hypokalemia.
4. Thiazides + beta-blockers: Therapeutic synergy can be achieved using this combination in high blood pressure.

POTASSIUM-SPARING DIURETICS (K⁺-sparing diuretics)
Potassium-sparing diuretics are mild diuretics seldom used as sole agents. Preferably, these diuretics are used in combination with other kaliuretic diuretics to maintain potassium level. Currently, spironolactone, amiloride and triamterene have been employed as K⁺-sparing diuretics in many clinical conditions. Generally, these are given by oral route with other diuretics.
Mechanism of Action
It is believed that all the K+-sparing diuretics act by different mechanisms as described below.

**Spironolactone**
Following administration, spironolactone undergoes extensive metabolism to liberate *canrenone*, which is an active metabolite. Being a steroid in structure, spironolactone acts as *aldosterone receptor antagonist*—blocks the aldosterone receptor competitively and increases sodium and water excretion by retaining potassium. At high doses, spironolactone inhibits key enzymes that take part in steroid synthesis.

**Amiloride**
This is a potent K+-sparing diuretic which acts by blocking apical membrane Na+ channels at collecting tubules.

**Triamterene**
The exact mechanism of action of triamterene is uncertain at present. However, there are evidences to believe that triamterene inhibits K+ as well as H+ secretion. Hydrogen ATPase is inhibited by triamterene.

Adverse Effects
Spironolactone causes impotence, gynecomastia, deepening of voice, hirsutism, and menstrual irregularities. In rats, spironolactone is found to be carcinogenic. Stray breast cancer incidences have been reported with spironolactone. Amiloride and triamterine, like spironolactone, cause hyperkalemia, leg cramps and dizziness.

Therapeutic Uses
Spironolactone is used in primary hyperaldosteronism.

All the K+-sparing diuretics are of good clinical value in combination with kaliuretic diuretics in the management of various edematous conditions and also hypertension.

Drug Interaction
K+-sparing diuretics + ACE inhibitors: This combination is invariably used in the drug management of hypertension. Hyperkalemia is one of the concerns of this combination therapy. However, if used with hypokalemic diuretic, potassium level may not rise. Nevertheless, periodic estimation of K+ level is desirable.

CONTRAINDICATIONS FOR DIURETIC THERAPY
1. Hypotension
2. Hypovolemia
3. Hyponatremia
EXERCISE AND DIURETICS

Diuretics are the drugs used in conditions of electrolyte imbalance due to renal dysfunction and other hypertension-related cardiovascular diseases. In these clinical situations patients may not be willing to go for exercise programme. This is understandable since patients’ condition may not permit for exercise. However, as the condition improves and by maintaining electrolyte balance, slow and brief exercise programme can be advised to these patients. Yet endurance exercise causes hyponatremia and diuretics produce natriuresis which may further aggravate the condition. Therefore, it is pertinent to watch constantly for the clinical improvement of the patient. Only on thorough assessment of the ability of the patient, slow, steady and simple exercise programmes may be advised.

DRUGS USED IN DIABETES INSIPIDUS

Diabetes insipidus is an endocrinal disorder characterized by increase in thirst and passage of large quantities of urine with low specific gravity.

*Diabetes insipidus may be due to:*
1. Deficiency of vasopressin
2. Disorder of renal water reabsorption which is called nephrogenic diabetes insipidus.

*Drugs used in diabetes insipidus are:*
1. Desmopressin: Intranasal spray, also given by intravenous and intramuscular routes.
2. Hydrochlorothiazide
3. Indomethacin
4. Amiloride

Nephrogenic diabetes insipidus may respond to combination therapy with hydrochlorothiazide + indomethacin or vasopressin + indomethacin or indomethacin + amiloride.
Lipids and Lipoproteins

Cholesterol and triglycerides are the main blood lipids, which are carried in globular packages made up of lipoproteins and apoproteins. Cholesterol is an essential substance for synthesis of steroids and bile acids, whereas triglycerides transform energy from food into cells.

Lipoproteins are generally classified on the basis of density, determined by triglycerides and apoproteins. The least dense particles are known as chylomicrons, the densest are high-density lipoproteins (HDLs), less dense are the low-density lipoproteins (LDLs) and least dense are very low-density lipoproteins (VLDLs). Very low-density lipoproteins consist of mainly triglycerides. The liver manufactures VLDL from fat and carbohydrates. After transferring triglycerides to cell, VLDLs eventually become LDL particles. Low-density lipoproteins carry cholesterol for cellular needs. Liver takes up excess LDL and cholesterol gets excreted in bile. Importantly, high-density lipoproteins facilitate the transfer of apoproteins among lipoproteins and also take part in cholesterol transfer into other lipoproteins and to liver.

Lipids are deposited into the walls of arteries (large and medium sized), which occlude the arterial lumen. The artery clogging plaque formation is more common in subjects with high level LDL cholesterol. The higher the level of LDL cholesterol, the greater the risk of atherosclerosis and heart disease. Conversely, higher the level of HDL cholesterol, the lower the risk of coronary diseases. However, the exact mechanism by which lipid-related diseases appear is not known. Nevertheless, several genetic disorders provide insight into the pathogenesis of hyperlipidemia-linked diseases.
CLASSIFICATION OF LIPID LOWERING AGENTS
(Based on chemistry or mechanism of action)

1. **HMG CoA reductase inhibitors**—statins
   - Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin
2. **Fibric acid derivatives**
   - Gemfibrozil, clofibrate, fenofibrate
3. **Bile acid-binding agents**
   - Cholestyramine, colestipol
4. **Niacin**

**HMG CoA REDUCTASE INHIBITORS**

HMG CoA reductase catalyses the rate-limiting step in the synthesis of cholesterol. Statins by inhibiting this enzyme reduce cholesterol formation in liver. As a result, there is a compensatory increase in LDL receptor in liver, which takes more cholesterol from the blood. Consequently, the level of circulating LDL cholesterol is reduced. In addition, statins are known to cause modest increase in HDL level and decrease triglycerides levels also. Atorvastatin, pravastatin and simvastatin and lovastatin produce more or less similar effects on LDL, HDL and triglycerides levels. Generally, these are given once a day in the evening to inhibit overnight cholesterol synthesis.

Lovastatin, simvastatin and atorvastatin are prodrugs, following administration are converted to their active hydroxy forms in the liver.

The incidence of adverse effects of statins on liver is about 1%. Hepatotoxicity appears to be dose related. Serious hepatic tissue disintegration is however rare. Myopathy is one of the sources of concern of statins therapy. All statins produce myopathy and rhabdomyolysis. When statins are given with other lipid-lowering agents like niacin and fibric acid derivatives the incidence of myopathy is more. This is probably due to inhibition of skeletal muscle sterol synthesis by combination therapy with lipid-lowering agents. Myopathic syndrome produced by statins causes fatigue, intense myalgia, myoglobinuria and renal failure.

Pregnant women and nursing mothers should not use statins since safety is not assessed till date.

Cerivastatin should not be used with gemfibrozil because the combination of these two hypolipidemic drugs produces severe myopathy. Therefore, cerivastatin is withdrawn from the market.

The choice of statins to reduce lipid levels is based on efficacy and cost. The statins therapy is almost always for lifetime. Hence, careful assessment must be done to achieve lipid reduction at target level.

**FIBRIC ACID DERIVATIVES**

Gemfibrozil, clofibrate and fenofibrate are the derivatives of fibric acid used to treat hypertriglyceridemia to prevent pancreatitis. How clofibrate-like drugs reduce triglycerides and raise HDL levels remains unclear.

Recently, it is said that fibric acid derivatives act on blood lipids by interacting with peroxisome proliferator-activated receptors, which regulate gene transcription. Liver, brown adipose tissue, kidney, heart and skeletal muscles have peroxisome proliferator-activated receptor at varying extent. In short, fibric acid derivatives reduce triglycerides level and
Lipid-Lowering Agents

raise HDL level, whereas in a patient with hypertriglyceridemia, LDL level may be increased. In addition, these drugs have antiatherothrombotic, anticoagulant and fibrinolytic actions, which may be beneficial in different cardiovascular disorders.

All the fibric acid derivatives are given by mouth. Gemfibrozil is short acting with a plasma half-life of 1.1 hours. The fibrates are excreted in urine as glucuronide conjugates.

**Adverse Reactions**
Myalgia, fatigue, headache, impotence, flu-like syndrome and may increase gallstone formation and gastrointestinal side effects are seen in about 5% of patients.

**Therapeutic Uses**
Hypertriglyceridemia is one of the clear indications for fibrates besides hyperlipidemia type III. Patients with the risk of pancreatitis are the suitable candidates for gemfibrozil therapy.

**Contraindications**
Renal failure and hepatic dysfunction are the contraindications for combined statin and fibrate therapy. Fibric acid derivatives should not be used by pregnant women as well as children.

**Drug Interactions**
1. Gemfibrozil + statins: Increased incidence of rhabdomyolysis
2. Fibrates + warfarin: Enhanced anticoagulant action

**BILE ACID-BINDING AGENTS**
Cholestyramine, colestipol, colesevelam

Therapeutically employed bile acid-binding agents are anion exchange resins, not absorbed from alimentary tract and hence safe. Currently, these are recommended for hypercholesterolemic patients aged between 11-20 years. By sequestrating bile acids these drugs promote their excretion. Consequently, bile acid synthesis increases which in turn, lowers the hepatic cholesterol content and LDL levels. Since bile acid-binding agents raise triglycerides level, they should not be used in severe hypertriglyceridemia. Bloating, dyspepsia and constipation have been infrequently seen as side effects on cholestyramine or colestipol administration. Bile acid-binding agents are known to interfere with absorption of drugs like digoxin, warfarin, statins, thyroxine, thiazides, furosemide and propranolol. Hence, these drugs should be administered 1 to 2 hours before giving bile acid-binding agents.

**NIACIN (NICOTINIC ACID)**
Nicotinic acid is a member of vitamin B complex. Virtually, niacin at higher doses affects all lipid levels. Niacin increases HDL level and reduces triglycerides level. In adipose tissues niacin inhibits the lipolysis and also hepatic triglyceride synthesis. Hypolipidemic doses of niacin produce two characteristic side effects—flushing and dyspepsia. Pruritus is also common. Hepatotoxicity and hyperglycemia are the severe adverse effects produced by niacin. Niacin is commonly used for hypertriglyceridemia with low HDL. Niacin should not be used with alcoholic beverages.
INTRODUCTION

Among many reasons to visit physician, high blood pressure commonly stands second to none. Generally, hypertension is an asymptomatic condition and usually discovered by the routine checking of blood pressure. Hypertension is more complicated and more interesting and is often the part of a syndrome of cardiovascular risk factors. Elevation of blood pressure singly exists rarely. It is well recognised that cardiovascular morbidity and mortality increase as both systolic and diastolic pressures rise. The complications of untreated high blood pressure is often alarming and at times bring diseases, disability and death. Many risk factors like obesity, high salt intake, alcohol, cigarette smoking, hyperlipidemia, diabetes mellitus and low potassium intake increase the prevalence rate of hypertension-related major cardiovascular morbidities. It is said that the risk approximately doubles for each 6 mm Hg rise in diastolic blood pressure, which may cause damage to heart, kidney and cerebral vessels. Hence, the identification of risk factors is of paramount clinical importance.

The pathogenesis of high blood pressure is multifactorial: genetic, high salt intake, defective natriuresis and increased sympathetic nervous activity all contribute to the development of high blood pressure. Clinically, hypertension has been classified into 3 major types:

1. Essential or primary hypertension: Cause unknown
2. Secondary high blood pressure: Due to other system diseases for example renal insufficiency.
3. White coat high blood pressure: Increased blood pressure is seen only in physician’s office, about 20% of patient belong to this group.

The principal aim of drug therapy of high blood pressure is to keep systolic blood pressure below 140 mm Hg and diastolic blood pressure < 90 mm Hg. In patients with high risk factors like diabetes mellitus, nephropathy heart failure, it is desirable to stabilize the patient’s blood pressure at 135/85 mm of Hg. There has been some concern about excessive reduction in diastolic blood pressure that cause myocardial ischemia. Antihypertensive drug therapy should not produce sudden precipitous fall in blood pressure. Therefore, based on the measure of the blood pressure, the drug therapy is optimized at individual level. To achieve this, it is important to know the internationally recognised different grades of high blood pressure, which are as follows:

- Optional: 125/80 mm of Hg
- Normal: 135/85 mm of Hg
- High normal: 135-39/85-89 mm of Hg
- Mild high blood pressure: 140-159/90-99 mm of Hg
- Moderate high blood pressure: 160-179/100-109 mm of Hg
- Severe high blood pressure: >180/>110 mm of Hg

The classification of high blood pressure based on blood measure range helps to design a standard drug regime. This generally defines the terms for mono or multiple antihypertensive drug therapy.

Generally, two main approaches have been followed in the management of high blood pressure.

**Non-pharmacological Approach**
Which comprises reduction of body weight, reduced alcohol drinking, cessation of tobacco smoking, a diet rich in fruits and vegetables, exercise, decrease salt intake and low saturated fat diet.

**Pharmacological Approach**
A wide variety of drugs have been used to control high blood pressure. These are classified into different groups based on their mechanism of action.

**CLASSIFICATION OF ANTIHYPERTENSIVES**

1. **Diuretics**
   a. **Thiazides:**
      - Hydrochlorothiazide, chlorothiazide
   b. **Thiazide-like drugs:**
      - Chlorthalidone, xipamide, clopamide, indapamide, metolazone
   c. **Loop diuretics:**
      - Torsemide, furosemide, bumetanide
   d. **K⁺-sparing diuretics:**
      - Spironolactone, triamterene, amiloride

2. **β-receptor blockers:** Propranolol, nadolol, atenolol, metoprolol, esmolol, nebivolol
3. **Angiotensin-converting enzyme inhibitors**: Enalapril, captopril, lisinopril, quinapril, ramipril, fosinopril

4. **Angiotensin receptor antagonists**: Losartan, valsartan, irbesartan, candesartan, telmisartan

5. **Calcium channel blockers**: Nifedipine, nimodipine, diltiazem, verapamil, amlodipine, felodipine

6. **α-receptor blockers**: Prazosin, trimazosin, doxazosin

7. **Central α agonists**: α-methyldopa, clonidine, guanfacine

8. **Both α and β receptor blockers**: Labetalol, carvedilol, bucindolol

9. **Vasodilators**: Hydralazine, minoxidil, diazoxide, pinacidil, sodium nitroprusside

10. **Ganglion blockers**: Trimethaphan, mecamylamine

11. **Adrenergic neuron blockers**: Guanethidine, bethanidine

12. **Miscellaneous**: Reserpine, α-methylparatyrosine

13. **Recently introduced**: Omapatrilat, fenaldopam, endothelin antagonists—bosentan

**THE RATIONALE OF DIURETIC THERAPY IN HIGH BLOOD PRESSURE**

Oral diuretic therapy is one of the main strategies to reduce high blood pressure. The pharmacological basis for diuretic administration in high blood pressure lies in their ability to alter Na+ balance.

Mainly, diuretics reduce extracellular volume, which in turn reduce cardiac output that leads to decrease in high blood pressure. When given on chronic basis, diuretics reduce peripheral vascular resistance. Further, diuretics when combined with other antihypertensives counteract the salt and water retention caused by latter. Hence, a combination of diuretics with other antihypertensive drugs is rational.

Loop diuretics are generally used to reduce severe edema in high blood pressure patients with azotemia. Oral supplementation of K+ may be necessary with kaliuretic diuretics. Otherwise, a combination of kaliuretic diuretic with K+-sparing diuretics is more desirable and beneficial.

**β-Blockers as Antihypertensives**

Beta-adrenergic receptor blockers are effective in all grades of high blood pressure. These drugs reduce myocardial contractility, reduce cardiac output, reduce renin level and bring a change in the baroreceptor sensitivity to alter the peripheral adrenergic neuronal activity. All these actions of β-blockers contribute to their antihypertensive effect. However, non-selective β-blockers are not to be used for hypertensive patients who have bronchial asthma.

**α-Blockers**

Alpha-receptor blockers reduce blood pressure by decreasing peripheral vascular resistance. Prazosin may be used in hypertensive patients with prostate hypertrophy. Alpha-receptor blockers do not disturb blood glucose, lipid profile and cause no exacerbation of bronchial asthma. However, first dose effect and postural hypertension induced by α-blockers needs more precautionary measures. Drugs that block both α and β receptors—labetalol have been recommended for hypertensive emergencies.
Calcium Channel Blockers as Antihypertensive Agents

Nifedipine, verapamil, amlodipine, diltiazem and felodipine have been used commonly as antihypertensive drugs currently. These drugs have arterial smooth muscle relaxant action. Calcium channel blockers dilate coronary, cerebral and peripheral arteries, therefore, reduce total arterial resistance and preload as well as afterload. Amlodipine is a long-acting coronary and peripheral artery dilator. Diltiazem is commonly prescribed for patients with hypertension and angina pectoris. Nifedipine is a short-acting calcium channel blocker generally recommended for hypertensive emergencies. Sublingual administration of nifedipine usually controls hypertension rapidly and minimises further tissue damage in hypertensive emergencies.

PHARMACOLOGY OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)

Angiotensin-converting enzyme inhibitors are now regarded as agents of choice to start antihypertensive therapy. These drugs inhibit the formation of angiotensin II, which is a potent endogenous vasoconstrictor. Angiotensin-converting enzyme inhibitors although indistinguishable in their efficacy and safety differ in their potency and kinetics.

Classification

Chemically angiotensin-converting enzyme inhibitors are divided into main 3 subclasses:
1. **Sulfhydryl group**: Captopril, pivalopril, zofenopril, alacepril
2. **Dicarboxyl group**: Enalapril, lisinopril, benezepril, ramipril, quinapril, perindopril, tendilapril
3. **Phosphorus-containing group**: Fosinopril

Pharmacodynamics

Angiotensin-converting enzyme inhibitors alone normalize blood pressure in mild to moderate high blood pressure by the following actions:
1. The formation of angiotensin II is inhibited which reduces the tone of vascular smooth muscle.
2. Bradykinin degradation is also inhibited, which dilates the blood vessels and via nitric oxide reduces the tissue hypertrophy.
3. Decrease peripheral resistance.
4. Aldosterone secretion is inhibited: Promotes Na\(^+\) excretion and retains K\(^+\).
5. Inhibits diuretic-induced hyperaldosteronism.
6. Reduces left ventricular hypertrophy and restores the normal elliptical shape of the heart.
7. Have renoprotective effects, which are useful in hypertensive diabetes mellitus patient.

Pharmacokinetics

Except captopril and lisinopril, other commonly used angiotensin-converting enzyme inhibitors are prodrugs. Enalapril undergoes metabolic activation to enalaprilat. Occasionally, angiotensin-converting enzyme inhibitors are given by intravenous route. Captopril can be administered by sublingual route. The half-life of enalapril is 12 hours and that of ramipril is 24 hours.
Pharmacology for Physiotherapist

Adverse Effects
Acute dysgeusia (abnormal taste perception), dry cough, skin rash, proteinuria, hyperkalemia, fetotoxicity, angioneurotic edema and neutropenia are the adverse effects seen with angiotensin-converting enzyme inhibitors.

Therapeutic Uses
Enalapril-like drugs are commonly indicated in:
1. Management of high blood pressure
2. Congestive cardiac failure
3. Renal diseases like renal scleroderma

Contraindications
All angiotensin-converting enzyme inhibitors are contraindicated in pregnancy, cardiogenic shock and severe hypotension.

Drug Interactions
- Angiotensin-converting enzyme inhibitors + digoxin: Clearance of digoxin is reduced and caution is necessary
- NSAIDs attenuate antihypertensive effects of angiotensin-converting enzyme inhibitors
- Angiotensin-converting enzyme inhibitors + thiazide diuretics: Prompt fall in blood pressure
- Angiotensin-converting enzyme inhibitors + lithium: Intoxication of lithium
- Angiotensin-converting enzyme inhibitors + K+-sparing diuretics: Hyperkalemia. To avoid this, monitoring of K+ level is necessary.

ANGIOTENSIN RECEPTOR ANTAGONISTS
Losartan, irbesartan, telmisartan, valsartan, candesartan

Angiotensin II receptor antagonists have been generally used in place of angiotensin-converting enzyme inhibitors or alone in high blood pressure. It has been well recognised that losartan-like drugs lower blood pressure in patients with high renin hypertension. Angiotensin II receptor antagonists block the action of angiotensin by competitive antagonism.

Losartan is converted into an active metabolite. This metabolite is 10-40 times more potent than losartan and blocks AT1 receptor by non-competitive antagonism. Losartan exerts antiproliferative effects by directly blocking the AT1 receptor. This drug is known to have tissue protective effect in hypertensive patients so that minimizes end-organ damage. Thus, losartan has vasoprotective and cardioprotective effects and causes regression of left ventricular hypertrophy (Fig. 6.1).

Losartan is well observed by oral route and undergoes first pass metabolism in liver and converted into active and inactive metabolites. Losartan is excreted mainly in urine and appears in milk.

Losartan is used in mild to moderate hypertension. Addition of diuretics, beta-blockers, calcium channel blockers or angiotensin-converting enzyme inhibitors results in an additive
antihypertensive effect. Losartan can also be used in congestive cardiac failure and to prevent recurrent stroke and myocardial infarction.

Losartan appears to have more safety and tolerability profile. Dizziness, fatigue, headache, edema and insomnia are infrequently reported with losartan therapy. Losartan is well tolerated by hypertensive patients with heart failure, diabetes, renal insufficiency and those undergoing haemodialysis. Unlike angiotensin-converting enzyme inhibitors, dry cough is not reported with losartan. Losartan should not be withdrawn suddenly. Losartan is contraindicated in pregnancy and nursing mother.

**CENTRAL α₂ AGONISTS**

Alpha methyl dopa and clonidine are commonly used to treat high blood pressure. However, guanfacine and moxonidine have also been recommended for the management of hypertension.

**Alpha-methyldopa**

Alpha-methyldopa is 3, 4 dihydroxy phenylalanine, undergoes decarboxylation on administration. Alpha methyl norepinephrine is the active metabolite, believed to act as false adrenergic neurotransmitter. However, α-methyldopa reduces blood pressure by the following mechanisms:

1. Stimulates central postsynaptic α₂ receptor and reduces the vasomotor tone.
2. Reduces plasma renin activity
3. Decreases the tissue concentration of dopamine, norepinephrine, epinephrine and 5-hydroxytryptamine.

Alpha methyldopa is generally given by mouth and absorbed by amino acid active transport. It crosses placental barrier and appears in milk.

Transient twilight sleep, decreased libido, postural hypotension, impotence, lack of concentration, loss of memory, parkinsonism, fluid retention, edema and haemolytic anaemia are the adverse drug reactions produced by α-methyldopa.

Alpha methyldopa is contraindicated in hepatic renal diseases, mental depression, parkinsonism and porphyria.

**Drug Interaction**

The combination of propranolol and α methyldopa may produce paradoxical hypertension. Alpha methyldopa reduces the efficacy of tricyclic antidepressant drugs.

**Clonidine**

Clonidine is a central α₂ receptor agonist. At high doses, clonidine stimulates peripheral α₂ receptors also. By the virtue of central α₂ receptor stimulation clonidine reduces systemic blood pressure. Recently, imidazoline – I₁ receptors have been described to involve in antihypertensive action which can be ascribed to reduction in sympathetic nerve electrical discharge. Intravenous clonidine may transiently increase blood pressure due to peripheral α-receptor stimulation. This is not seen with oral clonidine. Clonidine is more useful in high blood pressure with renal complications since it does not compromise renal blood flow. Usually, clonidine is indicated in hypertensive patients, who fail to respond to diuretic and β-blockers.

Generally, adverse effects of clonidine are mild and disappear with continuous administration. Yet, 7% patients discontinue clonidine due to adverse effects. Impotence, dryness of mouth, constipation and parotid gland swelling have been observed with clonidine therapy as adverse reactions. Caution is necessary not to stop clonidine abruptly because sudden withdrawal of clonidine causes potentially dangerous rebound hypertension. Probably, the rebound increases in blood pressure is due to excessive sympathetic nervous system activity and the development of supersensitivity.

**Other Uses**

Clonidine is also used for:
1. Prophylaxis of migraine
2. Menopausal flushing
3. Opioid withdrawal syndrome
4. Recurrent vascular headache

**Drug Interaction**

Clonidine when used with antidepressant drugs the hypotensive action is reduced.
VASODILATORS

Vasodilators used in the management of hypertension act directly on vascular smooth muscle and produce relaxation.

Angiotensin receptor antagonists, α-adrenergic receptor blockers and potassium channel activators do produce vasodilatation. Further, directly acting vasodilators are grouped into two:

1. **Arteriolar dilators**: Hydralazine, minoxidil
2. **Both arteriolar and ventular dilators**: Sodium nitroprusside, nitroglycerin

It is well recognised that antihypertensive vasodilators produce reflex tachycardia at varying degree and retain salt and water. Measures to be undertaken to counteract these unwanted effects of vasodilators have been quite satisfactory. Reflex tachycardia can be controlled by co-administration of β-receptor blockers. Diuretics given concomitantly can nullify salt and water retention caused by vasodilators.

**Hydralazine**

Hydralazine is a directly acting antihypertensive vasodilator. Arteries are dilated on hydralazine therapy predominantly. Hydralazine is known to inactivate complement protein C4 to cause arthritis and lupus erythematosus although the precise mechanism remains unclear. Acetylation is the chief metabolic process of hydralazine. The rate of hydralazine acetylation is genetically determined. In slow-acetylators, adverse reactions are frequently seen. Reflex tachycardia, fluid retention, arthritis, fever, myalgia, pleurisy and lupus erythematosus on long-term administration are the main adverse effects of hydralazine.

Hydralazine is used in hypertension as well as cardiac failure. It is used in the management of hypertension in pregnancy.
Minoxidil
Minoxidil is a direct vasodilator. This drug reduces total peripheral resistance and blood pressure. Moreover, within 3 to 6 weeks of continued administration, minoxidil produces hypertrichosis (abnormal growth of hair) in 80% of the subjects.

Minoxidil is known to stimulate angiogenesis and stimulate endothelial cells and activate K⁺ channel. Reflex tachycardia, weight gain, fluid retention, pericardial effusion and cardiac tamponade have been observed as adverse effects of minoxidil.

Besides, antihypertensive use, minoxidil is topically applied for scalp only to promote hair growth in male alopecia.

Sodium Nitroprusside
Sodium nitroprusside is a complex of iron, cyanide and nitrosoradical. This is the drug of choice to treat hypertensive crisis and act as nitric oxide donor. The liberated nitric oxide activates guanylate leading to relaxation of the vascular smooth muscle.

Sodium nitroprusside is rapidly acting anterio-venodilator and exclusively given by intravenous route. This drug is preferred to control blood pressure during surgery.

The solution of sodium nitroprusside is unstable to light. Hence, nitroprusside infusion bottle is wrapped with aluminium foil. The infusion rate must be slow and usually with 5% glucose solution.

Cyanosis, metabolic acidosis and hypotension are the adverse effects of sodium nitroprusside. This arteriolar-venodilator is used in hypertensive crisis and occasionally in dantrolene-refractory neuroleptic malignant syndrome.

OTHER DRUGS
Reserpine
Reserpine is an alkaloid obtained from Rauwolfia serpentina and a cost effective antihypertensive agent. It reduces the blood pressure by depleting the stored noradrenaline and other biogenic amines at the adrenergic nerve terminal.

Reserpine can be given alone. However, it is commonly administered with diuretic hydrochlorothiazide or chlorthalidone. This combination of drugs invariable achieves therapeutic synergy in the management of high blood pressure.

Adverse effects like mental depression, suicidal tendencies, peptic ulcer and parkinsonism have precluded the use of reserpine.

Reserpine is contraindicated in mental depression, peptic ulcer and parkinsonism.

Omapatrilat
Omapatrilat is a recently introduced drug for the management of high blood pressure. This drug inhibits angiotensin-converting enzyme and neutral endopeptidases. Inhibition of neutral endopeptidases result in poteniation of effects of endogenous atrial natriuretic peptide. The clinical experience with omapatrilat is not vast hence this drug is on the guard and details are awaited.

DRUG MANAGEMENT OF HYPERTENSIVE EMERGENCIES
Hypertensive emergencies may arise in the course of any hypertensive disease including renal hypertension, toxemia of pregnancy or phaeochromocytoma (tumor of adrenal medulla).
These situations regardless of cause of life threatening and require immediate, prompt and effective intervention to lower blood pressure. This is necessary to prevent the progression or avoid end organ damage. The management of hypertensive emergencies requires parenteral drug therapy and careful, intensive monitoring. A rapid reduction of blood pressure is not without risk and may lead to cerebral ischemia, inadequate tissue perfusion and angina pectoris. Therefore, a steady slow reduction in blood pressure needs to be achieved in hypertensive crisis. When time permits, the use of oral drugs provides a safer approach in the treatment of hypertensive crisis.

Drugs used in hypertensive emergencies are:

I Phase therapy:
- **Intravenous administration:**
  - Sodium nitroprusside
  - Nitroglycerin
  - Labetalol
  - Hydralazine
  - Diazoxide

II Phase therapy:
- **Oral drugs** to be administered to stabilize the patient and to avoid steep fall in blood pressure:
  - Clonidine
  - Captopril
  - Prazosin

**Sublingual Administration**

Nifedipine is a short-acting calcium channel blocker used sublingually, especially during the transit time of patient shifting from residence to hospital.

**IMPLICATIONS OF ANTI-HYPERTENSIVE DRUG THERAPY ON PHYSIOTHERAPY: HIGH BLOOD PRESSURE, EXERCISE AND DRUGS**

**Can a Hypertensive Patient Involve in Exercise Therapy?**

Drug therapy and exercise are not mutually contraindicated in cardiovascular diseases provided that the ways in which drug therapy interacts with exercise are clearly understood. An appreciation of the hemodynamic and biochemical changes induced by drugs during both acute and chronic exercise is important in achieving desirable benefit. Many studies have revealed the effects of various drugs on subjects during acute and chronic exercise. However, lack of uniformity in the exercise protocols used, variations of drug dosages in the long-term management of hypertension complicate the applicability of data.

Excessive diuresis with thiazides and other diuretics may accentuate exercise-induced tachycardia and post-exercise hypotension. Central α2 antagonists induce changes in serum potassium, renin and aldosterone level. Exercise-induced increase in renin level is blunted by clonidine. Transdermal clonidine patch adherence to the skin is minimally affected by exercise, however, it can be reinforced with tape if needed.

Beta-blockers allow patients to perform exercise of increased intensity and duration before onset of angina. Plasma levels of both propranolol and acebutolol increase significantly during
exercise. It has been reported that β-blockers inhibit exercise-induced stimulation of glucose metabolism and lipolysis which can impair exercise performance. Beta-blockers increase the plasma level of glucagon, significance of which is not clearly known. Prazosin has been tested in patients with borderline hypertensive heart failure and shown to improve haemodynamics and alternate increase in diastolic blood pressure associated with isometric exercise.

Angiotensin-converting enzyme inhibitors do not limit dynamic exercise in hypertensive patients. Enalapril-like drugs neither suppress exercise-induced rise in renin and angiotensin II nor influence microalbuminuria with prolonged physical activity. In fact, this has clinical significance in the management of hypertensive diabetic patients. However, constant medical supervision is mandatory. A physiotherapist needs to be more cognizant about the outcome of drug-exercise interaction in hypertensive patients.
INTRODUCTION
Chest pain is a common complaint in doctor’s clinic. Chest pain occurs when there is myocardial ischemia. How ischemia provokes pain is not clearly understood. Ischemic myocardial pain is multifactorial in origin. It is due to many causative factors and diseases. Diseases that predispose myocardial ischemia must be addressed well as a part of comprehensive therapeutic programme. Hypertension, anemia, thyrotoxicosis, obesity, heart failure, chronic and acute anxiety have been regarded as risk factors for myocardial ischemia. Smoking and alcohol consumption have also been identified as risk factors.

WHAT IS ANGINA PECTORIS?
Angina pectoris is a principal symptom of ischemic heart disease. This is a clinical syndrome. Angina pectoris is manifested by sudden, severe, pressing substernal pain, which often radiates to the left shoulder. Excessive effort or emotion or exertion exacerbates classic anginal pain. Angina pectoris has substantial risk of progression to myocardial infarction. Most of the modern human death is due to myocardial infarction. Exercise can also induce angina by reducing subendocardial perfusion. Angina pectoris that occurs after exercise is free from epicardial coronary stenosis.

Clinical Types of Angina Pectoris
Clinically, angina pectoris is described by following types:
1. Stable angina: Pain is brought on exertion and relatively bears a constant threshold for precipitation of attack. Coronary atherosclerosis may be the principal etiological factor for stable angina.
2. Unstable angina: The onset of pain is new and symptoms also appear at rest. The pain recurs with minimal exertion. Nocturnal symptoms are common.
3. Prinzmetal’s angina: This is also a type of variant angina, which is due to coronary vasospasm. Even at rest focal pain is present in Prinzmetal’s angina.

The pathophysiological mechanisms of various types of angina pectoris differ. Therefore, treatment approach is different. The ischemic myocardial pain is due to the imbalance between oxygen delivery and oxygen requirement of the heart. Factors like heart rate, ventricular wall tension and contractility increase oxygen demand of the heart. Reduced oxygen-carrying
capacity of the blood and decreased coronary blood flow, both determine oxygen supply
to the heart. Obviously, any variations in these factors contribute to pathophysiology of
angina pectoris.

Drug therapy of angina pectoris aims at improving oxygen supply to the myocardium
and reducing myocardial oxygen requirement or both.

CLASSIFICATION OF ANTIANGINAL AGENTS

Drugs used in angina pectoris are classified into:

1. **Organic nitrites and nitrates**: Nitroglycerin (glyceryl trinitrate), isosorbide dinitrate,
isosorbide 5-mononitrate, erythrityl tetranitrate, pentaerythrityl trinitrate, amylnitrite

2. **β-adrenergic receptor blockers**: Propranolol, metoprolol, atenolol, sotalol, nadolol

3. **Calcium channel blockers**: Nifedipine, diltiazem, verapamil, nicardipine, felodipine

4. **Miscellaneous coronary vasodilators**: Nicorandil, trimetazidine, molsidomine, dipyri-
damole, PGI2, perhexiline, chromonar, cyclandelate, papaverine.

ORGANIC NITRITES AND NITRATES

Nitrates used in angina pectoris include both short- and long-acting organic nitrites as well
as nitrates.

*Short acting*: Amyl nitrite, nitroglycerin

*Long acting*: Isosorbide-5-mononitrate, erythrityl tetranitrate

**Mechanism of Action**

Nitrates relieve anginal pain by dual mechanism. Following administration of nitrates, ischemic
myocardial pain is relieved as mentioned in Figure 6.3.

In short, nitrates are potent, directly acting smooth muscle relaxants. The relaxation of
vascular smooth musculature reduces preload, afterload and promotes redistribution of blood
in the myocardium, which relieves the pain of angina pectoris.

**Route of Administration**

Nitrates can be given by sublingual, oral and intravenous routes. Transdermal preparations
of nitroglycerin are also available. In acute attack of angina pectoris nitroglycerin is given
sublingually to have rapid onset of action for the prompt relief of pain. Oral nitrates are
generally indicated in long-term management of angina pectoris, for example, isosorbide-5-mononitrate. In advanced stages of congestive cardiac failure with hypertension, nitroglycerin may be administered intravenously.

**Adverse Effects**

Headache (often severe), dizziness, reflex tachycardia, postural hypotension, pallor, cold
sweat, methemoglobinemia, syncope, glaucoma, increased intracranial pressure and sublingual
nitrates may produce burning sensation under tongue.

**Therapeutic Uses**

Administration of nitrates is the mainstay in the management of angina pectoris. Nitroglycerin
is the agent of choice for acute attack of angina pectoris. Sublingual nitroglycerin promptly
Fig. 6.3: Mechanism of action of nitrates
relieves the pain. Orally, isosorbide-5-mononitrate is given for the long-term management of ischemic myocardial disease, to prevent subsequent morbidity and mortality.

Topical nitrate is of clinical value in Raynaud’s disease, a peripheral vascular disease. To relieve paroxysmal nocturnal dyspnoea, nitrates also have been used.

Mainly, the development of tolerance to nitrates on repeated administration is a source of concern to the physician. However, tolerance to nitrates can be minimized by careful titration of dose and keeping nitrate-free time interval by giving drug holidays.

**Drug Interaction**

Nitrates + propranolol: This combination is generally indicated in the management of chronic angina pectoris. These drugs offer many clinical advantages. Nitrates produce reflex tachycardia by decreasing peripheral resistance. Concurrent administration of propranolol suppresses nitrate-induced tachycardia. In addition, propranolol reduces oxygen demand of the heart.

**NITROGLYCERIN**

Nitroglycerin is a short-acting nitrate and the drug of choice to treat acute attack of angina pectoris. As soon as the attack begins a buccal tablet is placed under the tongue. Nitroglycerin buccal spray is also available as metered dose delivery system. This can also be used prophylactically before activities that are likely to precipitate an attack of angina. If the pain is not responding to three tablets taken at a stretch or lasting more than 20 minutes the patient must seek immediate medical help.

Sublingual nitrate therapy can cause headache, light-headedness and hypotension.

Nitroglycerin is also available as transdermal, slow, sustained release and ointment preparations. Intravenous nitroglycerin is advocated for the treatment of advanced congestive cardiac failure associated with hypertension.

**ISOSORBIDE-5-MONONITRATE**

A number of long-acting nitrates are available; among these isosorbide-5-mononitrate is widely used. Orally given isosorbide-5-mononitrate has more consistent bioavailability. The main limitation of chronic nitrate therapy is the development of tolerance. However, tolerance can be minimized by keeping wide time-interval (8-10 hours) between doses or drug-holiday concept may be followed. Adverse reactions profile of isosorbide-5-mononitrate is same as other nitrates.

**β-BLOCKERS FOR ANGINA PECTORIS**

Propranolol-like drugs prevent anginal pain by reducing myocardial oxygen requirement during rest, exertion and stress. Beta-Blockers produce cardiac depressant action, reduces heart rate and myocardial contractility which in turn decreases oxygen consumption of the heart. Propranolol also decreases blood pressure. During exercise β-blockers reduce systolic blood pressure. Beta-Blockers have unique advantage in angina pectoris that these drugs prolong life of patients with coronary artery disease. Hence, propranolol is considered for first line therapy in majority of patients with chronic ischemic myocardial disease. Metoprolol, nadolol and atenolol also have been used for this purpose.
Beta-blockers are not to be used in patients with bronchospasm, bradycardia and overt heart failure. These drugs are not effective in Prinzmetal’s angina (vasospastic angina).

When mono-drug therapy does not bring therapeutic response as desired, a combination of propranolol and nitrates would suffice the need. In chronic angina patients, a combination therapy with β-blocker and nitrates appears to be appropriate and beneficial.

CALCIUM CHANNEL BLOCKERS IN ANGINA PECTORIS
Nifedipine, diltiazem and verapamil relieve anginal pain by reducing myocardial oxygen requirements and by producing coronary vasodilatation. In vasospastic angina (Prinzmetal’s angina) calcium channel blockers are the agents of choice. However, these drugs are avoided in patients with congestive heart failure.

Diltiazem and verapamil are preferred calcium channel blockers as first line agents in angina pectoris. The reason is both diltiazem and verapamil which do not produce reflex tachycardia and diltiazem in particular has less adverse effects.

DRUGS USED IN MYOCARDIAL INFARCTION
Drug therapy for myocardial infarction aims at preventing complications and extension of an infarct, besides relieving pain. Following drugs have been used in myocardial infarction:

*Opioid analgesics*: Morphine or pethidine given intravenously to relieve pain and anxiety.

*Vasodilators*: Nitroglycerin sublingual

*Diuretics*: Furosemide given intravenously

*Thrombolytics*: Streptokinase, urokinase, alteplase

*β-adrenergic receptor blockers*: Propranolol may be given intravenously followed by oral therapy.

*ACE inhibitor*: When there is no hypotension—to be given after the first stage of treatment.

Oxygenation

*Low-dose aspirin*: As a part of post-infarction management—life-long therapy

*Anticoagulants*: Heparin, warfarin—to inhibit intramural thrombi formation

*Antiarrhythmics*: Lignocaine given intravenously for ventricular tachycardia

*Other platelet aggregation inhibitors*: Clopidogrel

*Dopamine with normal saline*: For hypotension and shock

*Exercise training*: Careful assessment is mandatory

EXERCISE AND ANTIANGINAL DRUGS
The most useful non-invasive procedure for evaluation of angina pectoris patient is exercise testing. Ischemia that is not present at rest is detected by exercise testing. This is done to confirm the diagnosis of angina. Exercise testing can determine the severity of limitation of activity due to angina and also assesses prognosis. To evaluate response to drug therapy,
exercise testing is indicated for angina patients. Individuals who continue to have pain at rest or minimal activity are at higher risk and should not be included for exercise testing. Patients with aortic stenosis are not to be employed for exercise testing. It is preferable to monitor exercise electrocardiography during evaluation for exercise tolerance. Exercise test should be terminated when hypotension, ventricular and supraventricular arrhythmias or more than 3 or 4 mm ST segment depression occurs in electrocardiogram (ECG). If exercise testing results do not confirm the clinical picture of the patient, stress scintigraphy or echocardiography needs to be done.

Patients with angina pectoris should avoid sustained isometric exercise because this type of exercise may induce left ventricular dysfunction which is reversed when exercise is terminated. Nitroglycerin has been shown to improve left ventricular function during isometric exercise. During exercise, calcium channel blockers reduce both systolic and diastolic blood pressures in hypertensive patients. Diltiazem when given with β-blockers and nitrates increases exercise tolerance in angina pectoris patients. If the patient experiences fatigue with β-blockers on exercise, alternatively, calcium channel blockers may be used.
WHAT IS CARDIAC ARRHYTHMIA?

Cardiac arrhythmia is an abnormality of rate, regularity, site of origin of cardiac impulse and disturbances of impulse conduction that alters the normal sequence of activation of atria and ventricles. The term dysrhythmia or arrhythmia is not limited to irregularities of the heart rhythmicity but is applied to disturbances of rate and conduction of cardiac impulses as well. Cardiac arrhythmias have been the source of concern for clinicians, which demand proper management. In the past two decades, understanding of cellular and molecular basis of both normal and pathological electrophysiology of heart has helped immensely in the control of various cardiac arrhythmias.

Classification

Cardiac arrhythmias may arise from abnormal impulse generation or impulse conduction or both in combination. Arrhythmias may be classified into:

1. Those associated with no structural diseases of heart
   a. Sinus tachycardia and bradycardia
   b. Premature beats
   c. Paroxysmal supraventricular tachycardia
   d. Atrial flutter and fibrillation

2. Associated with disease of heart
   a. Ventricular tachycardia
   b. Atrial flutter
   c. Atrial fibrillation

3. Drug-induced cardiac arrhythmias
   a. Digoxin
   b. Calcium
   c. Adrenaline
   d. Quinidine

CARDIAC ARRHYTHMOGENESIS

Cardiac arrhythmias may be due to failure of generation and propagation of cardiac impulses or abnormal impulse conduction. Normal cardiac rhythmicity is attributable to an intricate relationship between impulse generation, conduction velocity, pathlength and duration of
refractory period. When one or more of the above factors are altered, arrhythmias may result. In addition, high blood pressure, hypothyroidism, valvular diseases, ischemia, hypoxia, acidosis, electrolyte imbalance and excess of catecholamine concentration induce cardiac arrhythmias. In short, amplification of cardiac electrical heterogeneities produces arrhythmias as given in Figure 6.4.

More importantly, regional differences in electrical properties of the cardiac cells, gene mutations, which cause ion channelopathies have been found to be molecular mechanisms responsible for arrhythmogenesis in cardiac muscle.

In summary, cardiac arrhythmias are due to different mechanisms like enhanced automaticity, Ca\(^{2+}\) and Na\(^+\) dependent reentry, early and after depolarization and presence of parasystole. Therefore, drug therapy aims at modification of arrhythmogenic mechanisms—suppression of triggered activity and selective ion channel blockade, so as to normalize electrophysiological properties of cardiac muscle.
CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

I. Na+ Channel Blockers

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<td>Quinidine</td>
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<td>Procainamide</td>
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II. β-Adrenergic Receptor Blockers

Propranolol, esmolol (for acute arrhythmia intraoperative use), metoprolol

III. K+ Channel Blockers

Amiodarone, sotalol, ibutilide, dofetilide

IV. Calcium Channel Blockers

Verapamil, diltiazem, cibenzoline

Miscellaneous

Adenosine, digoxin, potassium, EDTA and bretylium

GENERAL MECHANISM OF ACTION OF ANTIARRHYTHMIC DRUGS

Drugs used to control cardiac arrhythmias act by diverse mechanisms and are selective in their effects. The efficacy of antiarrhythmic drugs is dependent on type of arrhythmias. Hence, accurate diagnosis of clinical type of arrhythmia is essential for the success of given drug treatment. Generally, antiarrhythmic drugs act by the following mechanisms:

1. Direct cardiac depressant effects—negative chronotropic and inotropic actions which reduce excitability and automaticity
2. Ion channel blockade: Different groups of drugs block Na+, Ca2+ and K+ channels to restore normal cardiac rhythm by decreasing conduction velocity
3. Suppress ectopic foci (additional pacemakers)
4. Inhibit re-entry mechanisms
5. Reduce phase-4 depolarization
6. Modify autonomic control over myocardium
7. Majority of antiarrhythmic drugs prolong ERP/APD ratio of the heart (effective refractory period versus action potential duration ratio)

All the above effects are seemingly involved in antiarrhythmic use of different groups of drugs. No single drug produces all these actions. However, broad-spectrum antiarrhythmics like quinidine and amiodarone are best known to act by multiple mechanisms.

Quinidine

Quinidine is an alkaloid obtained from the cinchona bark. It is the d-isomer of quinine. Quinidine is an antiarrhythmic, antimuscarinic, Na+ channel blocker and α-adrenergic receptor
antagonist. Like quinine, it has antimalarial and oxytocic actions. It is a broad-spectrum antiarrhythmic agent with a plasma half-life of 6 hours. Acidification of urine enhances the rate of renal elimination of quinidine.

Thromboembolic disorders, hypotension, syncope, diarrhoea, paradoxical arrhythmias, thrombocytopenia and cinchonism have been observed as adverse effects of quinidine. Prior digitalization of the patient may arrest quinidine-induced arrhythmias. Quinidine is used in both supraventricular and ventricular arrhythmias.

**Drug Interactions**

- Quinidine + digoxin: Co-administration of these drugs shows both kinetic and dynamic interactions. Quinidine is a vagolytic agent, digoxin is a vagotonic. This is said to control arrhythmogenic effects of quinidine. Quinidine displaces digoxin from tissue-binding sites and thus increases plasma level of digoxin which in turn precipitates toxicity. Nevertheless, these drugs are given together by titrating the doses of both the drugs.
- Quinidine + nitroglycerin: Quinidine promotes hypotensive action of nitroglycerin.

**Contraindications**

- Heart failure
- Thrombocytopenic purpura
- Digoxin intoxication
- Hypersensitivity
- Heart block

**Procainamide**

Procainamide is a short-acting less vagolytic sodium channel blocker with no alpha adrenergic receptor antagonistic effects. This drug can be used in emergency arrhythmic conditions in place of quinidine. Long-term administration of procainamide may produce fever, agranulocytosis, hypersensitivity reactions, systemic lupus erythematosus and cardiac tamponade. The rate of acetylation of procainamide appears to be genetically determined. N-acetyl procainamide is an active metabolite with a plasma half-life of 3 hours. Procainamide administration is not safe to continue over 3 months.

**Lignocaine**

Lignocaine is an amide local anesthetic sodium channel blocker. The antiarrhythmic action of lignocaine is confined to ventricular arrhythmias. It is the drug of choice to treat digoxin-induced ventricular tachycardia and postmyocardial infarction arrhythmias. It is administered by intravenous route in intensive care unit. It is not effective by oral route since it undergoes complete first pass metabolism.

**Amiodarone**

Amiodarone is a broad-spectrum antiarrhythmic known to act by several mechanisms as mentioned below.

- Causes perturbation of lipid milieu in which ion channels are situated—blocks $K^+$, $Na^+$, and $Ca^{2+}$ ion channels.
Cardiovascular Drugs: Drugs Used for High Blood Pressure

- Non-competitive antagonist of both $\beta$ and $\alpha$ adrenergic receptors.
- Prolong refractory periods of all cardiac tissues and inhibit cell-to-cell coupling.
- Interact with nuclear thyroxine receptors.

Amiodarone produces antianginal actions by reducing peripheral vascular resistance.

Pharmacokinetics

Amiodarone has unusual pharmacokinetic properties. It is a highly lipophilic agent having a high volume of distribution. Amiodarone is absorbed and eliminated slowly. The plasma half-life is up to 103 days. Frequent dosing produces cumulative toxicity. Diethylamiodarone is an active metabolite of amiodarone.

Adverse Effects

Amiodarone produces adverse reactions which are prominently due to extensive tissue accumulation. It gets concentrated in lungs, skin, liver, heart, fat, muscle and eye. Hence, toxic effects are numerous, unpredictable and at times idiosyncratic in nature.

Bradyarrhythmia, hypotension, heart block, precipitation of heart failure, corneal microcrystal deposits, both hypo- and hyperthyroidism, fatal pulmonary fibrosis, photosensitivity, peripheral neuropathy and cardiac arrhythmias have been reported as adverse effects of amiodarone.

Drug Interactions

- Amiodarone + warfarin: Warfarin action is augmented. There is a danger of hemorrhage.
- Amiodarone + digoxin: Increases the plasma concentration of digoxin necessitating reduction in digoxin dose.
- Amiodarone + inhalation anesthetics: Increased tendency for cardiac arrhythmias.

Amiodarone inhibits cytochrome P3D4, cytochrome P2C9 and P glycoprotein which may be responsible for multiple drug interactions.

BETA-BLOCKERS AS ANTIARRHYTHMIC AGENTS

Propranolol-like drugs produce therapeutically beneficial antiarhythmic action. Generally, $\beta$ blockers, by blocking the action of endogenous catecholamines in the heart, control various types of cardiac arrhythmias. Sotalol is a unique $\beta$ blocker which blocks $K^+$ channels and indicated in both supraventricular and ventricular arrhythmias. The advantages of $\beta$ blockers antiarrhythmic therapy is that reduction in recurrence of myocardial infarction. Esmolol is a short-acting $\beta$ blocker always given intravenously in the management of intraoperative cardiac arrhythmias.

CALCIUM CHANNEL BLOCKERS AS ANTIARRHYTHMIC DRUGS

It is common to use verapamil as $\alpha$ antiarrhythmic calcium channel blocker although diltiazem and nicardipine can also be used. The reason for using verapamil as antiarrhythmic lies in its nature of recovery from calcium channel. Verapamil is slow to dissociate from the calcium channel and blocks effectively both after and early depolarizations. It prolongs the refractory period of AV node. Administration of verapamil is better avoided with propranolol since both the drugs have propensity to precipitate heart failure.
DRUGS USED FOR VARIOUS TYPES OF CARDIAC ARRHYTHMIAS
Cardioversion has changed many indications for antiarrhythmic drugs. Ideally, before embarking on antiarrhythmic drug therapy, specific etiology may be identified for effective restoration of cardiac rhythm. Accurate diagnosis of the clinical type of arrhythmia is mandatory for rational and efficacious drug treatment. Drug therapy given on improper diagnosis could be ineffective and more dangerous than no drug therapy.

Paroxysmal Supraventricular Arrhythmias
Currently, adenosine is the drug of choice to treat this condition. It is given intravenously to activate ATP-sensitive K⁺ channels that control arrhythmia. Bronchospasm may be precipitated by adenosine. Care is necessary to avoid this in an asthmatic patient.

Atrial Flutter
Many drugs are useful in atrial flutter wherein heart rate is 250-350 per minute. Conventionally, digoxin, propranolol and verapamil have been used. Digoxin before restoring the normal cardiac rhythm, converts flutter into fibrillation. By prolonging the effective refractory period of AV node, digoxin reduces ventricular rate in atrial flutter. Warfarin anticoagulant therapy is also recommended to prevent the formation of intramural clot. As a prompt resort, cardioversion is also employed for atrial flutter.

Atrial Fibrillation
Atrial fibrillation wherein the heart rate ranges from 400-600 beats per minute was treated in the past by quinidine, digoxin and propranolol. Direct current counter-shock effectively defibrillates the heart. Further, verapamil or propranolol can be given orally to stabilize the patient.

Ventricular Tachycardia
Lignocaine, phenytoin and mexiletine are employed in this condition. Lignocaine given intravenously saves the life of the patient in digoxin-induced ventricular tachycardia. Bradyarrhythmias have been controlled by using electronic pacemakers.

EXERCISE AND ANTIARRHYTHMIC DRUGS
Unless the patient restores the normal sinus rhythm and stabilized, exercise program needs to be avoided. The reasons for this are many. Exercise-induced ventricular ectopy is seen in more than 2.5% of the patients. The prevalence of ventricular ectopy increases with age. Minor cardioacceleratory effects of exercise must be anticipated in patients who are on quinidine therapy. Both quinidine and procainamide therapy can mask exercise-induced ST segment depression in ECG and produce false negative results. Nevertheless, antiarrhythmic drugs may be used effectively during regular exercise program to reduce the risk of exercise-induced arrhythmias. Beta-blockers are effective in suppressing ectopic activity. More importantly, the patient must be supervised to know how drug therapy interacts with exercise.
INTRODUCTION
Heart failure is a common disorder in which cardiac reserve is reduced. Congestive cardiac failure is an inability of the heart to pump sufficient blood to satisfy the metabolic need of the body. In this condition, heart is unable to meet the blood flow to the major organs and body tissues during exertion and in severe cases, at rest also. When heart fails as a pump, body compensatory mechanisms operate to maintain tissue perfusion. These adaptive changes include:
- Increased adrenergic activity, which results in increased heart rate, venous tone and central venous pressure. Consequently, preload increases and corresponding increase in afterload is observed.
- Renin-angiotensin system is activated in chronic heart failure. Initially, all the above adaptive mechanisms tend to maintain the cardiac output and renal perfusion. However, as the contractile state of myocardium deteriorates, cardiac output declines leading to ventricular dilatation, hypertrophy, peripheral edema due to reduced renal perfusion. Hence, measures to improve cardiac contraction and control excessive adrenergic activity and mobilization of edematous fluid are the main goals of the management of heart failure.

CLINICAL FEATURES
The clinical features of chronic heart failure are: shortness of breath, exertional apnoea, orthopnoea, fatigue, exercise intolerance, tachycardia, reduced cardiac output, peripheral edema, hypotension, reduced pulse pressure and increased external jugular pressure, enlargement of heart, cough, ascites and oliguria.

DRUGS
A wide variety of drugs are used in the management of congestive cardiac failure along with salt restriction and rest. The drugs include:

Diuretics:
- Loop diuretics: Frusemide, bumetanide, torsemide
- Thiazides: Hydrochlorothiazide, metolazone, chlorthalidone
- K⁺-sparing diuretics: Spironolactone

ACE inhibitors: Captopril, enalapril, lisinopril, ramipril

Vasodilators: Hydralazine, nitroglycerin, isosorbide dinitrate, sodium nitroprusside (for acute severe heart failure)

Cardiac glycosides: Digoxin, digitoxin, medigoxin
**Inotropic agents:** Amrinone, milrinone, dobutamine, enoxomine  
**β-adrenergic receptor blockers:** Carvedilol, bisoprolol (used in second stage of management)  
**Others:** Prazosin, anticoagulants

**Diuretics in Congestive Cardiac Failure**

The rationale of use of diuretics in heart failure is to provide symptomatic relief and to reduce extra/intra-vascular volume. Oral diuretics produce euvolemia, reduce high blood pressure, causes natriuresis, kaliuresis and chloruresis. Thus, diuretics reduce volume load, which improves the haemodynamics in heart failure. It is recognised well that at the initial stages of management of heart failure, the combination therapy of diuretics and angiotensin-converting enzyme inhibitors offers substantial benefit.

**Angiotensin-converting Enzyme Inhibitors**

Administration of angiotensin-converting enzyme inhibitors in heart failure favours good prognosis. Enalapril-like drugs inhibit aldosterone secretion, reduce salt and water retention, produce vasodilatation, decrease blood pressure and increase exercise tolerance in chronic heart failure. Thus, they reduce mortality rate by 20% and, therefore, angiotensin-converting enzyme inhibitors have been used as first line of drugs in the management of heart failure.

**Other Vasodilators**

Vasodilators like hydralazine, nitroglycerin, isosorbide dinitrate and sodium nitroprusside have been used at different stages in the management of heart failure. Vasodilators act by reducing peripheral resistance as well as preload and afterload causing arterial and venodilatation. In acute severe heart failure sodium nitroprusside is given intravenously. For ambient patients, generally nitrates are used.

**Cardiac Glycosides**

Glycoside is defined as naturally occurring chemical substance that represents the combination of non-sugar moiety called ‘aglycone’ or ‘genin’ with two or more molecules of sugar. On acid hydrolysis, glycosides liberate reducible sugar. A glycoside that produces a selective and specific action on the heart, which is of therapeutic value, is known as ‘cardiac glycoside’. For example, digoxin and digitoxin.

**DIGOXIN**

Digoxin is obtained from leaves of *Digitalis lanata* also known as fox glove. The term ‘digitalis’ is a generic name used to designate digoxin-like drugs. Digitalis is not a drug. The chemistry of digoxin and digitoxin bears relationship with steroid hormones, plant sterols and bile acids.

**Mechanism of Action of Digoxin**

Digoxin is used in congestive cardiac failure for its ‘positive inotropic action’ on the heart. When administered to heart failure patient, digoxin by virtue of positive inotropic action improves the haemodynamics by the following actions:
Cardiovascular Drugs: Drugs Used for High Blood Pressure

(i) Increases cardiac output
(ii) Reduces heart rate by decreasing end-diastolic volume
(iii) Decreases venous blood pressure
(iv) Mobilizes the edematous fluid and reduces the blood volume.

As shown in Figure 6.5, the subcellular mechanisms that result in cardiotonic action of digoxin are:
(i) Inhibits membrane bound Na\(^+\)-K\(^+\)—ATPase enzyme
(ii) Depletes myocardial K\(^+\)
(iii) Increases intracellular Na\(^+\) concentration
(iv) Releases the Ca\(^{2+}\) from bound form: Increases Ca\(^{2+}\) influx during action potential, intracellular Ca\(^{2+}\) is increased.
(v) More Ca\(^{2+}\) is made available for the contractile proteins of myosin filament. In presence of digoxin more cardiac work is achieved with the consumption of less energy. Unlike adrenaline, digoxin does not increase myocardial oxygen consumption.

Actions of Digoxin

Digoxin predominantly acts on the heart and by improving haemodynamics in heart failure patients, produces mild diuretic action. Besides, digoxin acts as local as well as central emetic.

Cardiac Actions

Digoxin is a cardiotonic drug, increases both the force and rate of contraction, digoxin shortens systolic duration and speeds relaxation of the myocardium.

Digoxin being a vagotonic drug and also by direct action reduces the heart rate in heart failure. Digoxin increases cardiac output by reducing central venous pressure.

Actions of Digoxin on AV Node

Digoxin produces direct and indirect actions on AV node to induce first and second degree block at therapeutic dose level. Digoxin markedly prolongs the effective refractory period of AV node by direct action on nodal membrane-bound Na\(^+\)-K\(^+\)—ATPase enzyme. The vagus influence on AV node is augmented by digoxin. Consequently, sensitivity to noradrenaline

Fig. 6.5: Mechanism of action of digoxin
is reduced. In total, digoxin blocks AV node. These actions of digoxin are of great value when digoxin is administered for atrial flutter and fibrillation. By blocking AV node, digoxin protects the ventricle from impulse load. For this reason, digoxin is indicated in supraventricular tachyarrhythmias. However, it is contraindicated in Wolff-Parkinson-White syndrome.

Method of Administration
Digoxin is commonly administered by mouth and occasionally given as injection. Digoxin has long plasma, half-life, 36-48 hr and the therapeutic safety margin is narrow, i.e., safe to toxic dose is not wide. Hence, it is conventional to administer a loading dose of digoxin initially to create desirable plasma concentration of the drug for sustained effect. Thereafter, a maintenance dose is given as required. To start with, digitalisation of patient is done by giving a loading dose spread over to 24-48 hours. Since the patient's response is variable digoxin toxicity is often lethal, great care is necessary. Therapeutic drug monitoring would suffice the need here, particularly to alleviate digoxin toxicity

Recently, it has been recommended that digoxin therapy can be started with a daily dose 0.125 mg to 0.25 mg by mouth depending on patient’s lean body mass and renal function. After a week, plasma concentration can be estimated and maintained thereafter as required.

Therapeutic Uses
Digoxin is indicated in the management of congestive cardiac failure, atrial flutter, atrial fibrillation and paroxysmal supraventricular tachycardia.

Adverse Effects
Digoxin toxicity can be severe and lethal since all preparations of digitalis have low margin of safety.

Potassium depletion, hypercalcemia, hypoxia, hypothyroidism, cardiomyopathy and error in the administration are the factors that aggravate digoxin adverse effects.

Nearly 75-100% of patients who receive digoxin experience nausea, vomiting and abdominal discomfort. Approximately 25% of the patients report blurred vision, chromotopsia—abnormal colour perception to green or yellow. Digoxin can induce neurological adverse effects like headache, fatigue, malaise, anxiety, nightmares and delirium. Convulsions are rare. Cardiac toxicities of digoxin include sinus bradycardia, AV node block, pulsus bigeminy (couple beats), ventricular tachycardia, ventricular fibrillation and death. Besides hypokalemia, gynecomastia and thrombocytopenia have been observed.

The treatment for digoxin toxicity is as follows:
1. Withdraw digoxin and diuretic.
2. Supplement potassium intravenously if there is no complete heart block
3. Lignocaine 50-100 mg intravenous administration is often life saving.
4. Oral phenytoin 400-100 mg/day for 10 days
5. Administer activated charcoal
6. Measure serum electrolyte level and adequate measures to be undertaken
7. Pacing needs to be considered as a last resort
8. Antidigistics, antibodies—Fab may be given to reactivate Na\(^+\)-K\(^+\)-ATPase.
9. Propranolol and atropine administration is also useful to restore the normal sinus rhythm.
10. Cholestyramine can be given to reduce the intestinal absorption of digoxin.

**Drug Interactions**

1. Digoxin + quinidine: Both pharmacokinetic and pharmacodynamic interaction have been documented. Quinidine alters volume of distribution of digoxin, decreases the renal and non-renal clearance and increases plasma concentration of digoxin by displacing it from tissue protein-binding sites. Quinidine is a vagolytic drug. Vagotonic digoxin can minimise proarrhythmogenic action of quinidine. In presence of quinidine, dose of digoxin must be reduced up to 50% to avoid toxicity.

2. Digoxin + local anaesthetic + adrenaline preparation: There will be increased risk of cardiac arrhythmia.

3. Digoxin + kaliuretic diuretics: Hypokalemia, a factor that aggravates digitalis toxicity

4. Digoxin + succinylcholine: There is an increased risk of disturbed cardiac rhythm.

**Contraindications**

Digoxin is contraindicated in:

a) Myocardial infarction  
b) Hypercalcemia  
c) Rheumatic carditis  
d) Hypothyroidism  
e) Systemic alkalosis  
f) Wolf-Parkinson-White syndrome  
g) Ventricular fibrillation  
h) Subaortic hypertropic stenosis  
i) Systemic hypoxia  
j) Heart block (relative contraindication)

**HEART FAILURE AND PHYSIOTHERAPY**

Generally, congestive heart failure patients are advised to take rest till clinical stability is attained. In acute severe heart failure, bedrest is mandatory. On drug management, when the patients show exercise tolerance, a simple gradual exercise programme may be advised on an individual basis. Undoubtedly, a slow and steady increase in physical activity of heart failure patient improves the lifestyle. Hopefully, this will contribute for better prognosis, may deter fatigue in particular.
PHARMACOTHERAPY OF SHOCK

INTRODUCTION
Shock is a complex clinical syndrome in which circulatory system fails to maintain adequate tissue perfusion. It is a life-threatening impairment of oxygen delivery to organ system.

CLASSIFICATION
In clinical medicine, shock is classified as:
1. Hypovolemic shock
2. Cardiogenic shock
3. Septicemic shock
4. Anaphylactic shock
5. Neurogenic shock
6. Shock due to heat stroke

Hypovolemic Shock
It results from fluid loss and can be due to hemorrhagic or non-hemorrhagic causes. Non-hemorrhagic causes include severe vomiting and diarrhoea, polyuria and burns. Correction of hypovolemia is important in shock. Replacement of fluids and administration of plasma expanders and blood products often save the life of patient. Albumin, dextran, gelatins and esterified starches expand the intravascular volume more promptly and effectively, hence, administered in hypovolemic shock.

Cardiogenic Shock
Usually it is a consequence of acute cardiac failure. This is commonly associated with acute myocardial infarction. Reduced cardiac output and hypotension need to be addressed effectively in cardiogenic shock. Drugs used for these purposes are dopamine and dobutamine. The urgent need is to restore normal renal function. Dopamine is given intravenously for its renovasodilatory and positive inotropic action on heart. Dopamine can be used in all types of shock. Noradrenaline is re-emerging as a useful drug in septic shock.

Septicemic Shock
It occurs as a complication of infection with hypotension. This requires prompt treatment. Empirically, penicillin with aminoglycoside or third generation cephalosporin antibiotics and metronidazole have been used in sepsis syndrome. Other supportive measures like
administration of vasoconstrictors, fluid replacement and oxygenation have to be undertaken. Noradrenaline can be used in septicemic shock where the cardiac output is usually high but peripheral resistance is low. Methods to inhibit effects of bacterial endotoxin during sepsis syndrome are under investigation.

**Anaphylactic Shock**

It is the result of a hypersensitivity reaction and haemodynamic changes that occur in this condition are similar to septic shock. It is a type I hypersensitivity reaction to various allergens such as drugs, foods, latex and insect venoms. This is a medical emergency and life-saving prompt treatment is a must. The life-threatening laryngeal edema, bronchospasm and hypotension have to be addressed promptly. Adrenaline (intramuscular injection) is a life-saving drug in most of these conditions. In addition to this, intravenous fluids and other supportive measures need to be undertaken. Administration of H₁ receptor antagonists like chlorpheniramine and steroids like hydrocortisone hemisuccinate intravenously is also useful. Nebulized salbutamol may be required in serious conditions associated with bronchospasm.

**Neurogenic Shock**

It may be due to spinal cord injury, severe trauma, unbearable pain and fright. Reduced cardiac output, hypotension and decreased cerebral flow have been the impending clinical features of neurogenic shock, which requires effective drug treatment. The treatment of neurogenic shock is by and large in line with other type shock therapy. Vasoconstrictors, intravenous fluids and oxygenation are the mainstay during the treatment of neurogenic shock.

**Heat Stroke**

It is a life-threatening condition, resulting from failure of the thermoregulatory mechanisms. Cerebral dysfunction, impaired consciousness, high fever and absence of sweating are the main features of heat stroke. Hypovolemic or cardiogenic shock both may occur due to heat stroke. Fluid replacement, chlorpromazine and diazepam administration and body cooling measures have been recommended in shock caused by heat stroke.
A well-designed exercise program is of immense value for the ailing population to attain health benefits. However, it is not easy to prescribe an exercise program at an optimum level for preventive and rehabilitative purposes. Basically, the design of an exercise program depends on exercise training frequency and the progression of physical activity in the subject. Here, it is important to assess average conditioning capacity of the subject during the graded exercise stage. An unaccustomed vigorous exercise program may bring devastating consequences including death. One must be sure that even a simple exercise program does not cause stress and alarming changes in the vital functions of the body. This is of great significance in cardiac patients in particular.

Exercise brings pronounced physiological changes in a complex way involving nervous, cardiovascular, and musculoskeletal systems. Exercise can cause hypoxemia and bronchial asthma in susceptible individuals. Hence, before exercise program is suggested to needy patients, pulmonary and cardiac limitations must be assessed. Thus, it is necessary to integrate exercise-induced stress with drug regimen schedule. As exercise program has both diagnostic and therapeutic values, the impact of exercise training on drug therapy must be taken into consideration. This would determine the success of the exercise program. Clearly, a well-designed exercise program improves the general sense of well-being of a patient. Exercise lowers the risk that arises from hyperlipidemia and obesity. Pertinently, it is the job of the physiotherapists to design an exercise program, which maximizes the residual cardiovascular potential in a patient. Indeed, exercise program ought to concur with changes that occur in the body during drug treatment and exercise as well.

Obviously, the safety of proposed exercise program depends on type, intensity, duration and frequency of exercise, time, age and disease. How body responds to well-planned exercise training is significant for harvesting benefits. Exercise induces many physiological changes in the body. These changes occur mainly due to various compensatory mechanisms that involve complex organ processes. Firstly, cardiopulmonary system maintains an energy exchange process from mouth to mitochondria. Myoskeletal system and central nervous system integrate well for locomotion. Blood supply to the muscle is increased to 80% as against 20% at rest. Renal clearance enhances due to increase in cardiac rate and output.
Blood pressure is reduced approximately by 13 mm Hg systolic and 10 mm Hg diastolic. Exercise promotes clot lysis and liberates nitric oxide—an endogenous vasodilator. High density lipoprotein (HDL) levels increase with exercise and substantial utilization of triglycerides also increase. Regular exercise reduces platelet aggregation and plasma fibronogen level. As exercise escalates basal metabolic rate, it increases oxygen requirement. Carbon dioxide production is enhanced and the levels of aldosterone, potassium, glucagon and renin are reduced by exercise. It has been observed that exercise alters many risk factors in individuals who are under constant stress. Interestingly, how drug therapy adapts to changes brought by exercise is an intriguing matter of complexity. Conversely, how exercise-induced changes alter the kinetic and dynamic properties of a drug largely remains unknown as yet. Nonetheless, safe level exercise is determined by factors like functional capacity of the individual which is assessed during the graded exercise test, heart rate reserve, electrocardiogram changes and arterial blood pressure. At the same time, measures of exercise tolerance have been followed to determine exercise capacity. These measures of exercise tolerance are: i) maximum oxygen consumption ($V_{O2}$), ii) breathing fraction, iii) pulmonary gas exchange and iv) anerobic threshold.

It is crucial that health benefits caused by exercise must be assessed thoroughly and properly before conditioning the cardiac patients to exercise training. It is important to obtain the subject’s prognostic information. This can be gathered at the level of exercise testing itself by acquiring knowledge about disease-drug-exercise interaction. Drugs that permit normal exercise means they will not bring changes in vital functions of the body. Heart rate and cardiac stroke index should remain unaltered. But this is not easy to translate to reach safe level exercise program. Unfortunately, lack of uniformity in exercise protocols at different drug doses and disease breeds complexity. It is true that disease state, administered drug dose and duration of drug therapy are the factors that determine the sustenance of exercise-induced health benefits. This warrants for constant medical vigilance on individual basis and coordinated interaction between physiotherapist and physician.

Drug therapy is clearly not a contraindication to short-term or long-term exercise program. What is required here is the principles of exercise physiology must be translated well in relation to drug therapy in a patient. Certainly, an understanding of exercise principles is of great clinical significance, especially for patients with major cardiovascular disease.

Cardiac patients have been advised to go for exercise for two purposes—firstly, to assess the functioning capacity by exercise testing, secondly, to control the alarming implications of risk factors in cardiovascular disorders. Here the severity of disease, age of the patient and the nature of the drug actions are the important factors that guide physiotherapists to recommend a safe level exercise. Significantly, the role of physiotherapist is critical here in avoiding fatal variation during exercise testing in cardiac patients.

Generally, drugs prescribed for coronary heart diseases, high blood pressure and heart failure permit regular exercise within limits. At first, cardiac patients need not be unduly perturbed about the outcome of drug therapy which runs well with exercise. In fact, most of the antihypertensive drugs increase exercise tolerance (Table 7.1). However, this cannot be taken as a general rule. Obviously, the interaction between exercise and antihypertensive drugs does vary with number and types of administered drugs. Further, co-existing morbidities and psychosocial status of the patient play a significant role in gaining benefit
out of trained exercise program. Therefore, it is difficult to discern the extent and the nature of the drug disease exercise interaction. Moreover, intra- and interpatients’ response to exercise protocols vary at different stages of disease management.

Table 7.1: The influence of cardiovascular drug therapy on exercise tolerance

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Exercise tolerance</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>increase</td>
<td>reduce the incidence of early morning ischemic cardiac attacks</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>increase</td>
<td>may permit intense exercise</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>increase</td>
<td></td>
</tr>
<tr>
<td>Alpha-adrenergic receptors blockers</td>
<td>increase</td>
<td>workload capacity may be increased.</td>
</tr>
<tr>
<td>Nitrates</td>
<td>increase</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>may cause ventricular arrhythmias</td>
<td>increases work performance during exercise reduces oxygen consumption</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td>isometric exercise-induced dynamism is enhanced</td>
</tr>
</tbody>
</table>

More importantly, thorough hemodynamic and biochemical evaluation of cardiac patients is necessary even during exercise testing. It is imperative to subject the cardiac patient for physical conditioning prior to indulgence in exercise program irrespective of the positive outcome of exercise testing. Studies have demonstrated that physical conditioning of patient reduces the vulnerability to ventricular fibrillation.

Rest is mandatory for advanced congestive cardiac failure. Once the hemodynamics improve by angiotensin-converting enzyme inhibitor, diuretic or digoxin administration, exercise program may be advised. Particularly, when drug therapy reduces peripheral resistance, increases blood supply to skeletal muscles and decreases heart rate, simple exercise may be prescribed. Clearly, a well-designed simple exercise program increases life motivational spirits of heart failure patients. Here, care is absolutely necessary to avoid overindulgence in exercise program. Heart failure patients should not go for unaccustomed vigorous exercise without the consent of the physician.

Beta-adrenergic receptor blockers improve exercise tolerance in patients with high blood pressure, angina pectoris and cardiac arrhythmias. Interestingly, cardioselective beta-blocker atenolol is more useful than propranolol. More predictably, atenolol reduces myocardial oxygen requirements in rest and during exercise. Beta-blockers maintain heart rate and systolic blood pressure at optimum level during exercise although individual variation is common. In hot and cold environments, beta-blockers may impair body temperature regulation with exercise. Hyperthermia is often observed in patients with ischemic heart diseases following beta-blocker therapy. This calls for physiotherapists’ attention. It is better for ischemic cardiac patients to avoid sustained isometric exercise. As contrast to this, there are reports which suggest that avoiding exercise program by ischemic cardiac patients may reduce the prevalence of left ventricular dysfunction.

It is common to prescribe buccal tablet of nitroglycerin to provide relief in acute attack of angina pectoris. Anginal patients should not indulge in exercise while nitroglycerin tablet
is kept under the tongue. The consent of physician and physiotherapist is necessary for anginal patients to go for tolerable exercise program on long-acting calcium channel blockers like amlodipine.

Exercise does alter electrolyte balance in the body more particularly potassium level. Any change in electrolyte level in cardiac patients may prove fatal. It is important that great care is necessary to avoid electrolyte imbalance during and after exercise. If the patient is on chronic diuretic therapy and develops hypokalemia with physical exertion, potassium supplementation is a must. On the contrary, vigorous exercise is known to elevate serum potassium level. In this situation, potassium-sparing diuretics are more likely to cause hyperkalemia. Cardiac patients must take care of this dire consequence.

The quality of life escalates on regular exercise. But it is not always fruitful for all patients. For example, a diabetic patient without any complications may well improve with physiotherapy. This may not be true with diabetic patients with high blood pressure and ischemic heart disease. Hence, it is of great significance to condition the patient for exercise with drug treatment of different kinds. Otherwise, simple exercise like climbing a few steps may be detrimental to the patient. Here, a thorough understanding among the patient, physician and physiotherapist is absolutely necessary.

It is also important to know the ways and means to control bronchial asthma induced by exercise. Certainly, prophylactic administration of cromolyn sodium is helpful. The efficacy of cromolyn sodium is seen after continued therapy for 3–4 weeks.

Can a drug therapy improve exercise performance? Is this the reason for drug abuse among sportsmen? It is common that healthy athletes and other sportsmen seek support from drugs like anabolic steroids, amphetamine, diuretics, methylphenidate, doxapram, cocaine and alcohol with a hope to improve their performance. Currently, this is an absurd since science has not validated this claim. The big answer is many studies have categorically described that drugs cannot improve athletic performance. They have no role in maintaining the health of athletics too. On the other hand, if an athlete relies more on anabolic steroids, health is at stake. Anabolic steroids cause potential hazards like hepatic carcinoma, testicular atrophy, hypertension, increased body weight and decreased high density lipoprotein (HDL) level.

Alcohol, amphetamine and caffeine deter fatigue. But these do not have salubrious or beneficial effect on exercise performance. Alcohol increases lactate and uric acid accumulation in the muscles and this may be the cause for rhabdomyolysis observed, especially in humid environment. Amphetamine increases alertness, concentration and reduces the sense of fatigue but produces psychic dependence. Athletes who take amphetamine at high doses do exhibit increased anxiety, insomnia, chest pain and fear. Amphetamine has a direct effect on skeletal muscles and produces rhabdomyolysis. There is no rationale for the use of amphetamine in enhancing athletic performance.

Salicylates and other non-steroidal anti-inflammatory drugs reduce colonic motility and increase oxygen consumption during exercise. At the same time, increase susceptibility to heat injury thus causing paradoxical hyperthermia in an individual. Hence, regular use of salicylates to enhance sports performance has no basis and amounts to the misuse of drugs.

In summary, it is not easy to know the outcome of the drug and exercise interaction. There are many reasons for this. Patients’ response to different stages of drug therapy as
well as type of exercise program is phenomenally different. Neither the physiotherapist
nor the physician can expect what types of problems are confounded while drug treatment
and exercise go together. There is a compelling need to have an account of drug actions
on various decisive parameters of regular exercise program. Drug therapy may be safe.
Indeed, programmed exercise renders well but drug with exercise is not always potentially
beneficial. However, drugs and physiotherapy usually produce promising results in conditions
of motor neuron-related movement disorders.

In short, exercise has favorable effects on blood pressure, lipid profile, insulin resistance,
endothelial function, coagulation profile and cardiac as well as skeletal muscle conditioning.
Drugs acting on central nervous system are of great importance to mankind. These agents are invaluable in relieving pain, fever, sleep disorders, vomiting and offering solace in mental illness. One of the major concerns of treatment of neurological disorders is that etiology of these diseases remains to be known. If the causes of disorders are known, most of these are untreatable. Therefore, drug treatment in neurogenic disease is necessarily symptomatic. A number of neurotransmitters, neurohormones, neuromodulators, neurotrophic factors and peptides have been identified, isolated and their neurobiological roles are being explored.

Neurotransmitters of central nervous system have been classified into two categories: excitatory neurotransmitters and inhibitory neurotransmitters.

NEUROTRANSMITTERS OF CENTRAL NERVOUS SYSTEM

Acetylcholine
Glutamate, aspartate (excitatory)  Gamma-aminobutyric acid-GABA
Noradrenaline, Dopamine, Glycine (inhibitory)
Histamine, Serotonin

Carbon dioxide, ammonia, adenosine and steroids present in central nervous system are collectively referred to as neuromodulators. Peptides found in brain and spinal cord are grouped into two; opioid peptides—endorphins and dynorphins, other group includes substance P, secretin and vasoactive intestinal protein. Peptides exert actions on neurons on their own or in concert with co-exciting neurotransmitters or nerve factors. Besides various hormones, arachidonic acid metabolites do play a functional role in the central nervous system. Importantly, drugs by altering the neuronal energy metabolism, neurotransmitter
role, membrane integrity and transmembrane ionic equilibrium produce their therapeutic effect. Hence, a clear understanding about the neurophysiological role of substances that take part in neuronal activity is desirable for rational drug use.

CLASSIFICATION

Drugs acting on central nervous system are broadly classified into following groups.

I. **Stimulants (analectics)**: Doxapram, nikethamide, methylphenidate, d-amphetamine, nicotine, caffeine

II. **Depressants**: General anaesthetics, sedative hypnotics, ethyl alcohol, antiepileptics, opioid analgesics

III. **Psychopharmacological agents**
   - Neuroleptics (antipsychotics, psychosedatives)
   - Antianxiety agents (anxiolytics)
   - Antimanic
   - Antidepressants
   - Hallucinogenic drugs
   - Nootropics (memory enhancers)

ANALECTICS

Doxapram, nikethamide, caffeine, methylphenidate, dexamphetamine

Analectics are central nervous system stimulants, which have limited therapeutic uses. Doxapram is used in the treatment of acute respiratory failure. Doxapram is given intravenously in postoperative respiratory failure. This drug acts by stimulation of peripheral chemoreceptors and central respiratory centers and increase catecholamine release. Dyspnoea, hyperventilation, cough, bronchospasm, laryngospasm, hiccup and rebound hypoventilation have been observed as doxapram adverse effects. Doxapram should not be used in patients with epilepsy, head injury and acute severe bronchial asthma.

Analectics are also useful in narcolepsy—a state of irresistible sleep attacks during daytime. Dexamphetamine and methylphenidate have been used in narcolepsy with or without antidepressant imipramine.
SEDATIVE HYPNOTICS

INTRODUCTION
A sedative is an agent that allays excitement, decreases the activity and calms the person with little or no effect on motor and mental functions.

A hypnotic drug is defined as an agent that induces sleep, which resembles natural sleep in electroencephalogram characteristics and from which the subject may be easily aroused. Drug-induced sleep is neither fruitful nor restful. Hypnotic drugs produce after or residual effect—‘hangover’ (headache and residual sleepiness). No drug can produce sleep, which resembles natural sleep. However, in sleep disorders sedative and hypnotics are of therapeutic value.

CLASSIFICATION
Sedative hypnotics are classified into three groups based on their chemical nature.

Benzodiazepines
Diazepam, oxazepam, clonazepam, flurazepam, triazolam, midazolam, nitrazepam, lorazepam, alprazolam, chlordiazepoxide

Barbiturates
Phenobarbitone, pentobarbitone, secobarbitone

Non-benzodiazepine and Non-barbiturates
Chloral hydrate, meprobamate, ethchlorvynol, hydroxyzine, methequalone, diphenhydramine, doxylamine

Recently introduced sedative hypnotics
Zopiclone, zolpidem, zaleplon

BENZODIAZEPINES
Pharmacology of Diazepam
Benzodiazepines exert qualitatively similar effects. Nevertheless, general kinetic properties and duration of action differ among various benzodiazepines. These properties in fact determine the choice of benzodiazepines in a clinical condition.

Benzodiazepines act at all levels of central nervous system. All the actions produced by benzodiazepines are due to their effects on central nervous system. Benzodiazepines produce the following actions on neuroaxis:
• Sedative hypnotic
Pharmacology for Physiotherapist

- Anxiolytic
- Anticonvulsant
- Amnesia—loss of memory
- Anaesthesia
- Skeletal muscle relaxation
- Antidepressant (only few like alprazolam)

**Mechanism of Action**
Benzodiazepines potentiate the neural inhibition caused by gamma-aminobutyric acid (GABA). These act on GABA$_A$ receptor complex. Consequently, they regulate the entry of Cl$^-$ ions into post-synaptic cells. Further, benzodiazepines inhibit GABA-dependent calcium current generation and the uptake of adenosine. The action of benzodiazepines is antagonized by flumazenil.

**Pharmacodynamics**
Diazepam is a benzodiazepine sedative hypnotic, anxiolytic, anticonvulsant, anaesthetic and central skeletal muscle relaxant.

**Sedative Hypnotic**
Diazepam moderates excitement and calms the patient. It induces sleep and suppresses rapid eye movement sleep. Hence, diazepam produces hangover after hypnotic action. Diazepam is not a respiratory depressant at hypnotic dose levels and addiction liability is less. Therefore, benzodiazepines are widely used as sedative hypnotics.

**Anxiolytic**
Diazepam provides relief from anxiety. It reduces apprehension and quietens the recipient.

**Anticonvulsant**
Diazepam is the drug of choice to treat status epilepticus and febrile convulsions in children. It is not used for chronic management of epilepsy instead clonazepam is used.

**Intravenous Anaesthesia**
Diazepam when administered intravenously produces anaesthetic effect. It is also used as preanaesthetic medicament. Intravenous diazepam produces transient analgesia and anterograde amnesia. Diazepam is employed as anaesthetic for short surgical procedures although midazolam is preferred. In addition to anaesthetic effect, diazepam relaxes the skeletal muscle. The hallmark of diazepam anaesthesia is that awareness persists.

**Tolerance and Dependence**
Tolerance to diazepam has been observed particularly to its central actions. The development of tolerance depends on dose, duration and frequency of diazepam administration. Diazepam dependence liability is far less than barbiturates. Diazepam dependence is common after
regular use particularly with alcohol abuse. Diazepam should not be discontinued abruptly on chronic use. To avoid dependence, benzodiazepines must be used for short term. However, the development of dependence to diazepam cannot be predicted. Here, the emphasis has been placed on prevention of dependence by judicious use of benzodiazepines.

**Pharmacokinetics**
Diazepam is readily and completely absorbed from gastrointestinal tract. It is also given as suppository. Diazepam absorption is erratic following intramuscular injection. Intravenous administration of diazepam attains peak concentration rapidly. Diazepam binds to plasma proteins extensively up to 80-99% of the dose administered. On metabolism, diazepam liberates active metabolites like oxazepam, temazepam and desmethyl diazepam. Diazepam crosses placenta and appears in milk.

**Adverse Effects**
Like other benzodiazepines, diazepam is relatively safe and rarely fatal. The most frequent adverse effects of diazepam are drowsiness, sedation, hangover, muscle weakness and ataxia. Amnesia, light-headedness, disorganization of thought, confusion, slurred speech, anxiety, euphoria, hypomania and garrulousness have been observed on administration of diazepam. Overdose can produce respiratory depression and paradoxical excitation.

The treatment of diazepam overdosage is purely symptomatic and supportive. Benzodiazepine antagonist ‘flumazenil’ may be used with great care, especially in patients dependent on diazepam-like drugs.

**Therapeutic Uses**
Diazepam is used in the following clinical conditions on short-term basis:

1. **Management of insomnia:** Insomnia patient has difficulty in falling asleep and stay asleep. Diazepam short-term administration is an established method in the management of insomnia. Of late, zolpidem is preferentially used for insomnia since it produces rapid onset of action and less hangover.

2. **Status epilepticus and febrile convulsions:** Since diazepam is not a respiratory depressant, has rapid onset of action, safer and central skeletal muscle relaxant, it effectively controls status epilepticus. Intravenous administration of diazepam along with other measures is a life-saving step in status epilepticus. Diazepam is the drug of choice to treat febrile convulsions in children. It is also used for the initial control of eclampsia and pre-eclampsia.

3. **Tetanus and alcohol withdrawal syndrome:** Diazepam has been used in tetanus and for the relief of muscle spasm, including stiff-man syndrome and cerebral palsy. Alcohol withdrawal syndrome is effectively controlled by diazepam.

4. **Intravenous anaesthesia and pre-medication:** Diazepam can be used as short-acting intravenous anaesthetic and as pre-anaesthetic medicament. Diazepam pre medication produces sedation, which facilitates minor surgical or investigative procedures.

5. **Restless leg syndrome**

6. **Vertigo**
7. Premenstrual syndrome
8. Cardioversion and dissociative disorders (hysteria)
9. Chloroquine poisoning
10. Drug-induced convulsions, for example, organophosphorus compounds and lignocaine.

Drug Interactions
1. Diazepam + alcohol—impairment of driving skill and psychomotor skill
2. Diazepam + levodopa—attenuation of antiparkinsonism action of diazepam
3. Diazepam + general anaesthetics—synergism
4. Diazepam + aminophylline—antagonism—decreases diazepam induced drowsiness
5. Diazepam + oral contraceptive pill—diazepam metabolism is inhibited

Other Commonly Used Benzodiazepines (Table 8.1)

<table>
<thead>
<tr>
<th>Name</th>
<th>Route of administration</th>
<th>Therapeutic use</th>
<th>t½ (half-life) in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Oral</td>
<td>Anxiolytic antidepressant</td>
<td>12-14</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Oral</td>
<td>Anticonvulsant</td>
<td>23-28</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Oral</td>
<td>Insomnia</td>
<td>74-98</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Oral, IM, IV</td>
<td>Anxiolytic, premedicament, antiemetic</td>
<td>14-19</td>
</tr>
<tr>
<td>Midazolam</td>
<td>IV, IM</td>
<td>Intravenous anaesthetic</td>
<td>1.9-2.5</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Oral</td>
<td>Insomnia, anxiolytic</td>
<td>8-10</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Oral</td>
<td>Insomnia in elderly</td>
<td>3-4</td>
</tr>
</tbody>
</table>

ZOLPIDEM
Zolpidem is a nonbenzodiazepine sedative agent with minimal anxiolytic, anticonvulsant muscle relaxant properties. Zolpidem is used as hypnotic in short-term management of insomnia. It is also a GABA mimetic agent like diazepam. Zolpidem has rapid onset of action with inconsistent negligible effect on rapid eye movement sleep.
PHARMACOLOGY OF ETHYL ALCOHOL

INTRODUCTION
Since, the dawn of human history, alcohol has been the forerunner in bringing social and medical problems. It is well recognised that chronic excessive consumption of alcohol causes damage to many organs particularly brain and liver. Alcohol consumption has also been associated with an increased risk of some types of cancer. ‘Alcoholism’ refers to dependence on alcohol, which is a constant challenge to medical world. Alcohol interacts with many drugs resulting in potentially hazardous consequences. Hence, a comprehensive knowledge about the dynamic and kinetic properties of alcohol is necessary for a clinician and allied health personnel.

LOCAL ACTIONS OF ALCOHOL
Alcohol produces the following local actions:
- Refrigerant
- Rubefacient
- Antiseptic
- Astringent
- Anhidrotic
- Irritant
- Ulcerogenic
- Neurolytic—produces peripheral nerve degeneration

Clinical Uses of Local Actions of Alcohol
Alcohol is used to disinfect skin prior to venepuncture and injection. Alcohol is also used for its skin cooling effect and to harden the skin. Ethanol may be injected in the close proximity of peripheral nerves to relieve neuralgic pain. Alcohol sponging is advocated for bedridden patients to prevent bedsores and in conditions of hyperpyrexia as well.

SYSTEMIC ACTIONS OF ALCOHOL
Man consumes alcohol in large quantities in the form of different beverages. The alcohol content of beverages vary. It ranges from 4-6% in beer, 10 to 15% wine, 40% in whisky and up to 55-60% in gin and brandy. Alcohol produces predominant actions on central nervous system and significant effects on other organ systems.
Action on Central Nervous System

Alcohol is a central nervous system depressant. It disturbs the neuronal excitation and inhibition regulatory mechanisms. Consequently, alcohol produces behavioral disinhibition and euphoria. Since alcohol releases the neuronal inhibitory control, euphoria is produced. Primarily, alcohol-induced euphoria is due to its action on inhibitory control, over neurons of the brain.

The action of alcohol on central nervous system is proportional to the concentration in blood. Alcohol releases the cerebral cortex from integrated control. As a result, personality becomes expansive, lively, spirited, vivacious, confidence abounds and speech becomes eloquent. Self-criticism, hesitation and caution are lost under the influence of alcohol. Finer grade of discrimination, memory and concentration insight are lost. Alcohol neither increases mental nor physical activity. Mood swings and uncontrolled emotional outbursts are common. Chronic excessive consumption of alcohol produces neurological disorders including brain damage—encephalopathy. Acute alcohol intoxication induces coma respiratory arrest and death.

The development of tolerance to central actions of alcohol is common on continuous intake. Alcohol dependence may be attributable to neuronal adaptation in central nervous system. Sudden withdrawal of alcohol produces characteristic withdrawal syndrome. Alcohol withdrawal syndrome features vary with amount and duration of alcohol consumption. Sleep disturbances, tremors and delirium tremens characterized by hallucination, fever, and tachycardia are the main symptoms of alcohol abstinence syndrome. If medical aid is not given in time, fatalities may occur during delirium tremens.

Cardiovascular System

Moderate level of alcohol intake is known to be cardioprotective and antiatherogenic. Alcohol increases high-density lipoprotein level; reduces blood cholesterol level and low-density lipoprotein oxidation. However, it is not known that how much alcohol and how long to be taken to have cardioprotective action. At present, this remains uncertain. High dietary alcohol intake causes cardiac failure, cardiomyopathy, hypertension and stroke. Ischemic and haemorrhagic stroke is common in those who drink 40-60 gm of alcohol in a day.

Skeletal Muscle

Alcohol initially increases blood supply to skeletal muscle and postpones fatigue. Heavy chronic consumption of alcohol decreases the strength of the muscle and induces myopathy.

Liver

Alcohol is toxic to liver and a prohepatocarcinogenic. It produces fatty infiltration into liver and causes cirrhosis. Malnutrition commonly observed in alcoholics aggravate hepatotoxicity of alcohol.

Stomach

Alcohol is a gastric irritant, ulcerogenic and promotes gastrin and histamine release. Alcohol can induce haemorrhagic gastritis and enhance gastrointestinal bleeding caused by aspirin.
Sexual Function
It is a misconception to regard alcohol as an aphrodisiac—an agent that enhances sexual desire—libido. On chronic use alcohol causes impotence in men and reduces fertility.

Pregnancy
Alcohol is a teratogenic. It produces ‘fetal alcohol syndrome’ with a cluster of craniofacial abnormalities. Alcohol produces pre- and post-natal stunting of fetal growth with central nervous system dysfunction.

Motor Driving
Alcohol impairs the skill of motor driving. It increases distractibility and over confidence of driver which brings inability to deal crisis. Excessive caution on the road and bad judgment are the hallmarks of motor driving on alcohol. Hence, more prone for accident. In many countries alcohol concentration in expired air and urine is fixed for safe driving to avoid accidents.

Body Temperature
Alcohol is a hypothermic agent. It increases the loss of heat from body producing a feeling of warmth. In extreme cold climate, loss of heat from the body on repeated intake of alcohol is dangerous. Alcohol increases sweating.

Plasma Lipoproteins
Moderate intake of alcohol increases plasma high-density protein level. Presumably, alcohol is a cardioprotective. However, cardioprotective action of alcohol depends on the quantity of alcohol consumed and other lifestyle activities and co-morbidities.

Alcohol increases the release of steroid hormones, inhibits antidiuretic hormone release and causes transient hyperglycemia followed by hypoglycemia.

PHARMACOKINETICS
Alcohol is rapidly absorbed from stomach and follows first order kinetics at first and later exhibits zero order kinetics. Presence of food delays absorption of alcohol. Alcohol crosses placenta readily.

In man, the alcohol is metabolized at the rate of 10 ml/hr and maximum 450 ml/day under normal circumstances. Alcohol undergoes both microsomal and non-microsomal oxidation.

\[
\text{Ethyl alcohol} \quad \xrightarrow{\text{Dehydrogenase}} \quad \text{Acetaldehyde} \quad \xrightarrow{\text{Aldehyde dehydrogenase}} \quad \text{Acetylco-A} \quad \xrightarrow{\text{Krebs’ cycle}}
\]

Drugs like disulfiram, griseofulvin, chloramphenicol, cephalosporins and metronidazole, inhibit the metabolism of alcohol to produce plasma aldehyde syndrome.
Ethyl alcohol competes with methyl alcohol for metabolic pathways and blocks the formation of toxic metabolites of methyl alcohol. For this reason, ethyl alcohol is administered intravenously in acute methyl alcohol poisoning.

Alcohol is excreted by lungs and also appears in sweat, bile, tears, gastric juice and saliva.

**THERAPEUTIC USES**

1. Alcohol is used as a hypothermic agent.
2. Alcohol is given perineurally to provide relief from pain in trigeminal neuralgia.
3. Ethanol is an antidote for acute methanol poisoning to protect from methanol-induced neurotoxicity.
4. Alcohol is extensively used as antiseptic.
5. Alcohol can be used as appetizer.

**Contraindications**

Alcohol should not be taken during pregnancy, urinary tract infections and hepatic diseases. Alcohol should be avoided in hypertension, epilepsy and with oral sulphonylurea antidiabetic therapy.

**DRUG INTERACTIONS**

1. Alcohol potentiates the action of all central nervous system depressants.
2. Alcohol + aspirin: Increased gastrointestinal hemorrhage
3. Alcohol + paracetamol: Increased hepatotoxicity

**ACUTE ETHANOL POISONING**

Alcohol intoxication is a common occurrence in modern society. If the plasma level of alcohol is 50-100 mg%, it is regarded as moderate intoxication, more than 150 mg% gross intoxication and 300-400 mg% plasma alcohol concentration is fatal. The signs and symptoms of acute alcohol poisoning include stupor and hypothermia. Palpitation, slow and noisy respiration, hyperexcitability, increased intracranial pressure and hypoglycemia are the other features of alcohol poisoning. The treatment of acute ethanol poisoning is purely symptomatic and supportive. Inducing hyperpnoea, keeping the patient warm, gastric lavage and haemodialysis with thiamine and glucose supplementation are different measures undertaken to treat acute ethanol poisoning.

**ACUTE METHANOL POISONING**

Methyl alcohol (wood alcohol) is a common industrial solvent, especially for paints and varnishes. It is an antifreeze liquid. Methanol poisoning is common among labourers who drink methanol mixed beverages. Methanol liberates toxic metabolites like formaldehyde and formic acid following biotransformation. As little as 15 ml of methanol can cause total blindness and 70 ml is fatal. Headache, vertigo, vomiting, severe upper abdominal pain, dehydration, blurred vision, blindness, delirium and severe acidosis are the major signs and symptoms of acute methanol poisoning.
In order to save eyesight of the patient, ethyl alcohol is given intravenously in acute methanol poisoning. Ethyl alcohol competes for metabolic pathways with methanol and blocks the formation of formaldehyde and formic acid, which are toxic to optic nerves. Besides, correction of acidosis, 4-methyl pyrazole a specific inhibitor of alcohol dehydrogenase enzyme can be used.

AVERTION THERAPY FOR ALCOHOLISM

For alcoholics who are co-operative with the physician and to discourage drinking of alcohol, aversion therapy is employed. The drugs used for aversion therapy do not produce cure for alcoholism. However, these drugs will certainly help an alcoholic to desert drinking habits provided conviction is strong to get rid of alcoholism. The drugs used for aversion therapy are:

1. Disulfiram
2. Citrated calcium carbamide

Disulfiram

Disulfiram is an inhibitor of alcohol biotransformation. It inhibits aldehyde dehydrogenase enzyme and increases plasma aldehyde level when given prior to alcohol intake. This produces throbbing headache, flushing, copious vomiting, thirst, sweating, confusion and hypotension that lasts for 30 minutes to a few hours. Consequently, disulfiram makes an alcoholic not to drink any more. However, success rate in producing aversion towards alcohol intake on disulfiram therapy is not substantial.
### DRUGS USED IN EPILEPSY

- WHAT IS EPILEPSY?
- EPILEPTIC DISORDERS
- CLASSIFICATION OF ANTIEPILEPTICS
- PHENYTOIN
- PHENOBARBITONE
- SODIUM VALPROATE
- CARBAMAZEPINE
- LAMOTRIGINE
- CLONAZEPAM
- ETHOSUCCIMIDE
- NEWER ANTIEPILEPTICS
- DRUG TREATMENT FOR STATUS EPILEPTICUS

### WHAT IS EPILEPSY?

Epilepsy is a neurological abnormality, which affects 0.5 to 1% of human population. Epilepsy refers to disorder of brain neurons characterized by periodic unpredictable occurrence of seizures. It is an episode of recurrent seizures usually of impaired consciousness and amnesia. Seizures are occasional, sudden, excessive rapid local discharge of gray matter. These are thought to arise from cerebral cortex. A variety of factors and reasons cause epilepsy. Trauma, meningitis, childhood fever, brain tumours, uremia, degenerative disease and drugs can produce epilepsy. Epilepsy can also be due to hyperexcitability of neurons produced by excitatory neurotransmitters like glutamate or reduction of GABAergic inhibitory control over neurons.

The clinical manifestation of epilepsy may involve motor, sensory, autonomic nervous system and impair or complete loss of consciousness. Motor disturbances may include convulsions involving violent spasmodic or prolonged contractions of skeletal muscles. The rational management of epilepsy requires a clear understanding and diagnosis of accurate type of epilepsy.

### EPILEPTIC DISORDERS

Epileptic disorders are broadly classified in the following way.

**Partial Seizures (Focal)**

Partial seizures are due to localized neuronal discharge in one area of brain. There is no loss of consciousness and associated with motor and sensory disturbances. Further, partial seizures are subdivided into three types.

a. Simple partial seizures
b. Complex partial seizures
c. Partial seizures evolving to generalized.

**Generalized Seizures**

Generalized seizures are characterized by neuronal discharge involving both cerebral hemispheres and consciousness may be impaired or lost during the attack of epilepsy. Clinically,
based on the presence or absence of different types of convulsions, generalized seizures are subclassified into following groups:

a. **Absence seizure (petit mal epilepsy):** This occurs in children. It is characterized by brief sudden loss of consciousness lasting for a few seconds.

b. **Myoclonic seizure:** It is sudden brief shock-like contraction of musculature

c. **Clonic seizure:** It is characterized by repetitive rhythmic muscle jerks

d. **Tonic seizure:** It presents rigid violent contractions of muscles with limbs fixed.

e. **Tonic-clonic seizure (grand mal epilepsy):** It is characterized by loss of consciousness and disordered muscle contractions with tonic-clonic motor activity invariably with ‘aura’. Aura is a premonition, which indicates the patient about the onset of an imminent attack.

f. **Atonic seizure:** It is characterized by loss of postural tone and the head sags or the patient falls.

g. **Epileptic syndrome:** Infantile spasms belong to epileptic syndrome type and generally unresponsive to conventional antiepileptic drugs.

### CLASSIFICATION OF ANTIEPILEPTICS

Drugs used as antiepileptics in various convulsive disorders are classified into the following groups based on their chemical nature:

1. **Hydantoins derivatives:**
   - Phenytoin

2. **Barbiturates:**
   - Phenobarbitone, mephobarbitone, primidone (deoxybarbiturate)

3. **Benzodiazepines:**
   - Diazepam, clonazepam, clobazam, lorazepam

4. **Dipropylacetate derivative:**
   - Sodium valproate (valproic acid)

5. **Iminostilbines:**
   - Carbamazepine, Oxcarbazepine

6. **Succinimides:**
   - Ethosuccimide, Phenacemide

7. **GABA action enhancers:**
   - Gabapentin, vigabatrin

8. **Acetylureas:**
   - Pheneturide, phenacemide

9. **Oxazolidinediones:**
   - Trimethadione, paramethadione

10. **Recently introduced antiepileptics:**
    - Lamotrigine, topiramate, felbamate, tiagabine

11. **Miscellaneous:**
    - Sulthiame, acetazolamide, magnesium sulphate, ACTH, clormethiazole, paraldehyde

### PHENYTOIN (DILANTIN SODIUM, DIPHENYL HYDANTOIN)

Phenytoin is a hydantoin antiepileptic drug commonly used in the management of grand mal epilepsy. It is used as antiarrhythmic, especially for digoxin-induced ventricular
tachycardia. Phenytoin monodrug therapy would normally control grand-mal epilepsy well-provided the drug is taken regularly.

**Mechanism of Action**
Phenytoin acts as antiepileptic drug by several mechanisms. It tends to limit the spread of epileptogenic activity by the following ways.

1. Phenytoin is a Na⁺ channel blocker, enhances inactivated phase of channel and inhibits sustained neuronal bursting.
2. Inhibits the reuptake GABA and increases its affinity with receptor thereby augments inhibitory control over neuronal activity.
3. Suppresses excitatory amino acid neurotransmitter release.
4. Inhibits calmodulin activated kinase-dependent intracellular phosphorylation.
5. Decreases Ca²⁺ entry and reduces the spread of Na⁺ discharge to control electrical excitability.
6. Besides phenytoin decreases the level of β-endorphin and somatostatin role in seizures. Further, phenytoin enhances blood supply to neurons and alters blood-brain barrier permeability to convulsive substances. The net result of these effects is epileptic attack no longer occurs provided the drug is used judiciously.

**Pharmacokinetics**
Phenytoin is generally given orally after food and the oral absorption is slow and complete. It is extensively bound to plasma proteins (90%). Phenytoin exhibits zero order kinetics and undergoes enterohepatic circulation. Bioavailability of phenytoin varies from brand to brand. Therefore, monitoring plasma concentration is needed to achieve the required therapeutic range of plasma phenytoin concentration. Phenytoin has variable dose-dependent half-life. However, mean plasma half-life is 22 hours.

**Therapeutic Uses**
1. Phenytoin is an agent of choice to control tonic-clonic seizures (grand-mal epilepsy) as well as partial seizures. It is also used in the emergency treatment of status epilepticus. As a prophylactic anticonvulsant, phenytoin is used in neurosurgery and trauma of the head.
2. Phenytoin is class Ib antiarrhythmic agent, valuable in the management of digitalis-induced cardiac arrhythmias.
3. As an alternative drug, phenytoin is used in various neuralgias including trigeminal neuralgia.
4. Phenytoin is tried for migraine of childhood.

**Adverse Effects**
Phenytoin produces fairly frequent side effects, structural toxicities and teratogenicity. The common side effects reported are nausea, vomiting, anorexia, headache, dizziness, constipation and tenderness of gums. Gingival hyperplasia is common in younger patients. Acne and hirsutism have also been observed.
Phenytoin toxicity may be seen as cerebellar syndrome with vestibular and ocular effects. Phenytoin at large doses produces hyperglycemia and interfere with vitamin D and folate metabolism to produce rickets and osteomalacia. Phenytoin causes megaloblastic anaemia and peripheral neuropathy.

‘Fetal hydantoin syndrome’ is a congenital malformation that occurs in the babies born to phenytoin receiving pregnant women. Abnormal facial features, low birth weight, delayed development, hirsutism and distal nail and phalangeal hypoplasia are the few characteristic features of fetal hydantoin syndrome.

**Drug Interactions**
1. Phenytoin is a potent enzyme inducer and stimulates the metabolism of many drugs like corticosteroids, anticoagulants, sex hormones and antimicrobials.

**PHENOBARBITONE**
Phenobarbitone is a barbiturate, non-selective, inexpensive antiepileptic drug. Primarily, phenobarbitone is a central nervous system depressant known to enhance the effects of inhibitory neurotransmitter GABA. Phenobarbitone also acts by decreasing excitatory amino acids synaptic transmission.

Phenobarbitone is given by mouth and major part of the administered dose is excreted in urine as unchanged form. It can be given parenterally to control acute seizures.

Phenobarbitone at the recommended dose level is relatively less toxic. However, it can cause sedation, megaloblastic anaemia and confusion. Sometimes in children phenobarbitone increases irritability and hyperactivity and in elderly, agitation. Phenobarbitone is an enzyme inducer and increases the metabolism of various endogenous substances including bilirubin.

At high dose, phenobarbitone produces nystagmus, ataxia and severe respiratory depression. Overdosage of phenobarbitone may be fatal due to severe respiratory and cardiovascular failure. There is no specific antidote for barbiturate poisoning. Hence, the treatment is purely supportive and symptomatic.

Phenobarbitone is contraindicated in porphyria.

**Drug Interactions**
1. Phenobarbitone + antidepressants: Antagonism
2. Phenobarbitone + warfarin: Increase the rate of anticoagulant metabolism
3. Phenobarbitone + valproate: Increased plasma concentration of phenobarbitone

**SODIUM VALPROATE (VALPROIC ACID)**
Valproic acid is a broad-spectrum antiepileptic drug. Particularly, valproate is an agent of choice to treat absence seizures in children.

The mechanism of action of valproate is complex. Valproate is known to control epilepsy by the following mechanisms:
1. Inhibits GABA metabolism and augments its action
2. Reduces aspartate level
3. Inhibits ‘T’ type Ca\(^{2+}\) channel current generation  
4. Known to increase the glycogen content in the brain.

**Pharmacokinetics**  
Valproate is given orally and rapidly absorbed by carrier-mediated transport. Valproate remains bound to plasma proteins extensively. Plasma half-life of valproate is 15 hours. It undergoes complete metabolism by glucuronide conjugation.

**Adverse Effects**  
To start with, valproate frequently produces gastrointestinal disturbances. This can be minimized by giving valproate with food or enteric-coated formulation may be used.  
Heartburn, sedation, fine tremor, ataxia, appetite stimulation, weight gain, alopecia, thinning and curling of hairs are the other adverse effects of valproate.  
Valproate is a hepatotoxic agent. It can produce fulminant type of hepatitis and could be fatal. The risk of hepatotoxicity is high in patients aged less than two years. Valproate is a teratogenic—causes *spina bifida*. Acute pancreatitis and hyperammonemia have also been reported with valproate.

**Other Uses**  
Besides as an antiepileptic drug, valproate is used in acute manic phase and for the prophylaxis of migraine.  
Valproate is contraindicated in pregnancy and severe hepatic disease.

**Drug Interactions**  
1. Valproate + aspirin: Increased incidence of hepatitis  
2. Valproate + clonazepam: May lead to absence seizures  
3. Valproate + erythromycin: Increased level of valproate in plasma causing toxicity.

**CARBAMAZEPINE**  
Carbamazepine is an antiepileptic, antimanic agent and used for neuralgic pain. The mechanism of action of carbamazepine is similar to that of phenytoin. It inhibits the uptake of GABA and potentiates the action of inhibitory neurotransmitter.  
Carbamazepine is given by mouth and may be administered by rectal route. It crosses placental barrier and appears in milk.

**Therapeutic Uses**  
1. Carbamazepine is a drug of choice to treat partial seizures. It is also useful in tonic clonic seizures and primary generalized seizures.  
2. Trigeminal neuralgic pain can be controlled by carbamazepine.  
3. Carbamazepine is used in the prophylaxis of bipolar disorder unresponsive to lithium.  
4. Carbamazepine is the drug of choice to treat glossopharyngeal neuralgia.
Adverse Effects
It is common to observe drowsiness, dizziness and ataxia following carbamazepine administration. Anorexia, dry mouth and diarrhea may also be seen. Hyponatremia, erythematous rashes, agranulocytosis, aplastic anaemia, drug fever and lymphadenopathy have been reported rarely with carbamazepine which demand discontinuation of carbamazepine. Carbamazepine also is a teratogenic antiepileptic agent. Carbamazepine is contraindicated in conditions like atrioventricular conduction abnormalities and bone marrow suppression.

Drug Interactions
- Carbazepine + alcohol: Toxicity of carbamazepine is increased
- Carbamazepine + diuretics: Causes hyponatremia

LAMOTRIGINE
Lamotrigine is an antiepileptic used to treat partial or complex seizures either as monotherapy or in adjunct with other drugs. It is a Na⁺ channel blocker and inhibits the release of excitatory amino acid neurotransmitter. Lamotrigine is administered orally and the plasma half-life is 24 hours. The pharmacokinetic properties of lamotrigine are altered by other antiepileptics. Severe skin reactions may occur with lamotrigine therapy, especially in children. Nausea, vomiting, influenza-like syndrome, facial edema, swollen ankles, irritability and photosensitivity reactions have been reported as adverse effects of lamotrigine. Co-administration of valproate increases the plasma half-life of lamotrigine. If the skin rashes are severe, withdrawal of lamotrigine should be considered.

CLONAZEPAM
Clonazepam is a benzodiazepine antiepileptic useful in the treatment of myoclonic type of seizures. Clonazepam antiepileptic usefulness is often limited by the development of tolerance. This is a GABA mimetic agent. Clonazepam is given by mouth. The plasma half-life of clonazepam is 20-40 hours. It crosses placenta readily and secreted in milk. Clonazepam can be used in panic disorders and anxiety neurosis. This drug is well tolerated and drowsiness is observed as a frequent side effect. Alcohol may affect the patient’s response to clonazepam.

ETHOSUCCIMIDE
Ethosuccimide is a preferred antiepileptic for the treatment of absence seizures to valproate. The exact mechanism of action of ethosuccimide remains to be elucidated. However, ethosuccimide is known to act by blocking ‘T’ channels of calcium and inhibition of Na⁺-K⁺-ATPase enzyme. Ethosuccimide does not have GABA mimetic action. Ethosuccimide is administered by oral route. It has a plasma half-life of 60 hours. Ethosuccimide crosses placental barrier and is distributed into breast milk. Nausea, vomiting, anorexia and abdominal pain occurs readily with ethosuccimide. Euphoria, hiccup, Parkinson-like syndrome, skin rashes and ataxia also occur on ethosuccimide therapy.
Since, ethosuccimide is not a hepatotoxic antiepileptic, it is used as a drug of choice in absence seizures. Further, ethosuccimide is a narrow spectrum antiepileptic and not effective in grand-mal epilepsy.

**NEWER ANTIEPILEPTICS** (Table 8.2)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Types of epilepsy used</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Partial seizures</td>
<td>Sedation, dizziness, ataxia, fatigue, nystagmus</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Inhibitor of GABA metabolism, resistant petit mal epilepsy</td>
<td>Drowsiness, fatigue, blurred vision, diplopia</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Refractory partial seizure</td>
<td>Dizziness, fatigue, tremor</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Refractory partial and tonic-clonic seizures</td>
<td>Ataxia, fatigue, difficulty in cognition</td>
</tr>
</tbody>
</table>

**DRUG TREATMENT FOR STATUS EPILEPTICUS**

Status epilepticus is a state in which repetitive seizures occur with incomplete recovery of the baseline neurological function. It is a neurological emergency and early diagnosis and specific therapy must be considered to reduce mortality.

The drug of choice to treat status epilepticus is diazepam. Diazepam is preferred for status epilepticus because it is not a respiratory depressant, produces rapid onset of action and a central skeletal muscle relaxant. Diazepam is administered intravenously to control this situation. Lorazepam can also be used as an alternate to diazepam. Following diazepam infusion, phenytoin is to be given to have a sustained therapeutic benefit. Subsequently, oral phenytoin is to be administered on long-term basis.
GENERAL ANAESTHETICS

INTRODUCTION
Before 1846, painless surgery was unheard and uncommon because there was no anaesthesia. Modern surgery is painless, thanks to the advent of anaesthetics. Dentists were instrumental in the development of anaesthesia. William TG Morton in the year 1846 gave the first public demonstration of surgical anaesthesia using diethylether as anaesthetic. In fact, from the day of successful ether anaesthesia, surgery has become smooth without pain.

DEFINITION AND STAGES
Anaesthesia means ‘absence of sensation’. Although there is no exact definition for anaesthesia, it is described as a state of drug-induced reversible loss of perception of all sensations. Alternatively, anaesthesia is defined as a state of reversible loss of consciousness in which all modalities of sensations are lost accompanied with skeletal muscle relaxation. In addition, anaesthetic states render to immobility, blunt reflexes and induce amnesia.

Conventionally, general anaesthesia is described to have four stages:
- Stage I : Stage of analgesia
- Stage II : Stage of delirium
- Stage III : Stage of surgical anaesthesia
- Stage IV : Stage of medullary paralysis.

Modern anaesthesiology has eliminated stage IV as it is due to anaesthetic overdose that causes respiratory arrest.

CLASSIFICATION AND MECHANISM OF ACTION
General anaesthetics are classified into two broad groups on the basis of their route of administration.
1. Inhalation anaesthetics:
   a. Gas: Nitrous oxide
   b. Liquids: Halothane, desflurane, sevoflurane, isoflurane
2. Intravenous anaesthetics
   a. Benzodiazepines: Diazepam, midazolam
   b. Barbiturates: Thiopental sodium (pentothal sodium), methohexital, thiamylal
   c. Others: Propofol, ketamine, etomidate, propanidid
INHALATION ANAESTHETICS

1. Liquids
   - Halothane
   - Isoflurane
   - Sevoflurane
   - Desflurane

2. Gas
   - Nitrous oxide

Halothane

Halothane is a colourless potent general anaesthetic with pleasant odor. It is a non-inflammable, non-irritant and inexpensive liquid stored in amber bottle to render stability. Halothane suppresses salivary, bronchial and gastric secretions. It is a bronchodilator general anaesthetic—an added advantage for asthmatic patients. However, the disadvantages of halothane are:
1. Hepatotoxicity: Halothane causes hepatitis and necrosis of hepatic tissue.
2. Halothane is not a good analgesic.
3. Halothane blocks ganglia, depresses central vasomotor area and reduces heart rate.
4. Increased myocardial excitability is observed with halothane since it sensitizes the heart to endogenous catecholamines. This may lead to cardiac arrhythmias.
5. Halothane produces nausea, vomiting, shivering and malignant hyperthermia when co-administered with succinylcholine—a genetically determined abnormal effect.

Isoflurane

Isoflurane is a commonly used inhalational anaesthetic. Unlike halothane, it does not produce cardiac sensitization to catecholamines. Isoflurane produces coronary vasodilatation. It is neither expensive nor explosive anaesthetic agent. Isoflurane is also a bronchodilator and known to produce uterine smooth muscle relaxation.

Isoflurane is an irritant and causes cough and laryngospasm. It is not a hepatotoxic agent. Isoflurane is mutagenic and teratogenic and potentiates the respiratory depression produced by opioid analgesics.

Nitrous Oxide

Nitrous oxide is an inorganic gas used as inhalation anaesthetic. It is common to use nitrous oxide in combination with halothane. Nitrous oxide cannot be used as a sole anaesthetic as it is not a potent anaesthetic. It produces profound analgesia but a poor skeletal muscle relaxant. It has rapid onset of action and recovery from anaesthesia is smooth. Nitrous oxide is neither inflammable nor irritant.

Nitrous oxide is always administered with oxygen, otherwise hypoxia will occur. Hypoxia during anaesthesia is dangerous; hence, nitrous oxide should not be given alone. At least, 20-30% oxygen must be given with nitrous oxide.

The uptake of nitrous oxide by lung is rapid. This bears a distinct advantage when nitrous oxide is co-administered with halothane. The rapid absorption of nitrous oxide accelerates the alveolar concentration of halothane by second gas effect.
Repeated exposure to nitrous oxide inhalation may cause megaloblastic anaemia and peripheral neuropathy.

**INTRAVenOUS ANAESTHETICS**

Thiopental sodium, propofol, ketamine, diazepam, midazolam.

Administration of intravenous anaesthetic is now regarded as a part of modern anaesthetic technique. Intravenous anaesthetics are frequently used to induce general anaesthesia and to increase effectiveness of inhalation general anaesthetics. Nonetheless, intravenous anaesthetics are commonly employed for short surgical procedures like endoscopy electroconvulsive therapy and narcoanalysis in psychiatric practice. A distinct advantage of using intravenous anaesthetic with inhalation anaesthetics is that the dose of inhalation anaesthetic agents can be reduced.

**Thiopental Sodium (Pentothal)**

Thiopental sodium is an ultra short acting, thiobarbiturate intravenous anaesthetic. Thiopental is a commonly used anaesthetic. As intravenous anaesthetic, it offers advantages like:

i. Rapid induction
ii. Eliminates stage of delirium and
iii. Postoperative discomfort is low.

Being a barbiturate, thiopental produces respiratory depression, hyperalgesia and depresses myocardial contractility. Thiopental has the tendency to cause laryngospasm. This is a source of concern.

Thiopental is a highly lipid-soluble drug. Following intravenous administration, thiopental acts for a few minutes on brain to produce anaesthesia. Later, being highly lipid soluble, thiopental is redistributed to adipose tissue. The administered dose is very much inside the body but not at the site of action-brain. This is known as “redistribution tolerance”.

Thiopental is not only used for induction of anaesthesia but also useful to control convulsions during anaesthesia. It is contraindicated in porphyria and for children aged less than one year.

**Ketamine**

Ketamine is a rapidly acting profound analgesic and myocardial stimulant intravenous anaesthetic. It produces ‘dissociative anaesthesia’ characterized by a trans-like state with amnesia and marked analgesia. Ketamine is of particular value as a paediatric anaesthetic, especially when repeated anaesthesia is required.

During recovery from anaesthesia ketamine produces ‘emergence reactions’ characterized by vivid unpleasant dreams, confusion, hallucination and irrational behaviour. Patients may also show increased muscle tone. Diazepam premedication inhibits ketamine-induced emergence phenomenon.

Unlike other anaesthetics, ketamine increases blood pressure and heart rate. Laryngospasm is also reported as an adverse effect of ketamine.

Ketamine is also used for intradermal analgesia in war surgery. It is contraindicated for hypertensive patients in whom elevation of blood pressure is hazardous.
Propofol
Propofol is a highly lipophilic intravenous anaesthetic generally used as induction agent. It can be readily employed as outpatient anaesthetic. Propofol produces rapid recovery with no residual effects. To sedate the head injury patient and to control status epilepticus, propofol is also useful. Propofol anaesthesia requires supplementation of analgesics to provide adequate analgesia.

Apnoea, fever, hypotension, bradycardia and anaphylactic reactions have been reported with propofol use. Myoclonic twitches are also observed on propofol administration. Propofol should be used with care in epileptic patient. Propofol should not be used in patients known to be allergic to it.

NEUROLEPTANALGESIA/ANAESTHESIA
Neuroleptanalgesia, as the name suggests, neuroleptic droperidol is administered intravenously with an opioid analgesic fentanyl to induce utter quiescence. It is a state in which the subject remains calm and indifferent to surroundings, yet is responsive to command. This technique is useful for diagnostic or therapeutic procedure like change of severe wound dressings, bronchoscopy, endoscopy and minor surgery.

Neuroleptanaesthesia is a condition produced by nitrous oxide and oxygen administration with intravenous droperidol and fentanyl. Neuroleptanaesthesia is usually reserved for getting more co-operation from patients.

Currently, neither neuroleptanalgesia nor neuroleptanaesthesia is employed. These techniques were reserved where inhalational and parenteral anaesthetics are relatively contraindicated.

PREANAESTHETIC MEDICATION (PRE-MEDICATION)
Preanaesthetic medication is the administration of drugs to facilitate the induction, maintenance and recovery from anaesthesia. Pre-medication reduces fear and anxiety in patients who are undergoing surgery. Drugs used for pre-medication inhibit unwanted exocrine secretions and protects the heart from arrhythmogenic actions of a few general anaesthetics. Some of the pre-medicaments produce amnesia and analgesia.

Drugs used for Pre-medication
1. Sedative hypnotics: Diazepam, hydroxyzine, promethazine
2. Opioid analgesics: Morphine, pethidine, fentanyl
3. Antimuscarinic anticholinergics: Atropine, scopolamine
4. H₂ receptor blocker: Ranitidine, famotidine
5. Antiemetics: Metoclopramide, domperidone
6. Neuroleptic: Droperidol
7. Intravenous anaesthetics: Propofol, thiopental

Morphine as Pre-anaesthetic Medicament
Morphine is an opioid analgesic given either subcutaneously or intramuscularly for pre-medication.
Advantages of Morphine Pre-medication

- Morphine relieves apprehension on the part of the patient
- Prevents anaesthesia-induced tachypnoea
- Provides analgesia
- Suppresses cough
- Helps to reduce the dose of anaesthetic

Disadvantages of Morphine Pre-medication

- Produces postoperative constipation
- Postoperative vomiting may be more, since morphine stimulates vomiting centre
- Produces respiratory depression, bradycardia, hypotension and urinary retention
- Interferes with pupillary sign as morphine induces miosis.

Atropine Premedication

Atropine is an antimuscarinic anticholinergic drug given by mouth for pre-medication. Intramuscular atropine is also given 60 minutes before anaesthetic administration. Atropine pre-medication blocks all the exocrine gland secretions and prevents anaesthetic-induced cardiac arrhythmias. Atropine antagonizes bradycardia and salivation induced by succinylcholine—a skeletal muscle relaxant given usually with anaesthetic. Atropine reduces opioid-induced postoperative vomiting.

Atropine causes thick tenacious mucus formation in respiratory tract. It may produce tachycardia and pyrexia. These are the demerits of atropine pre-medication.
LOCAL ANAESTHETICS

- DEFINITION
- CLASSIFICATION
- MECHANISM OF ACTION OF LOCAL ANAESTHETICS
- PHARMACODYNAMICS
- TECHNIQUES OF LOCAL ANAESTHETICS
- THERAPEUTIC USES
- ADVERSE EFFECTS
- DRUG INTERACTIONS
- LOCAL ANAESTHETIC SPRAYS

DEFINITION
Local anaesthetics are the agents that reversibly inhibit both the generation and conduction of nerve impulse. These are often referred to as regional anaesthetics or local analgesics. The effects of these drugs are limited to part of body to be operated on. Unlike general anaesthetics, after effects are less. Local anaesthetic technique is simple, anaesthetizes a circumscribed/localized area without causing loss of consciousness, economical, complicated equipment are not required and need for postoperative care is not high as local anaesthetics do not affect central control of vital parameters.

CLASSIFICATION
Local anaesthetics are classified based on source, chemical nature and duration of action (Fig. 8.1).

Classification of Local Anaesthetics based on Duration of Action
1. Short acting (< 20 minutes)
   - Procaine, Cocaine
2. Intermediate acting (up to 2 hours)
   - Lignocaine
   - Mepivacaine
3. Long acting (more than 3 hours)
   - Bupivacaine
   - Ropivacaine
   - Tetracaine

MECHANISM OF ACTION OF LOCAL ANAESTHETICS
Local anaesthetics act on all types of nerve fibers. However, all nerve fibers are not equally sensitive to local anaesthetics. Sympathetic nerve fibers are affected by local anaesthetics at first followed by pain, other sensory fibers and motor nerves at last. This is of clinical significance since pain sensation disappears at first. Therefore, it may be possible that selective ‘sensory block’ can be achieved with local anaesthetics by adjusting concentration of local anaesthetics and duration of exposure of nerve fibers to these agents.

Local anaesthetics act by the following mechanisms.
**LOCAL ANAESTHETICS**

- Natural  
  e.g. Cocaine

- Synthetic

- **Amides**
  - Lignocaine (Lidocaine)
  - Bupivacaine
  - Ropivacaine
  - Mepivacaine
  - Prilocaine

- **Esters**
  - Tetracaine
  - Procaine
  - Piperacaine

- **Others**
  - Dyclonine
  - Pramoxine
  - Eugenol
  - Saligenin

- **Esters of Benzoic acid**
  - Cocaine
  - Tetracaine

- **Esters of Aminobenzoic acid**
  - Cyclomethicaine

- **Esters of Paraaminobenzoic acid**
  - Propracaine

**Fig. 8.1:** Local anaesthetics

**Site of action:** Nerve membrane

1. **Block Na⁺ channels:** These drugs block activated ion channels more readily than resting channels. This determines the potency of a given local anaesthetic.

2. Local anaesthetics non-specifically act on membrane by virtue of their surface activity. It is recognized that this action also contributes to paralyse the nerve fibers.

3. Local anaesthetics also interfere with the role of Ca²⁺ in opening Na⁺ channels and at higher dose disturb Ca²⁺ as well as K⁺ channel functions.

Local anaesthetics affect the sensory functions of most nerves in a predictable order. Although there is great individual variation, pain is lost at first followed by cold, warmth, touch, deep pressure and finally motor function. Sequential block of nerve fibers—autonomic, sensory and motor fibers by local anaesthetics offer practical advantage of beneficial modulation of pain and stress.
PHARMACODYNAMICS

The intensity of local anaesthetic action is dependent on the following factors:

a. Solubility of the drug
b. pH of the site of action
c. Nerve diameter
d. Molecular size of the local anaesthetics
e. Charged ion channel frequency state.

Local anaesthetics virtually plug the Na⁺ ion channel pore at the inner surface of the membrane. Lipid-soluble local anaesthetics readily cross the membrane to block ion pore. The action of local anaesthetics is pH dependent. Alkaline pH favors the action well. Since the pH of inflamed area is acidic, prompt local anaesthetic action may not be seen at the usual strength of drugs. Here, tissue buffer ability determines the potency of local anaesthetics.

Small nerve fibers are more susceptible to the action of local anaesthetics. Therefore, pain fibers are affected at first than large motor nerves. The diameter of nerve fiber is an important factor that governs the intensity of the action of local anaesthetic. Recently, it is reported that the structure of neuronal membrane and the distance between nodes of Ranvier also account for varied response to local anaesthetic. Small molecular local anaesthetic can dissociate readily from the membrane receptor during repolarization. This has bearing on the antiarrhythmic action of local anaesthetics.

A frequency of ion channel stimulation enhances the binding of local anaesthetics. This is critical for antiarrhythmic action of lignocaine-like drugs and usually described as frequency and voltage dependent effect. For this reason, the local anaesthetic efficacy is more when more number of Na⁺ channels are stimulated by any factors including ischemia.

TECHNIQUES OF LOCAL ANAESTHESIA

Local anaesthesia can be achieved by different ways to suit the clinical need. The commonly employed methods to induce local anaesthesia are:

a. Surface anaesthesia
b. Infiltration anaesthesia
c. Nerve block anaesthesia
d. Spinal anaesthesia
e. Epidural anaesthesia
f. Intravenous regional anaesthesia.

Surface Anaesthesia

It is a type of local anaesthesia in which a local anaesthetic is applied to skin or mucous membrane to anaesthetize surface nerve endings. Surface anaesthesia is generally employed to paralyse the nerve endings of nasal, oral, tracheal mucosa, urinary tract, cornea and skin. Topical application of local anaesthetics may be in the form of spray, ointment, jelly and cream. Generally, the action is produced within 3-5 minutes and may last for 30-45 minutes. Examples of surface anaesthetics are: lignocaine, prilocaine, tetracaine, cocaine, etc. Procaine lacks adequate surface penetration power, hence, not preferred as surface anaesthetic.
Infiltration Anaesthesia

The local anaesthetic is injected hypodermically to paralyse terminal branches of somatic nerves around the area of operation. This method is commonly employed in dental practice. Here, the local anaesthetic injection is given with vasoconstrictor like adrenaline to prolong the duration of action of anaesthetic (see below drug interaction).

Xylocaine, ropivacaine, prilocaine and most of the local anaesthetics have been used for infiltration anaesthesia including procaine.

A modified method of infiltration anaesthesia known as field block anaesthesia has been employed to anaesthetize scalp, anterior abdomen wall and volar surface of forearm. Here, a series of subcutaneous injection of local anaesthetic is advocated to anaesthetize wider area.

Nerve Block Anaesthesia

In this method, the local anaesthetic is injected close to nerve trunk, plexus of nerves, intercostal nerves and mandibular nerve (especially in dentistry). Accurate placement of needle is important. The knowledge of neuroanatomy is essential. The quantity of local anaesthetic used is less as compared to infiltration anaesthesia. The duration of anaesthesia can be prolonged by using a vasoconstrictor.

Spinal Anaesthesia

This is a method of local anaesthesia in which spinal nerve roots are paralysed by intrathecal injection of a local anaesthetic. Local anaesthetic is injected into the subarachanoid space at the level between L2 and L5. Intrathecal administration of local anaesthetic causes unwanted complications, which are attributable to the drug and technique as well. Spinal anaesthetic blocks pelvic autonomic flow and the cranial spread of anaesthetic solution also effect upper sympathetic flow. As a result of this, bradycardia, hypotension, headache, respiratory depression and urinary retention may be observed. Headache may be one of the aftermaths of cerebrospinal fluid leakage. To minimize these complications, efforts should be undertaken. The measures employed for this aim at controlling the cranial spread of local anaesthetic. Head down position of the patient, using hyperbaric solution of local anaesthetic and resorting to epidural anaesthesia have been the effective means to minimize spinal anaesthesia complications.

Epidural Anaesthesia

It is a modified spinal anaesthetic technique in which local anaesthetic is administered just above the duramater into the space between duramater and the bony spinal canal. Central nervous system-related complications including respiratory paralysis are less with epidural anaesthesia. Most of the local anaesthetics including ropivacainé are used for spinal and epidural anaesthesia.

Saddle block anaesthesia is also a modified spinal anaesthetic technique for inducing obstetric analgesia. Hyperbaric solution of local anaesthetic is injected into the lower part of dural sac when the patient is in sitting position. The terminal segmental nerve root of the cord is paralysed by this method to provide relief from the labour pain.
THERAPEUTIC USES
The choice of local anaesthetic is based on its duration of action, safety and efficiency. Also, operative needs to be considered on an individual basis besides the site/area to be anaesthetized by local anaesthetic.

Local anaesthetics are also useful in alleviating the following:

- Intractable cough
- Hiccups
- Cancer pain
- Spasticity
- Soft tissue rheumatism
- Mouth ulceration
- Before the instrumentation of body cavity and catheterization of urinary tract.

Xylocaine and its congeners are indicated to control ventricular tachycardia in particular.

ADVERSE EFFECTS
Adverse reactions produced by local anaesthetics are mainly related to central nervous and cardiovascular systems. Nevertheless, allergic reactions to ester type of local anaesthetics have been reported. Allergy to amide type is rare. Idiosyncratic reactions to local anaesthetics like oculomotor palsy, blurred vision and death have also been observed.

Stimulation of central nervous system, headache, sleepiness, restlessness, lightheadedness, dizziness, anxiety, depression, and convulsions are seen with local anaesthetics. Convulsions caused by local anaesthetics can be alleviated promptly by diazepam.

Vasovagal syncope, hypotension and bradycardia are the frequently encountered cardiovascular adverse effects on repeated exposure to high doses of local anaesthetics. Prilocaine can cause methaemoglobinemia. Etilocaine often produces bleeding as its side effect. Bupivacaine is known to cause cardiotoxicity, whereas ropivacaine is free from cardiotoxicity.

DRUG INTERACTIONS
1. Xylocaine + adrenaline: Local anaesthetics are commonly administered with adrenaline to prolong the duration of anaesthesia. Adrenaline is a powerful vasoconstrictor of skin and mucosal blood vessels. Vasoconstriction decreases the blood supply to the local anaesthetic injection. Decrease in blood supply reduces the systemic absorption of anaesthetic drug and enhances the action. Further, adrenaline can effectively stall allergic reactions if any to the administered local anaesthetic. The quantity of adrenaline used with local anaesthetic should not exceed 0.2 mg. Adrenaline and local anaesthetic combination should not be injected to the tissues which have end-arteries like fingers, toes, ears, tip of the nose and penis. Local anaesthetic and adrenaline combination is contraindicated for patients with ventricular arrhythmias, hyperthyroidism, hypertension and angina pectoris.

2. Procaine + penicillin: Procaine forms an insoluble complex with penicillin. Procaine penicillin is given intramuscularly. Penicillin is slowly released to systemic circulation giving a stable plasma concentration of the antibiotic, which prolongs the action. At the same time, procaine relieves the pain of injection.
### Table 8.3: Comparative features of commonly used local anaesthetics

<table>
<thead>
<tr>
<th></th>
<th>Xylocaine (lidocaine, lignocaine)</th>
<th>Bupivacaine</th>
<th>Ropivacaine</th>
<th>Procaine</th>
<th>Cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amide type</td>
<td>Amide</td>
<td>Amide</td>
<td>Ester of PABA</td>
<td>Natural, ester of benzoic acid, alkaloid from <em>Erythroxylon coca</em></td>
<td></td>
</tr>
<tr>
<td>Widely used</td>
<td>Long acting, cardiototoxicity</td>
<td>Long acting, free from cardiototoxicity</td>
<td>Short acting</td>
<td>Short acting</td>
<td></td>
</tr>
<tr>
<td>intermediate acting</td>
<td>precludes wide use</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antiarrhythmic</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td></td>
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<tr>
<td>particularly for digoxin-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>induced arrhythmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used to induce all types of local</td>
<td>Mainly for nerve block spinal</td>
<td>Nerve block spinal anaesthesia</td>
<td>Infiltration anaesthesia useless as surface anaesthetic</td>
<td>As surface anaesthetic only</td>
<td></td>
</tr>
<tr>
<td>anaesthetic techniques</td>
<td>anaesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleepiness, lightheadedness, dizziness</td>
<td>Cardiotoxicity</td>
<td>-</td>
<td>Depresses respiration</td>
<td>Euphoriant, mydriatic, tachycardia, vasoconstrictor, hypertension, habit forming drug, pyrogenic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occasionally as anticonvulsant in status epilepticus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

3. Local anaesthetic + succinylcholine: Ester type of local anaesthetics can prolong the action of succinylcholine by competing for plasma esterases which hydrolyze both.
4. Procaine + sulphonamides: Procaine on biotransformation increases the concentration of PABA, which may blunt the antimicrobial action of sulphonamides.

**LOCAL ANAESTHETIC SPRAYS**

Various local anaesthetics are available as sprays and aerosols for topical use. Benzocaine 20%, lignocaine 0.5%, pramoxine 1% and ethylchloride spray 15 to 25% have been widely used. Ethylchloride spray is commonly employed to control pain associated with minor surgical procedures, for example, lancing boils, drainage of small abscess, athlete injuries, sprains restricted motion and muscle spasm. Local anaesthetic sprays can also be used in local skin disorders including pruritus, prickly heat, abrasions, plant poisoning, insect bites, eczema and as local analgesics on normal intact skin. Occasionally, topical local anaesthetic sprays may cause stinging, burning, tenderness and sloughing. Sprays can be applied to the affected area as needed and these preparations are meant for external or mucous membrane use only. These agents should not be used for eyes.
PAIN AND MECHANISMS OF PAIN

Pain is a universal experience, misery and overturns all patients. It cannot be defined precisely except, one defines pain introspectively for one’s self. Nevertheless, pain can be a psychological language, which illustrates the particular type of sensory experience. Pain is an unpleasant sensory and emotional experience with actual and potential tissue damage or described in terms of it. The point at which pain is perceived is referred to as ‘pain threshold’. Factors like gender, temperature, anxiety, circulatory change, $P_{CO_2}$, and emotion alter pain in different ways.

Pain may be described as bright, dull, choking, aching, pricking, cutting and burning sensation. Reaction to pain is an emotional/psychic component of pain. This is to say that pain and suffering due to pain are the two different ways which describe what is happening in patient’s body and mind respectively.

Drug therapy is fundamental to pain management. Pain is the most common symptom causing patients to seek medical attention. Therefore, drug therapy for pain must be effective, inexpensive, relatively low risk and rapid in onset. To achieve this, a clear understanding of pain perceptive mechanism is necessary.

Pain is invariably due to nociceptive stimulation. Nociceptive means intense unpleasant hurting (Greek: $noxa$=injury). The causes for pain are numerous: trauma, infection, inflammation, ischemia and immune injury. The WHO describes pain at different grades:

1. Mild to moderate pain
2. Increased persistent pain
3. Intractable intense pain

Treatment strategies for all the above three types have been outlined explicitly with reassurance. As with any drug therapy for diseases, the aim of drug treatment is to knock out the causative mechanisms of the disorder. Therefore, pain management must aim at removing the precipitating factors that produce pain. This can be achieved only by understanding the clinical pathology and physiological mechanism of pain. Ideally, pain-causing nociceptive stimuli need to be addressed properly regardless to ischemia, inflammation, infection and trauma either. Alternatively, the mechanisms that make the patient to perceive pain must be blocked.
Definition
Drugs that provide relief from pain sensation without inducing sleep or unconsciousness are referred to as ‘analgesics’.

CLASSIFICATION OF ANALGESICS
Broadly analgesics are classified into two groups:
1. Opioid analgesics

OPIOID ANALGESICS
Opioid analgesics include a different class of natural, semisynthetic and synthetic agents. The term ‘opioid’ means that an analgesic which resembles opium alkaloid morphine in its pharmacological properties. ‘Opium’ signifies that it is an extract obtained from the unripe seed capsule of Papaver somniferum. Whereas the word ‘opiate’ means that it is a derivative of opium. Nevertheless, the term opioid is most commonly employed with reference to drugs, which act like morphine.

Opium Alkaloids
Opium contains two types of alkaloids namely:
1. Phenanthrene alkaloids: Morphine, codeine
2. Benzyl isoquinolines: Noscapine, noscine

Classification of Opioid Analgesics
Currently employed opioid analgesics are classified into three groups based on their source and receptor activity:
1. Natural opioids: Morphine, codeine
2. Semisynthetic opioids: Heroin, pentazocine
3. Synthetic opioids: Pethidine (meperidine), fentanyl, nalbuphine, buprenorphine, methadone, tramadol, dextropropoxyphene, sufentanil, alfentanil, remifentanil

Mechanism of Action of Opioids
Opioids induce analgesia due to their actions at several sites within the central nervous system. In general, opioids reduce the ability of the patient to perceive pain probably by an action on thalamus. Opioids alter the psychic reaction to pain by an action on cerebral cortex. It is well recognised that opioids reduce apprehension on the part of patients which is known to increase the pain threshold. Opioids promptly relieve continuous dull visceral pain as well as excruciating acute sharp pain by three main ways:
1. Interaction with opioid receptors
2. Inhibition of the release and action of substance P
3. Augmentation of descending inhibitory pain pathway.
Opioid Receptors

Throughout the central nervous system, several types of opioid receptors are distributed in distinct patterns. The main subtypes of opioid receptors are $\mu$ (mu), $\kappa$ (kappa) and $\delta$ (delta). Opioids differ in their affinity for particular subtype of receptor.

<table>
<thead>
<tr>
<th>Type of receptor</th>
<th>Effects</th>
<th>Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$ (mu)</td>
<td>• Supra spinal analgesia euphoria</td>
<td>Morphine</td>
<td>Naloxone</td>
</tr>
<tr>
<td>($\mu_1 + \mu_2$)</td>
<td>• Respiratory depression constipation</td>
<td>Pethidine</td>
<td>Naltrexone</td>
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<tr>
<td></td>
<td>• Physical dependence</td>
<td>Fentanyl</td>
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<tr>
<td></td>
<td>• Bradycardia</td>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial agonist: Buprenorphine</td>
<td></td>
</tr>
<tr>
<td>$\kappa$ (kappa)</td>
<td>• Spinal analgesia</td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sedation</td>
<td>Pentazocine</td>
<td></td>
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<tr>
<td></td>
<td>• Respiratory depression</td>
<td>Butorphanol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Miosis</td>
<td>Nalbuphine</td>
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<tr>
<td></td>
<td>• Dysphoria</td>
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<td></td>
<td>• Psychotomimetic</td>
<td></td>
<td></td>
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<tr>
<td>$\delta$ (delta)</td>
<td>• Enkephalin pathways</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Probably analgesia</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>• Role is less uncertain</td>
<td></td>
<td></td>
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<tr>
<td>$\sigma$ (sigma)</td>
<td>Not clearly elucidated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\epsilon$ (epsilon)</td>
<td>Uncertain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Opioid analgesics act at one or more of receptors as full agonists, partial agonists or mixed agonist-antagonists (Table 8.4). Accordingly, opioids have been classified into the following groups. However, clinically used opioids are mostly full $\mu$ (mu) agonists.

1. $\mu$ (mu) agonists: Morphine, pethidine, methadone, fentanyl, alfentanil, sufentanil, remifentanil
2. Partial $\mu$ agonists: Buprenorphine, dezocine
3. Kappa agonists + $\mu$ antagonists mixed agonist and antagonists: Pentazocine, butorphanol, nalbuphine
4. Atypical opioid analgesic: Tramadol

ENDOGENOUS OPIOID PEPTIDES

Endogenous opioid peptides are synthesized in various organ systems. Central nervous system, adrenal medulla, nerve plexuses, exocrine glands and intestine are endowed with opioid peptides. Mainly, there are three types of opioid peptides:

1. Enkephalins: Leucine enkephalin, metenkephalin
2. Endorphins: $\beta$-endorphin
3. Dynorphins

Apparently, opioid peptides are known to involve in many functions of neuroendocrine system. Opioid peptides may modulate neurotransmission and endocrinal function of hypothalamus. Opioid peptides may as well be the precursors for hormone synthesis.
MORPHINE
Morphine is an opium alkaloid. It has been known to produce some of actions like endogenous opioid peptides. Morphine as an opioid analgesic produces its actions through opioid receptors. Morphine is an agonist of \( \mu \) receptors and perhaps acts on \( \kappa \) and \( \delta \) receptors. Like other opioid analgesics, morphine should be used with discrimination to avoid physical and psychological dependence. The addiction liability of morphine is less than its semisynthetic derivative heroin. Morphine produces predominant actions on central nervous system and smooth muscle.

Actions of Morphine
Predominantly, morphine is a central nervous system depressant. However, it can produce some stimulant actions and behavioural effects as given in Fig. 8.2.

![Central Actions of Morphine](image)

**Fig. 8.2**: Central actions of morphine

**Analgesia**
Morphine is a potent opioid analgesic which can relieve pain arising from viscera more readily. It alters the psychic response to pain and induces sleep. Morphine is effective in relieving severe pain due to myocardial infarction, pulmonary edema and left ventricular failure. The analgesic effect may persist for 2.5 to 4.7 hours. Morphine is preferred in the management of acute pain that arises from diverse mechanisms. Opioid analgesics are not to be used for chronic management of pain for the fear of drug dependence produced by them. Hence, morphine-like analgesics have been used for short-term management of pain only.

As already referred, morphine-like other opioids inhibit substance P, activate opioid receptors and augment descending pain inhibitory pathway to produce analgesic effect.

**Respiratory Depression**
Morphine is a central respiratory depressant. In fact, all opioids produce respiratory depression and the intensity may vary with individual drugs and doses administered. Morphine is a direct depressant of respiratory centre in brain. It inhibits the respiratory stimulant action of carbon dioxide. Opioids reduce the rate, minute volume and tidal exchange. At high doses, death may result due to severe respiratory depression and failure. Opioids, which belong to kappa receptor agonists group, do not cause severe respiratory depression readily.
Suppression of Cough
Morphine and other opioids suppress cough centre to produce antitussive action. Codeine is preferred to morphine as cough suppressant in the management persistent unproductive cough.

Anaesthesia
Morphine induces anaesthesia when administered by epidural injection. Invariably, intraspinal route is employed for providing relief from chronic pain or terminal cancer pain on morphine. Morphine is commonly used as pre-anaesthetic medicament. It reduces apprehension and provides analgesia. But, morphine may increase postoperative vomiting which can be controlled by an antiemetic.

Central Stimulant Actions
Morphine stimulates vagal nuclei, 3rd nerve nucleus and vomiting centre to produce bradycardia, miosis and emesis respectively. Opioids with $\mu$ receptor agonistic effects produce stimulant actions and high doses may even cause convulsions.

Tolerance and Dependence
The development of tolerance and dependence is a characteristic feature of opioid analgesics. Especially, $\mu$ receptor agonists have high addiction liability. Repeated administration of morphine is associated with both physical and psychic dependence. Dependence may develop more readily when opioids are regularly misused for their euphoriant effects. Abrupt withdrawal of opioid from an addict precipitates drug withdrawal syndrome or abstinence syndrome. If a pregnant woman is an opioid addict delivers a baby, the baby suffers from opioid abstinence syndrome. The treatment of opioid withdrawal syndrome is the replacement therapy with an opioid like methadone. Planned withdrawal, psychic counselling and symptomatic supportive therapy have been employed to deaddict the patient.

Gastrointestinal System
Morphine increases gastric acid secretion, inhibits propulsive movement of intestine and a spasmogenic drug consequently induces constipation. The tone of anal sphincter is markedly increased by morphine. It reduces the rectal secretion. Therefore, an opium containing mixture is used as antidiarrhoeal agent.

When morphine is administered to relieve biliary colic and other colicky pain, the spasmogenic effect is not desired and in fact troublesome. Therefore, in the management of biliary colic morphine is given with an antispasmodic drug like atropine. Atropine nullifies the spasmogenic effect of morphine on sphincter of Oddi and intrabiliary duct pressure does not rise. Thus, analgesic efficacy of morphine becomes satisfactory. Comparatively, pethidine and atropine combination appears to be more advantageous than morphine and atropine combination. Pethidine is less spasmogenic and rapidly acting analgesic.

Morphine has no major effect on cardiovascular system. Nevertheless, morphine liberates histamine, which may reduce blood pressure.

Opioid analgesics are known to stimulate secretion of prolactin and antidiuretic hormone.
Pharmacokinetics
Morphine undergoes extensive first pass metabolism and oral bioavailability is poor. Hence, morphine is generally administered by subcutaneous, intramuscular, intravenous, epidural and rectal routes. It can also be given by sublingual route. Morphine is conjugated with glucuronic acid in the liver. Morphine-3-glucoronide may antagonize the analgesic action of morphine. In fact, this may be the reason for paradoxical pain observed in some patients on morphine administration. Morphine diffuses across placenta and traces appear in milk and sweat.

Therapeutic Uses
Morphine is used to provide relief from pain associated with cancer, myocardial infarction, biliary colic and surgery.

Morphine is commonly employed as preanaesthetic medicament. Since it relieves anxiety produces sleep and analgesia.

Morphine is used in acute pulmonary edema due to left ventricular failure to relieve dyspnoea.

Morphine has also been used as anaesthetic for specialized surgical procedures. It is also given with non-opioid analgesic to achieve analgesic synergism.

Adverse Effects
Nausea, vomiting, urinary retention and constipation may be observed as side effects of opioid analgesics and morphine in particular. Hypothermia, restlessness, changes of mood, confusion, decreased libido, hallucinations and miosis are also seen as opioid side effects.

High doses of morphine produce respiratory depression, hypotension, bradycardia, circulatory collapse and coma. Respiratory depression, miosis, pin-point pupil and coma are the major clinical features of acute opioid poisoning. Intravenous administration of naloxone reverse the respiratory depression caused by opioid analgesics.

Morphine is contraindicated in respiratory depression, obstructive airway diseases, head injuries, acute alcoholism, epilepsy and constipation.

PETHIDINE (MEPERIDINE)
Pethidine is an opioid analgesic and a synthetic agent, which acts mainly on μ receptors. It is more lipid soluble, rapidly and short acting less potent than morphine. Moreover, pethidine is less spasmogenic and has lower potential to increase biliary pressure. Hence, pethidine is more suitable to manage pain due to biliary colic and pancreatitis. Pethidine has negligible effect on cough and diarrhoea.

Although pethidine undergoes substantial first pass metabolism, it is orally effective. It is also given by subcutaneous, intramuscular and intravenous routes. Pethidine undergoes metabolism in liver by hydrolysis. Norpethidine, a metabolite, is pharmacologically active and its accumulation can produce neurotoxicity and mydriasis. Pethidine crosses placental barrier and distributed into milk.

Pethidine is used to provide relief of moderate to severe acute pain including the pain of labour. It is also used as preanaesthetic medicament. Pethidine is an obstetric analgesic,
since it is used to control pain of labour and postoperative pain following caesarean section or other surgical procedures.

**Adverse Effects**
Pethidine produces sedation, respiratory depression, nausea, vomiting and constipation occurs less frequently. At higher doses, pethidine produces central nervous system stimulation and convulsions. Naloxone is the specific antidote to treat acute pethidine poisoning conditions.
Pethidine, like other opioid analgesic, is contraindicated in respiratory depression and obstructive airways diseases. Pethidine should not be given to comatose patient. Caution is necessary for administration of pethidine with history of epilepsy.

**Drug Interaction**
Pethidine + selegiline: Leads to severe reactions, intense respiratory depression, coma, cyanosis and hypotension.

**METHADONE**
Methadone is an orally effective, long acting, $\mu$ agonist synthetic opioid analgesic. It is also a cough suppressant. Methadone causes less sedation than morphine. It is readily absorbed from gastrointestinal tract. Methadone is distributed into milk. Methadone accumulates in the body and produces more intense respiratory depression than morphine on repeated administration. Methadone can be given by subcutaneous or intramuscular injection. Methadone is used in the management of opioid dependence. But prolonged use of methadone itself produces dependence. Methadone is used as cough suppressant in intractable cough associated with terminal lung cancer.

**BUPRENORPHINE**
Buprenorphine is a synthetic opioid analgesic used to relieve moderate to severe pain. It is also used as an adjunct drug in anaesthesia. Buprenorphine is a partial agonist of $\mu$ receptor. It is given by sublingual or intramuscular or intravenous route. Buprenorphine is used in balanced anaesthesia and to provide relief from pain. Nausea, vomiting and respiratory depression are the common adverse effects of buprenorphine.

**FENTANYL**
Fentanyl is a potent opioid analgesic structurally related to pethidine. It is primarily a $\mu$ agonist. Fentanyl has a rapid onset of action and action lasts for less than 2 hours. Fentanyl is more lipid soluble and following intravenous administration the action is evident almost immediately. The short duration of action of fentanyl is probably due to rapid distribution into the tissues rather than metabolism and excretion. Fentanyl can be administered by intramuscular route. It crosses placental barrier and has been detected in breast milk.
Fentanyl is used as analgesic preoperatively, during operation and postoperatively. It is an adjunct drug to general anaesthesia. Fentanyl is given with droperidol to induce a state of neuroleptanalgesia to quieten the patient before anaesthesia and surgery.
Respiratory depression, transient hypotension, bradycardia, muscle rigidity, restlessness and hallucinations have been observed as adverse effects of fentanyl.
PENTAZOCINE

Pentazocine is an opioid analgesic having mixed agonist and antagonist actions on opioid receptors. It is an agonist of kappa receptor and a weak antagonist of μ (mu) opioid receptor. Pentazocine is orally effective and can be given along with aspirin and paracetamol. It undergoes extensive first pass metabolism and oral bioavailability is low. Pentazocine is also administered by subcutaneous, intramuscular and intravenous routes. Pentazocine suppositories are also available for rectal administration.

Pentazocine is used to provide relief from moderate to severe pain. Since pentazocine is a mixed agonist – antagonist opioid may precipitate withdrawal syndrome if given to patients who are physically dependent on μ receptor agonist opioids.

Adverse reactions produced by pentazocine are different from that of morphine. Pentazocine causes tachycardia, increases blood pressure, enhances cardiac load and depresses respiration. Toxic epidermal necrolysis has been reported after pentazocine administration.

Pentazocine should not be used to relieve pain due to myocardial infarction as it increases ventricular workload.

DEXTROPROPOXYPHENE

Dextropropoxyphene is an opioid analgesic chemically related to methadone. It is a weak analgesic and generally given by mouth to relieve mild pain. Dextropropoxyphene can be given with aspirin or paracetamol. Unlike its analogue levopropoxyphene, it has a weak cough suppressant effect. Orally administered dextropropoxyphene may not cause constipation and therefore it is preferable to codeine.

Nausea, vomiting, drowsiness, dizziness, liver function, impairment and at high doses dextropropoxyphene can cause cardiac arrhythmias. Prolonged administration of dextropropoxyphene must be discouraged, as it is known for potential abuse liability.

OPIOID ANTAGONISTS

Naloxone and Naltrexone

Opioid antagonists are the competitive receptor blockers used in acute opioid poisoning conditions. Naloxone or naltrexone is used as specific antidote for acute opioid poisoning. Intravenous administration of naloxone promptly reverses the respiratory depression produced by opioid analgesics.

Opioid antagonists are given orally as adjunct drugs in the maintenance of an opioid free state in detoxified former opioid addict. Naltrexone is preferred for this purpose since it is a long-acting opioid antagonist. Nevertheless, naloxone should be given cautiously to opioid-dependent individual as severe withdrawal effects may be precipitated.

Naloxone is given by intravenous route in opioid poisoning. Opioid antagonists do not block all the actions of opioids. Respiratory depression, sedation, analgesia, hypotensive and psychotomimetic effects of opioids are promptly reversed by naloxone or naltrexone either.

Naltrexone is also being tried to reverse the coma induced by alcohol and in refractory shock.
PSYCHIATRIC DISORDERS

Modern psychopharmacology largely deals with the interpretation of behavioral consequences of drugs used in psychiatric medicine. Different classes of drugs used in psychiatry are selective in their ability to modify clinical course of mental illnesses. The appropriate use of these drugs thus requires accurate diagnosis and basic knowledge about the efficacy and safety of drugs. In general, psychototropic drugs are not disease specific and provide clinical benefit for a range of symptoms.

It is common to classify psychiatric disorders into two broad types although clinical features often overlap. These are:

- Psychoses
- Neuroses

*Psychoses* are most severe behavioral impairment characterized by inability to think coherently and delusions and hallucinations are common. The major psychosis that is commonly encountered in psychiatric clinic is ‘schizophrenia’.

*Neuroses* refer to personality disorders, which may or may not respond to medical intervention.

CLASSIFICATION

Generally, psychiatric disorders are classified into four types:
1. **Psychoses**: Schizophrenia, paranoia
2. **Cognitive disorders**: Confusion, disorientation
3. **Mood disorders**: Depression, bipolar disorders (manic depressive illness)
4. **Anxiety disorders**: Panic, dysphoria

The etiology of mental illness is not completely understood. It involves genetic, physiological and environmental factors. Many biological hypotheses of mental illness proclaim that failure of neurotransmitter related biological functions in the brain, coupled with exigencies of everyday life contribute well for psychiatry disorders. In addition, failure of psychodynamic adaptation, precisely the mind-body function plays a central role in mental illness.

DRUGS

Drugs used in mental illness are grouped into four classes:
1. Antipsychotics (neuroleptics)
2. Antidepressants
3. Antimanic drugs
4. Antianxiety drugs
Besides drug therapy, psychiatric patients require supportive, educative, cognitive and persuasive modalities of treatment.

**Drugs Used in Psychoses**

Psychosis is a severe impairment of social and personnel functioning characterized by social withdrawal. There is an inability to perform the daily routine household and occupational works. The patient may suffer from dissociative identity disorders. This is commonly known as “schizophrenia”. Schizophrenia is characterized by delusions, hallucinations, disorganized speech, lack of pleasure, social withdrawal, agitation and impairment of attention. Schizophrenia is believed to be due to overactivity of dopamine neurons in the mesolimbic system of the brain. Hence, drugs that block dopamine receptors have been used in the treatment of psychoses.

**CLASSIFICATION OF NEUROLEPTICS**

Neuroleptic drugs are otherwise known as *antipsychotics*. Neuroleptics based on their chemical nature are classified into the following groups:

1. **Phenothiazines**: Chlorpromazine, triflupromazine, thioridazine, fluphenazine, perphenazine
2. **Butyrophenones**: Haloperidol, fluperidol, benperidol, properidol, droperidol, penfluridol
3. **Thioxanthines**: Chlorprothixene, thiothixene, flupenthixol, clopenthixol
4. **Other heterocyclics**: Clozapine (atypical neuroleptic), loxapine, molindone, sulpiride, pimozide
5. **Newer neuroleptics**: Risperidone, olanzapine, sertindole, seroquel

**Pharmacodynamics of Neuroleptics**

Several prominent observable effects of typical neuroleptic agents are strikingly similar. However, these drugs differ in their classical central nervous system depressant effects and all tend to regularize disturbed sleep pattern seen in psychoses. Generally, neuroleptic action results in emotional quietening, psychomotor slowing and reduction in aggressive and impulsive behaviour. Hallucinations, delusions and disorganized thought gradually decline. The spontaneous locomotor activity is reduced by neuroleptics. The patient becomes more responsive and communicative. Although neuroleptics act on central nervous system, they are free from abuse potential.

**Mechanism of Action**

Neuroleptics produce a wide variety of effects on central nervous system. The pathophysiology of schizophrenia is unclear. Nevertheless, classical neuroleptics block dopamine D₂ receptors in the midbrain to provide clinical efficacy. However, neuroleptics do modulate 5-HT, adrenergic and cholinergic effects in the brain. How far these effects contribute to their antipsychotic action remains obscure. Newer neuroleptics are more potent in blocking D₄, 5-HT₂, α and H₁ receptors. The neuroleptics which act by inhibiting D₄, 5HT and α receptor have little propensity to produce neurological toxicities including extrapyramidal syndrome. It is uncertain that how neuroleptics act to improve psychotic manifestations.
Chlorpromazine

Chlorpromazine is a phenothiazine neuroleptic which acts by virtue of blocking D₂ receptor in mesolimbic system. It has a wide range of activities. The antidopaminergic action of chlorpromazine not only produces antipsychotic effects but also increases prolactin secretion and reduces growth hormone release. Other actions of chlorpromazine are antiemetic, α receptor blockade anti-5-HT, antihistamine, antitetany, antifertility and antiallergic. A rare reaction is associated with potent neuroleptics called “neuroleptic malignant syndrome” may cause death. This syndrome is characterized by hyperpyrexia, muscle hyperrigidity, confusion, stupor and coma. Neuroleptic malignant syndrome may be due to sudden withdrawal of neuroleptic drug, increased dopamine receptor density, decreased level of serum iron and poor neuroleptic dosage. The treatment of neuroleptic malignant syndrome involves administration of dantrolene, diazepam and bromocriptine with other supportive measures.

Chlorpromazine is given by mouth. Oral absorption is satisfactory and undergoes first pass metabolism. It can be given by intramuscular route. It enjoys enterohepatic circulation. Chlorpromazine crosses placental barrier and appears in milk.

Therapeutic Uses
Chlorpromazine is widely used in many clinical conditions as given below:
1. Acute and chronic schizophrenia
2. Acute mania
3. Nausea and vomiting (except for motion sickness)
4. Intractable hiccup
5. As an adjunct drug in tetanus
6. Acute intermittent porphyria
7. Alcoholic hallucinosis

Adverse Effects
Chlorpromazine has high therapeutic index and is remarkably safe. However, a wide range of actions produced by chlorpromazine cause many side effects and neurological toxicity on long-term administration. The side effects of chlorpromazine are faintness, dry mouth, blurred vision, palpitation, nasal stiffness, hypothermia and orthostatic hypotension.

The common neurological toxicities of neuroleptic agents are:
a. Acute dystonia: It appears within 1 to 5 days. Spasm of muscles of face, neck, back and tongue have been observed
b. Akathisia: It may be seen after 5 to 60 days of neuroleptic administration, characterized by motor restlessness.
c. Parkinsonism: Tremors, muscle rigidity and bradykinesia
d. Tardive dyskinesia: Perioral tremors, tics, orofacial dyskinesia, twisting of tongue
e. Neuroleptic malignant syndrome

Besides, chlorpromazine can produce hyperpigmentation, agranulocytosis, cholestatic jaundice, galactorrhea, photosensitivity reactions, pigmentary retinopathy, pseudopregnancy, gynaecomastia, impotence and infertility.
**Drug Interactions**
Chlorpromazine potentiates the action of all central nervous system depressants like analgesics, anaesthetics, alcohol, antihistamines.
   *Chlorpromazine antagonizes the actions of Levodopa.*
   *Chlorpromazine is generally not recommended in late pregnancy.*

**Haloperidol**
Haloperidol is a butyrophenone antipsychotic drug with general pharmacological properties similar to those of chlorpromazine. However, it is more potent, long acting, less hypotensive, less sedative and least anticholinergic when compared to chlorpromazine. Haloperidol is generally given by oral route and can be administered intramuscularly.

Haloperidol is readily absorbed by gastrointestinal tract and undergoes first pass metabolism in liver. It undergoes enterohepatic circulation and excreted in urine, bile and faeces. The plasma half-life of haloperidol is between 12-38 hours. Haloperidol is distributed into breast milk.

**Therapeutic Uses**
Haloperidol is indicated in the treatment of various psychotic diseases, which are as follows:
1. Acute and chronic schizophrenia
2. Bipolar disorders
3. Tourette’s syndrome
4. Severe tics
5. Severe anxiety
6. Nausea and vomiting of various causes

**Adverse Effects**
Adverse reactions produced by haloperidol are similar to chlorpromazine. It can cause all the neurological toxicities observed with commonly used antipsychotic drugs. Haloperidol is associated with higher incidence of extrapyramidal syndrome. Sedation is less with haloperidol. Severe dystonic reactions have followed the administration of haloperidol in children.
MENTAL DEPRESSION

Mental depression is one of the most common types of mental illnesses. This is a complex disorder of mood and may coexist or alternate with mania. Mental depression is a complex syndrome often underdiagnosed and under treated. Depression is characterized by intense sadness, despair, mental slowing, loss of concentration, pessimistic worry and self-depreciation.

Types of Mental Depression

Clinically, mental depression is classified into two types:
- Bipolar depression
- Unipolar depression

Bipolar depression is otherwise known as manic depressive illness. This is a mixed affective disorder. Patient of bipolar depression presents alternating episodes of hypomania or mania and depression.

Unipolar depression is a disturbance of mood, which may be accompanied by a variety of mental or somatic symptoms. Unipolar depression is also defined as single recurrent melancholic episodes characterized by insomnia, anorexia, weight loss, decreased libido and suicidal tendencies. Unipolar depression occurs without mania. Atypical depression includes symptoms associated with overeating and oversleeping.

There are several modalities of treatment of mental depression. The nature of treatment approaches depend upon severity, type of depression and the patient’s response to therapy. Drug therapy with antidepressants and electroconvulsive therapy are the common approaches for the treatment of depression. However, psychotherapy may be effective in conjunction with antidepressants. Light therapy is also effective in mood disorders with drug therapy.

CLASSIFICATION OF ANTIDEPRESSANTS

Antidepressants have been subdivided into following groups either based on their structure or mechanism of action.

1. Tricyclic antidepressants: Imipramine, desipramine, trimipramine, lofepramine, nortriptyline, amitriptyline, doxepin, dothiepin, amoxapine

2. Heterocyclics: Maprotiline, trazodone, bupropion

3. Selective serotonin reuptake inhibitors (SSRIs): Fluoxetine, fluvoxamine, citalopram, venlafaxine, paroxetine

4. Monoamine oxidase inhibitors (MAOIs)
   a. Nonselective (both MAO-A and B inhibitors): Tranylcypromine, phenelzine
   b. Selective (MAO-A inhibitor): Moclobemide
TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants have long been used in the treatment of mental depression. All tricyclic antidepressants have similar pharmacodynamic profile. Clinical experience with tricyclic antidepressants is wide and hence these drugs are used as agents of choice in depression. However, the sedative properties of some tricyclic antidepressants are the sources of concern. Moreover, selection of an antidepressant for patient considered to be at high suicidal risk assumes great clinical significance. More importantly, in the early stages of antidepressant therapy risk of suicide may increase during recovery.

Imipramine

Imipramine is a tricyclic antidepressant. It acts by potentiating the effects of biogenic amines neurotransmitter in central nervous system. Imipramine blocks the reuptake of released noradrenaline and 5-hydroxy tryptamine. Moreover, tricyclic antidepressants are believed to cause downregulation of $\beta_2$, $\alpha_2$ and 5-HT$_2$ receptors in central nervous system. In addition, tricyclic antidepressants produce antihistaminic, antimuscarinic and $\alpha_1$ receptor blocking effects. It is probable that all these neuropharmacological effects may contribute at least in part for the antidepressant effects of imipramine-like drugs.

Imipramine is given by mouth and it undergoes substantial first pass metabolism. Side effects are relatively common with tricyclic antidepressant drugs. These are attributable to their antimuscarinic and $\alpha_1$ receptor blocking activities. Dry mouth, constipation, blurred vision, urinary retention, sedation, postural hypotension, weight gain, sweating and depression to mania or hypomania may occur during transitional phase of antidepressant administration.

Therapeutic Uses

Imipramine and other tricyclic antidepressants have been used in the following conditions:
1. Mental depression
2. Migraine
3. Nocturnal enuresis
4. Cluster headache
5. Chronic pain
6. Fibromyalgia
7. Pathological laughing and weeping
8. Irritable bowel syndrome

Drug Interactions

1. Imipramine + cigarette smoking: Nicotine increases the rate of metabolism of imipramine
2. Antidepressants + antiepileptics: Antagonism
Fluoxetine

Fluoxetine is an antidepressant belonging to the group selective serotonin reuptake inhibitors. On continuous administration fluoxetine increases the biogenic amine serotonin levels in central nervous system. Fluoxetine has some advantages over conventional tricyclic antidepressants. Fluoxetine is relatively free from sedative effect, does not cause postural hypotension, no weight gain and does not produce disturbing antimuscarinic side effects. Therefore, currently main antidepressant drug therapy involves the administration of selective serotonin reuptake inhibitors. However, fluoxetine group of drugs when used with monoamine oxidase inhibitor antidepressants have the propensity to induce ‘serotonin syndrome’. This syndrome is characterized by hyperthermia, myoclonus, muscle rigidity, changes in mental activity, delirium and coma.

Fluoxetine produces nausea, vomiting, headache, abdominal pain, agitation and sexual dysfunction. Fluoxetine has the tendency to cause epilepsy with non-steroidal anti-inflammatory drugs as well fluoroquinolones antimicrobials.

Other Antidepressants (Table 8.5)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main neurological action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Inhibition of noradrenaline and 5-HT reuptake</td>
<td>Sedation, atropine-like effects, hypotension, palpitation, sexual dysfunction</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Inhibition of noradrenaline and 5-HT reuptake</td>
<td>Seizures, sedation, cardiac effects</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Selective serotonin reuptake inhibitor</td>
<td>Nausea, vomiting, headache, sexual dysfunction</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Atypical antidepressant inhibits reuptake of dopamine</td>
<td>Agitation, seizures, gastrointestinal disturbances</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Inhibition of 5-HT and noradrenaline uptake</td>
<td>Sedation</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>Increases the level of noradrenaline, 5-HT and dopamine by inhibiting their metabolism</td>
<td>Agitation, sexual dysfunction</td>
</tr>
</tbody>
</table>

ANTIMANIC DRUGS (MOOD STABILIZER)

Mania is usually followed by depression although isolated episodes of mania can occur. In clinical practice it is accepted to include mania as a part within the bipolar depression. Mania is characterized by elation, increased energy, feeling of grandiosity and decreased need for sleep. Bipolar depression is a mixed affective disorder with alternating episodes of mania or hypomania and depression.

Drugs used to treat bipolar depression are known as mood stabilizing agents. Lithium, carbamazepine and valproate are effective in the treatment of manic depressive illness.

Lithium

Lithium is the drug of choice to treat acute mania and also effective in recurrent attacks of mania. Lithium can be used to prevent the attacks of mania. Lithium as ion can compete with Na⁺ ion at many sites of the body. It is known to act by blocking the hydrolysis of inositol phosphate. Lithium may increase the synthesis of acetylcholine. How far these effects help in stabilization of mood is not known.
Lithium is administered by oral route. It accumulates gradually in tissues and gets secreted in urine, saliva, tears and milk.

Lithium has a low therapeutic index and many of the adverse effects of lithium are dose related. Nausea, diarrhoea, vertigo, muscle weakness, dazed feelings, fine hand tremors, polyuria and polydypsia, weight gain and edema. Lithium may produce more serious effects like cardiac arrhythmias, albuminuria, hypercalcemia, hypermagnesemia, hyperparathyroidism, acne, psoriasis, hyperreflexia, seizures and coma.

Lithium when administered with routinely used diuretics, lithium toxicity may increase and hence lithium is avoided with diuretics.

Lithium should be avoided in patients with cardiac disease and renal impairment.

**ANXIOLYTIC DRUGS**

Anxiety is a universal human emotion and a cardinal symptom of psychoneurotic disorders. Anxiety is characterized by feelings such as apprehension and fear. If it is severe, anxiety disables the individual. Palpitation, shortness of breath, choking spells, sweating and trembling are the autonomic manifestations of anxiety.

Mild anxiety disorders have been successfully treated by psychotherapy alone. Serious anxiety states may require anxiolytic drug therapy. Clinically used antianxiety drugs are:

1. **Benzodiazepines:** Diazepam, alprazolam, clorazepate, chlordiazepoxide, oxazepam, clonazepam

2. **Nonbenzodiazepines:** Buspirone, hydroxyzine

Diazepam and other benzodiazepines are the agent of choice to treat anxiety disorders. Ideally, antianxiety drugs must be given for short duration and should not be withdrawn abruptly. If withdrawn abruptly, rebound anxiety may be observed.

**Buspirone**

Buspirone is a non-sedative, non-benzodiazepine anxiolytic drug. Buspirone does not produce withdrawal syndrome. It does not have anticonvulsant action unlike diazepam. Buspirone has low potential for tolerance. Buspirone modulates 5-HT<sub>1A</sub> receptor responses in addition to dopaminergic and adrenergic effects to relieve anxiety. It has a good safety profile. Dizziness, chest pain and tinnitus have been observed as adverse effects on buspirone therapy. Buspirone does not potentiate the action of alcohol and motor skills are not disturbed. Buspirone does not produce dependence. Therefore, it is preferred to benzodiazepines to treat anxiety disorders.
INTRODUCTION

A wide variety of drugs have been used as anti-inflammatory, analgesic and antipyretic. Some of these drugs are over-the-counter drugs that can be purchased without valid medical prescription. Aspirin, paracetamol and ibuprofen are popular as household analgesics. Drugs that suppress inflammation are broadly classified into two—namely steroidal anti-inflammatory drugs, for example, hydrocortisone, prednisolone and dexamethasone. The second group comprises non-steroidal anti-inflammatory drugs (NSAIDs), which represents a heterogeneous group of drugs.

Non-steroidal anti-inflammatory drugs are a group of unrelated organic acids, which produce anti-inflammatory, analgesic and antipyretic actions. Generally, it is believed that there is a little difference in anti-inflammatory activity between the various NSAIDs and, therefore, choice of NSAID is largely empirical. However, NSAIDs with lower risk of gastrointestinal toxicity should be preferred and lowest effective dose must be employed.

CLASSIFICATION

The classification of non-steroidal anti-inflammatory drugs is based on chemical nature and mechanism of action.

1. Salicylates: Aspirin, sodium salicylate, diflunisal
2. **Propionic acid derivatives**: Ibuprofen, naproxen, ketoprofen, flurbiprofen
3. **Hetero arylacetic acid derivatives**: Ketorolac, diclofenac, tolmetin
4. **Indole derivatives**: Indomethacin, sulindac, etorolac
5. **Oxicams**: Piroxicam, tenoxicam
6. **Fenamates**: Mefenamic acid, meclofenamic acid
7. **Pyrazolone**: Oxyphenbutazone
8. **Selective COX-2 inhibitors**: Nimesulide, meloxicam, celecoxib, rofecoxib, valdecoxib
9. **Antipyretic analgesic**: Paracetamol
10. **Disease-modifying antirheumatic drugs (DMARDs)**: Gold salts, hydroxychloroquine, d-penicillamine, methotrexate, azathioprine
11. **Others**: Nefopam

**GENERAL MECHANISM OF ACTION OF NSAID**

**Anti-inflammatory Action**

Non-steroidal anti-inflammatory drugs are the novel agents that suppress inflammatory response to mechanical, thermal, ischemic, immunological and infection-induced injury. Injury leads to an orderly occurring of several cell processes (Fig. 9.1).
All non-steroidal anti-inflammatory drugs that suppress inflammation have similar mechanism of action. Many of the effects of NSAIDs appear to be due to their inhibitory action on prostaglandin synthesis. Aspirin, the prototype of NSAIDs, irreversibly inhibits cyclooxygenase enzyme to arrest prostaglandin synthesis (Fig. 9.2). There are two forms of cyclooxygenases:

a. Cyclooxygenase-1 (COX-1)
b. Cyclooxygenase-2 (COX-2)

The inhibition of cyclooxygenase-2 is thought to be involved at least in part anti-inflammatory, analgesic and antipyretic actions of NSAIDs. Whereas inhibition of COX-1 is responsible for some of the toxic effects produced by NSAIDs. Most of the NSAIDs currently used are non-selective cyclooxygenase inhibitors, i.e., both COX-1 and COX-2 are inhibited. Recently, selective COX-2 inhibitors have been introduced to the market as less toxic NSAIDs. However, the efficacy of COX-2 inhibitors on long-term use has raised doubts. Further, new types of alarming adverse effects have been documented with selective COX-2 inhibitors. Therefore, selective COX-2 inhibitor NSAIDs may not offer substantial advantages over conventional non-selective cyclooxygenase inhibitors, especially for the management of chronic inflammatory diseases.

Besides prostaglandin synthesis inhibition, NSAIDs may act by antagonizing the action of bradykinin, a mediator of inflammation. Moreover, NSAIDs like sulindac, piroxicam and ibuprofen have scavenging effects on oxygen free radicals consequently minimizing the tissue injury. Finally, NSAIDs are known to promote the release of glucocorticoids, which may also contribute to their anti-inflammatory action.

**Analgesic Action**

Non-steroidal anti-inflammatory drugs provide analgesia secondary to their anti-inflammatory effects. Generally, NSAIDs are referred to as ‘non-opioid analgesics’. Some of the NSAIDs like aspirin, paracetamol and ibuprofen are available as over-the-counter and household analgesics.

Non-opioid analgesics relieve mild-moderate pain effectively. Pain arising from integumental system is more amenable to NSAIDs. These are not effective in non-inflammatory pain and in acute pain of visceral origin.
Several mechanisms have been proposed for analgesic action of NSAIDs as mentioned below:

a. Aspirin-like NSAIDs reduce the generation of mediators of pain at the site of tissue damage. They inhibit prostaglandin synthesis thereby arrest the sensitization of polymodal nociceptors of pain fibres.

b. Bradykinin exacerbates pain sensation. Aspirin-like drugs antagonize the action of bradykinin. Undoubtedly, this effect does add to their analgesic action.

c. It is probable that NSAIDs inhibit pain stimuli at subcortical level in central nervous system. However, at present this remains unclear.

Antipyretic Action

The antipyretic action of NSAIDs is commonly useful to control fever. Paracetamol, aspirin and other NSAIDs are readily used as antipyretic agents. Antipyretics reduce elevated body temperature by the following mechanisms:

a. Block the synthesis of endogenous pyrogens. Fever may be due to the release of pyrogens like prostaglandin E₂, interleukins 1 and 6, and interferon α, β. Paracetamol inhibits prostaglandin synthesis and the liberation of leukocyte pyrogens.

b. Increase heat dissipation, balance heat production and heat loss in the body.

c. Modulate temperature control at hypothalamic level. Antipyretics are known to reset the thermodynamic centre of hypothalamus to the point of normal body temperature.

SALICYLATES

Salicylates are the salts of salicylic acid and have anti-inflammatory, analgesic and antipyretic actions. Therapeutically used salicylates are:

a. Aspirin (acetyl salicylic acid)

b. Sodium salicylate

c. Diflunisal

Aspirin

Aspirin is a century old anti-inflammatory, antirheumatic, analgesic, antipyretic and cardioprotective drug. It is a prostaglandin synthesis inhibitor. Aspirin is non-selective cyclooxygenase enzyme inhibitor, which acts on both COX-1 and COX-2. It arrests thromboxane synthesis by irreversibly inhibiting the platelet cyclooxygenase. Consequent to this, platelet aggregation cannot occur.

Pharmacological Actions

Aspirin produces actions on many systems, some of which have attained therapeutic value as well as toxicological importance.

Central Actions

Aspirin causes stimulation of central nervous system. At high doses, it leads to convulsions followed by depression. It increases labyrinthine pressure and produces tinnitus and reversible high tone deafness.
Respiratory System

A dose-dependent direct and indirect effects of aspirin on respiratory system contributes to serious acid-base disturbance as mentioned in Fig. 9.3.

At therapeutic dose level
- Direct action: Hyperventilation
- Indirect action: Uncouples oxidative phosphorylation, rise in $P_{CO_2}$, stimulate respiration

At higher doses
- Respiratory alkalosis: Increased renal clearance of bicarbonate
- Stage of compensated respiratory alkalosis
- Medullary depression: centre paralysis, increased CO$_2$ retention, no plasma bicarbonate reserve

At toxic doses
- Respiratory acidosis
- Renal activity decreases and dehydration: K$^+$ depletion
- Accumulation of metabolic acids
- Metabolic acidosis

Fig. 9.3: Respiratory system

In acute salicylate poisoning condition, measures to combat dehydration and metabolic acidosis are necessary to save life.

Gastrointestinal System

Aspirin is a gastric irritant and ulcerogenic agent. Epigastric distress, heartburn and dyspepsia are common on oral administration of aspirin. Haemorrhagic gastritis and occult blood loss is a source of concern with aspirin therapy.
Blood
Aspirin is a cardioprotective drug. It inhibits platelet aggregation and acts as an antithrombotic agent. Aspirin acetylates platelet cyclooxygenase and blocks the generation of thromboxane A\textsubscript{2}. Thus, thromboxane A\textsubscript{2} promoted platelet aggregation does not occur. As a result, it prevents the formation of thrombus inside the blood vessel. This action of aspirin is of great clinical significance in coronary thrombosis. It is common to administer aspirin at low doses for cardioprotective action in view of achieving its action only on platelet cyclooxygenase. Aspirin prevents reinfarction, which prolongs the lifespan of patients of myocardial infarction.

Metabolism
Aspirin produces multiple actions on metabolism. By virtue of increasing glucocorticoid and epinephrine release, aspirin causes hyperglycemia and glycosuria. Aspirin reduces lipogenesis by blocking incorporation of acetate into fatty acid. Oxidative phosphorylation is blocked by aspirin, which inhibits ATP-dependent reactions.

Pregnancy and Aspirin
There is no evidence of aspirin caused fetal damage in human beings. However, babies born to pregnant mothers who were on aspirin therapy do show some abnormal features. Low body weight, anaemia and increased perinatal mortality are a few aspirin fetotoxicities reported. Despite, aspirin is not contraindicated in pregnancy. Nevertheless, aspirin may be avoided in third trimester of pregnancy.

Aspirin and Children
The use of aspirin in paediatric patients aged below 12 years is not recommended because of the risk of Reye’s syndrome. This syndrome occurs exclusively in children typically with viral infections after aspirin administration. Reye’s syndrome is characterized by acute encephalopathy, fatty degeneration of liver, nausea and vomiting. Aspirin should not be given to children suffering from chickenpox infection.

Pharmacokinetics
Aspirin is rapidly absorbed from stomach and intestine. It is widely distributed and 80-90% of the dose administered remains as bound form in plasma. The plasma half-life of aspirin is 2-3 hours. Biotransformation of aspirin involves oxidation and conjugation reactions. Partly aspirin is excreted by active renal tubular secretion. Aspirin can be removed from the body by haemodialysis.

Therapeutic Uses
Aspirin is used to suppress inflammation, provide relief from pain and reduce fever in wide variety of clinical conditions as mentioned below:
1. Acute rheumatic fever
2. Rheumatic carditis with steroidal anti-inflammatory drugs
3. Arthritis
4. Osteoarthritis
5. Headache
6. Dysmenorrhea
7. Angina pectoris and myocardial infarction as cardioprotective
8. Dental pain
9. Influenza fever with muscle and joint pain
10. Antidiarrhoeal agent in radiation-induced diarrhoea
11. Prophylaxis of colorectal cancer
12. Stroke

Contraindications
1. Peptic ulcer
2. Hypoprothrombinemia
3. Viral infections in children
4. Dehydration
5. Haemophilia
6. Aspirin hypersensitivity

Adverse Effects
The most common adverse effects of aspirin at therapeutic doses are: nausea, vomiting, dyspepsia, gastric irritation, ulceration, erosion and haematemesis. Gastrointestinal haemorrhage can occur at any site with melaena. Aspirin-induced gastrointestinal toxicities can be minimized by giving the drug after food. H₂ receptor blockers and prostaglandin analogue misoprostol may be co-administered with aspirin to reduce gastrotoxicity.

Aspirin in patients with asthma exhibit notable sensitivity, provoking various reactions like urticaria, rhinitis and severe fatal bronchospasm and dyspnoea.

Mild chronic toxicity is often called salicylism. Dizziness, tinnitus, deafness sweating, mental confusion and headache are observed as symptoms of salicylism. Generally, reduction in the dose of aspirin may well control the salicylism.

Acute salicylate poisoning following overdoses of aspirin produces more alarming symptoms like hyperventilation, fever, restlessness, acidosis, dehydration, central nervous system depression, coma, cardiovascular collapse and respiratory failure. In children hypoglycemia and metabolic acidosis commonly occur. There is no specific antidote for acute salicylate poisoning. Gastric lavage, forced alkaline diuresis, correction of acidosis and dehydration, haemodialysis or haemoperfusion are the effective methods of removing salicylate from the body.

Drug Interactions
1. Aspirin gastrointestinal toxicity is reduced by co-administration antacids or H₂ receptor blockers (ranitidine) or proton pump inhibitors (omeprazole) or sucralfate or misoprostol.
3. Aspirin + warfarin: aspirin displaces warfarin from plasma protein and increases the toxicities of warfarin by reducing prothrombin level.
4. Aspirin + ACEI
   Aspirin + β blockers \{ \text{reduction in the efficacy of antihypertensive effects} \}
   Aspirin + Diuretics
5. Aspirin + fluoroquinolones: Increased incidence of convulsions
6. Aspirin + aminoglycoside antibiotics: Increased ototoxicity
7. Aspirin + probenecid: Antagonism of uricosuric action
8. Aspirin + cyclosporine: Increased nephrotoxicity

**IBUPROFEN**

Ibuprofen is a propionic acid derivative non-steroidal anti-inflammatory drug. It is also a prostaglandin synthesis inhibitor and effective in relieving mild to moderate pain. Ibuprofen suppresses inflammation-induced tissue damage by inhibiting the generation of superoxide radical. Ibuprofen is absorbed well from gastrointestinal tract. The plasma half-life of ibuprofen is 2 hours.

Ibuprofen is commonly used for toothache, dysmenorrhoea, arthritis, ankylosing spondylitis and osteoarthritis. It is also used in rheumatoid arthritis, bursitis and tenosynovitis. It can be used as an alternate drug in patent ductus arteriosus.

Unlike aspirin, ibuprofen is well tolerated and more severe toxicity is uncommon. Like other NSAIDs, ibuprofen can precipitate bronchial asthma in susceptible individuals.

**INDOMETHACIN**

Indomethacin is a potent, poorly tolerated indole acetic acid derivative NSAID. It resembles other NSAIDs in producing anti-inflammatory, analgesic and antipyretic actions. Indomethacin is regarded as relatively selective COX-1 inhibitor. It should not be used as a simple routine analgesic because it produces frequent adverse effects.

Indomethacin is usually given by oral route. It can be administered as suppository. Absorption by oral and rectal routes is comparatively good. Indomethacin is about 99% bound to plasma proteins. The plasma half-life is about 11 hours. Indomethacin readily reaches the synovial fluid, central nervous system and fetus.

As indomethacin is more potent and more toxic, it should not be used routinely. Indomethacin is the drug of choice in patent ductus arteriosus, ankylosing spondylitis, acute gout, pericarditis and Barter’s syndrome. It is also used to treat bursitis and tendinitis.

Indomethacin produces more frequent adverse effects. Gastric ulceration, bleeding, depression, tinnitus, convulsion, hypertension, edema, weight gain, epistaxis, haematuria, hypersensitivity reactions, skin rashes, haemolytic anaemia, aplastic anaemia, hyperglycemia, hyperkalemia and vaginal bleeding are the adverse effects reported with indomethacin administration.

Indomethacin is contraindicated in peptic ulcer and hypertension.

**DICLOFENAC**

Diclofenac is a phenylacetic acid NSAID. It is an anti-inflammatory analgesic and antipyretic agent, used to provide relief from rheumatoid arthritis. Diclofenac is also useful in acute gout, renal colic, dysmenorrhoea and ankylosing spondylitis. Diclofenac inhibits both cyclooxygenase and lipoxygenase enzymes to block the release of inflammatory mediators.
Diclofenac is administered by oral route. It is available as ophthalmic solution and as gel for topical application. Diclofenac can be given intramuscularly to relieve postoperative pain. If there is need, diclofenac can be administered by intravenous route. Diclofenac suppositories are also available for rectal administration.

Adverse reactions of diclofenac are similar to that of other NSAIDs. At the sites of injection, diclofenac may cause pain and tissue damage occasionally. Transient burning and stinging may occur with diclofenac eye-drop instillation.

Intravenous diclofenac is contraindicated in bronchial asthma and hemorrhage. Patients who wear contact lens should not use diclofenac eye-drop preparation.

PIROXICAM
Piroxicam is a long-acting oxicam NSAID used in joint and myoskeletal disorders. It permits single dosing in a day. Piroxicam is useful in osteoarthritis, acute gout, ankylosing spondylitis, rheumatoid arthritis and also for local treatment of various inflammatory pain. Piroxicam is a prostaglandin synthesis inhibitor. There is an evidence to believe that piroxicam also acts by inhibiting superoxide generation and minimizes tissue damage.

Piroxicam is administered by oral, rectal, intramuscular and local application. Piroxicam is well absorbed by gastrointestinal tract and it has a plasma half-life of average 57 hours (42-76 hours). Piroxicam appears in milk.

Apparently, piroxicam has acceptable gastrointestinal tolerability. Adverse effects produced by piroxicam are similar to that of other NSAIDs.

PARACETAMOL
Paracetamol is an analgesic and antipyretic over-the-counter drug. Paracetamol is not an anti-inflammatory drug. It is a household analgesic and fever reducing agent. For patients who cannot take aspirin and children with high risk of Reye’s syndrome, paracetamol is a preferred analgesic and antipyretic.

Mechanism of Action
Paracetamol is a prostaglandin synthesis inhibitor, yet cannot suppress inflammation because inflammatory lesions are rich in peroxides. In presence of peroxides, paracetamol fails to inhibit the synthesis of prostaglandins. Therefore, paracetamol is not used as analgesic in inflammatory diseases.

Paracetamol is given by oral route as well as per rectum. Oral absorption is rapid and complete. Paracetamol crosses placental barrier and presents in breast milk. At normal therapeutic doses, plasma protein binding of paracetamol is negligible. The plasma half-life of paracetamol is 1.2 to 3 hours. Paracetamol is metabolized in liver and a liberated metabolite ‘N-acetyl-para-benzoquinone-imine’ (NAPQI) is toxic. N-acetyl-para-benzoquinone-imine accumulates at higher doses to produce disintegration of hepatic parenchyma.

Paracetamol is a choice of analgesic in bronchial, asthmatic and peptic ulcer patients. It is given in the dose of 325-500 mg every 4-6 hours up to a maximum of 3 g/day.
Adverse Effects
Adverse effects of paracetamol are rare and if appear, are usually mild. However, prolonged administration of paracetamol at higher doses can produce methaemoglobinemia and renal toxicity. Mixed analgesic preparation on chronic administration may cause interstitial analgesic nephropathy.

Acute poisoning with paracetamol may occur accidentally or deliberately. Ingestion of 10-15 g of paracetamol causes severe hepatocellular necrosis, renal tubular necrosis with nausea, vomiting, sweating and abdominal pain. Paracetamol metabolite N-acetyl-para-benzoquinone-imine depletes glutathione enzyme system and produces hepatotoxicity. Acidosis, cerebral edema, hypoglycemia, hypotension, hepatic failure, renal failure, coma and death may result.

Prompt treatment for acute paracetamol is necessary to minimize hepato-renal toxicities. **N-acetyl-cysteine** or methionine is employed as antidote for acute paracetamol poisoning. Gastric lavage, administration of activated charcoal and other supportive measures should also be instituted.

Care is necessary to administer paracetamol to patients with hepatic and renal failure. Hepatotoxic drugs may potentiate paracetamol hepatotoxicity. Aspirin and paracetamol can be given together. Propranolol increases paracetamol plasma level by inhibiting the metabolism of paracetamol.

SELECTIVE COX-2 INHIBITORS
Nimesulide, celecoxib, rofecoxib, meloxicam, valdecoxib

Earlier, selective COX-2 inhibitors are believed to be less gastrotoxic and have encouraging safety profile over non-selective conventional NSAIDs. As of today, clinical experience with COX-2 inhibitors did not support this claim. On the other hand, potency and toxicity of selective COX-2 inhibitors are under severe scrutiny. Nimesulide-induced hepatotoxicity in paediatric patient and prothrombotic actions of selective COX-2 anti-inflammatory drugs are the great concern in clinical medicine. Many countries have already restricted the use of nimesulide for paediatric purposes. As things stand today, one cannot be sure whether selective COX-2 inhibitors offer any advantage over non-selective COX-2 anti-inflammatory drugs. Especially the efficacy of selective COX-2 inhibitors on chronic administration is not impressive according to some projected opinions of experts of clinical medicine.

ANTIRHEUMATIC DRUGS
Drugs used in the treatment of rheumatoid arthritis, soft tissue rheumatism, juvenile chronic arthritis and other spondyloarthropathies are grouped into two:
1. Non-steroidal anti-inflammatory drugs
2. Disease-modifying antirheumatic drugs (DMARDs)

Disease-Modifying Antirheumatic Drugs
Hydroxychloroquine, gold salts: Auranofin, sodium aurothiomalate, sulphasalazine, d-penicillamine, cyclophosphamide, azathioprine, methotrexate, cyclosporine.
DMARDs are second line of drugs mainly used to arrest the progression of rheumatoid arthritis. However, the long-term use of DMARDs is limited by their toxicity. Immunosuppressants like methotrexate and cyclophosphamide have been used in rheumatoid arthritis with substantial clinical benefit. The clinical value of DMARDs although debatable, methotrexate can suppress disease activity on once-a-week administration. This dose regimen of methotrexate may be well tolerated by the patient. In brief, rheumatologists now use DMARDs after diagnosis to arrest the deterioration of disease. Nevertheless, it remains unclear that long-term use of DMARDs will reduce disability.

**Properties of DMARDs** (Table 9.1)

<table>
<thead>
<tr>
<th>DMARDs</th>
<th>Indication and route</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold salts (auranofin, sodium aurothiomalate)</td>
<td>Progressive rheumatoid arthritis Oral, I.M</td>
<td>Diarrhoea, stomatitis, skin rash, alopecia, dermatitis, glossitis, vaginitis, tracheitis, photosensitivity, aplastic anaemia</td>
</tr>
<tr>
<td>d-penicillamine</td>
<td>Rheumatoid arthritis</td>
<td>Stomatitis, taste abnormality, fever, pruritus, proteinuria</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Rheumatoid arthritis</td>
<td>Nausea, vomiting, headache, diarrhoea, blurred vision</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>Progressive rheumatoid arthritis, ulcerative colitis</td>
<td>Headache, hemolytic anaemia, hypersensitivity reactions, autoimmune hemolysis</td>
</tr>
</tbody>
</table>

**ANTIGOUT DRUGS**

Gouty arthritis is due to metabolic disorder with hyperuricemia. Acute gouty arthritis is an intensely painful inflammation, which occurs due to deposition of urate crystals in joints and other tissues. Chronic gout is characterized by accumulation of urate crystals in soft tissues like finger joints, ears and leads to urolithiasis (uric acid stone in the kidney). The treatment of gout aims at preventing acute attack and reducing plasma uric acid level so that joints and kidney damage is averted.

Drugs used in gout are:

1. **Antigout and anti-inflammatory agents**: Colchicine, indomethacin, piroxicam, diclofenac
2. **Uricosuric drugs**: Probenecid, benzobromarone, sulfinpyrazone
3. **Uric acid synthesis inhibitor**: Allopurinol

**Colchicine**

Colchicine is a unique antigout drug; in the sense, it produces anti-inflammatory action only in gouty arthritis. It is neither an analgesic nor alters blood uric acid level. Colchicine is an antimitotic agent and acts as a spindle poison. It is known to decrease leukocyte mobility and produces dramatic response in acute gout. Colchicine reduces the synthesis of pain-inducing proinflammatory leukocyte glycoproteins thereby provides relief within 12 hours of administration.

Colchicine is an alkaloid obtained from *Colchicum autumnale* and generally administered by mouth. It is used for the treatment as well as prophylactic for acute gout. It has also been used in amyloidosis and idiopathic thrombocytopenic purpura.
Colchicine is a poorly tolerated drug, hence, indomethacin is now used as drug of choice to treat acute gout. Nausea, hemorrhagic diarrhoea and abdominal pain are the first signs of toxicity of colchicine, which indicate discontinuation of therapy. Colchicine produces cumulative toxicity.

Bone marrow depression, agranulocytosis, peripheral neuritis, myopathy, skin rashes and alopecia are also being observed as adverse effects of colchicine.

**Probenecid**

Probenecid is a uricosuric drug, which is used to reduce the severity of hyperuricemia in chronic gout. It inhibits active renal tubular reabsorption of uric acid. Probenecid enhances uric acid secretion. It has no analgesic and anti-inflammatory actions and, hence, not to be used in acute gout. Probenecid is given along with penicillins to prolong their duration of action.

Probenecid is given by mouth. It may produce sore gums, headache, flushing, dizziness and urinary frequency as its adverse effects. During first few months of probenecid therapy in chronic gout, it may precipitate acute gout. Probenecid is contraindicated in patients with the history of uric acid renal calculi.

**Allopurinol**

Allopurinol is a uric acid synthesis inhibitor used to treat hyperuricemia associated with chronic gout, recurrent uric acid, stone formation and cancer chemotherapy.

Allopurinol is a xanthine oxidase enzyme inhibitor. As a result, it inhibits the conversion of hypoxanthine to xanthine to uric acid. Oxypurinol (alloxanthine), a metabolite of allopurinol, is a non-competitive inhibitor of xanthine oxidase.

Allopurinol is completely absorbed by oral route. Patients should be advised to drink more water. Alkalinization of urine is advocated to prevent xanthine stone formation.

The most common adverse effect of allopurinol is skin rash. Severe hypersensitivity reactions can occur. Fever, chills, leucopenia and arthralgia are seen in severe hypersensitivity reactions which may be fatal. Patients with gout may experience an increase in acute attacks in the initial stages of allopurinol administration.

Allopurinol should not be used in the treatment of acute gout. Allopurinol inhibits the metabolism of 6-mercaptopurine. Co-administration of 6-mercaptopurine with allopurinol is usually recommended at reduced dose in acute lymphoblastic leukemia.
AUTACOIDS

Autacoids are the endogenous substances, widely differing in structure, employed by the body to execute function in health and diseases. An array of substances are referred to as autacoids (Autos: self, koid: remedy) namely histamine, 5-hydroxytryptamine (5-HT), prostaglandins, leukotrienes, kinins and angiotensin. Autacoids mediate different biological functions including inflammatory and immune responses, although their precise role is not yet clearly defined.

Histamine is synthesised and stored in many tissues like intestine, lungs and skin. Mast cell and basophils are rich in histamine content. Many drugs release histamine. Morphine, d-tubocurarine and vancomycin are the potent histamine liberators. Histamine acts on H₁, H₂ and H₃ subtypes of receptors.

H₁ receptors are distributed mainly in smooth muscles of intestine, bronchi and blood vessels. Gastric mucosa, blood vessels and heart are the tissues where H₂ receptors are located, whereas H₃ receptors are found at presynaptic sites in brain and other tissues. It is believed that activation of H₃ receptors result in histamine release. This also results in the inhibition of release of a wide variety of neurotransmitters.

The biological functions of histamine include:
1. Mediation of allergic manifestations
2. Powerful gastric acid secretagogue
3. Promotes the release of other inflammatory autacoids like leukotrienes, prostaglandins and kinins
4. Role in inflammatory process
5. Brain temperature regulation
6. Microcirculation and
7. T and B lymphocyte functions

Intradermal injection of histamine characteristically produces triple response, i.e. (a) red (flush), (b) flare, and (c) wheal formation at the site of injection. This is due to histamine-induced (a) vasodilatation, (b) augmented local axon reflex and (c) increased capillary permeability respectively.

Histamine is used as a diagnostic agent in allergic skin test as well as nerve sensitivity test. Drugs that block selectively H₁ and H₂ receptors have been extensively used in different clinical conditions.
INTRODUCTION

Since histamine is a predominant causative factor in allergic, inflammatory and gastric acid secretory pathological conditions, drugs that counteract histamine actions have potential therapeutic value. Therefore, a host of agents that block histamine receptors render clinical benefit in various clinical conditions. Every now and then more potent and more safer antihistaminic is being added to the list of antiallergic drugs to rationalise the drug therapy.

CLASSIFICATION

Histamine Receptor Blockers

Antihistamines are classified based on their selective receptor-blocking effect into three groups.

1. **H₁ receptor blockers**: Traditionally referred to as antihistamines. Even today the word antihistamine, unless otherwise qualified, refers to this group of drugs.
2. **H₂ receptor blockers**: Mainly used to inhibit acid secretion in the stomach.
3. **H₃ receptor blockers**—thioperamide: Currently there is no therapeutic indication for H₃ receptor blockers. Though some of these are promising as antihistamine and antiarrhythmic agents.

**H₁ Receptor Blockers**

Currently used H₁ receptor blockers mainly comprise two subclasses of agents, which are divided based on their sedative effects:

1. **Sedative antihistamines** (I generation)
   1. Alkylamines (low sedation): Chlorpheniramine, pheniramine, tripolidine
   2. Ethanolamines (most sedative): Diphenhydramine, clemastine, doxylamine, dimenhydrinate
   3. Ethylenediamines (modest sedation): Mepyramine, tripelennamine
   4. Piperazines (low sedation): Cyclizine, chlorcyclizine, meclizine, buclizine, cinnarizine
   5. Phenothiazines (most sedative): Promethazine, methdilazine
   6. Miscellaneous: Hydroxyzine, mebhydroline, phenindamine, cyproheptadine, ketotifen

All the H₁ receptor blockers used therapeutically act by competitive antagonism with histamine. However, H₁ receptor blockers do not inhibit the release of histamine. Further, histamine-induced vasodilatation may not be totally blocked by H₁ receptor blockers alone.
PHARMACODYNAMICS

Traditionally, antihistamines produce two types of actions:

i. that are related to histamine antagonism and
ii. that are not related to antagonism of histamine.

Antiallergic actions produced by H₁ receptor blockers have been well explored in medicine. These drugs reverse the vascular, inflammatory responses in the target tissue. Nevertheless, bronchial asthma is not effectively relieved by antihistamines alone. The reason for this is bronchial asthma is not solely caused by histamine. Hence, administration of antihistamines alone may not be rewarding in airway hyper-responsiveness disorders.

At the therapeutic doses employed, H₁ receptor blockers produce the following actions that are not related to histamine antagonism.

Sedation

Generally, first generation antihistamines produce sedation by central nervous system depression. Newly introduced second-generation drugs like fexofenadine and loratadine do not produce sedation since these agents fail to cross blood-brain barrier. The degrees of sedation produced by first generation antihistamines vary from drug to drug. Hydroxyzine in addition is known to produce antianxiety action.

Diphenhydramine is occasionally used as an adjuvant drug in the management of parkinsonism. The rationale is diphenhydramine produces therapeutically useful central anticholinergic action.

Antiemetic

First generation H₁ receptor blockers depress vomiting centre by their sedative action. Promethazine acts as central anti-muscarinic and antihistaminic agent and effectively blocks the labyrinthish impulses reaching vomiting centre. Therefore, promethazine is used as one of the drugs of choice to prevent motion sickness.

Some H₁ receptor blockers like mepyramine produce local anaesthetic action and a few antihistamines block the α₁ adrenoceptors. Cyproheptadine has a significant anti-5HT action.

PHARMACOKINETICS

Antihistamines are completely absorbed on oral administration. Astemizole takes time to manifest its effect, whereas loratadine acts immediately. Hepatic metabolism is the main pathway of antihistamine biotransformation.

ADVERSE EFFECTS

The adverse drug reactions of antihistamines vary with each drug and individual patient. Sedation produced by antihistamines is often disturbing for motor driving activity and other skilful heavy machinery operative jobs. Dry mouth, palpitation, urinary retention, blurred vision, and teratogenicity are a few of the reported adverse effects of antihistamines—first generation in particular. To avoid sedation, second generation antihistamines may be preferred, especially for truck drivers and those who operate machines skilfully.
THERAPEUTIC USES

1. **Antiallergic uses:** Antihistamines are commonly used drugs in various allergic disorders. However, for severe allergic reactions like anaphylactic shock, adrenaline is a life-saving drug. For the symptomatic relief of hypersensitivity reactions, the antihistamines are widely employed. This includes urticaria, angioedema, pollinosis, conjunctivitis, pruritus, rhinitis, atopic eczematous itching, insect bite, skin rashes and drug-induced allergic reactions.

2. **Pre-anaesthetic medication:** Antianxiety and sedative antihistaminic drugs have been used as pre-medicaments, for example, hydroxyzine and promethazine. The short-term management of insomnia sometimes involves administration of sedative antihistamines.

3. **Vertigo:** Vertigo is a symptom of vestibular disorders characterised by a sensation of rotation of the surroundings and static objects. Vertigo is seen in a variety of disorders—head injury, Ménière’s disease, migraine, epilepsy and infections. Buclizine, diphenhydramine, cyclizine and promethazine are commonly used for vertigo.

4. **Parkinsonism:** An antihistamine with central anticholinergic action is used as add-on drug in the management of Parkinson’s disease—diphenhydramine.

5. **Antiemetic:** Antihistamines remain the agents of choice in vomiting due to motion sickness. Doxylamine may be used in conditions of severe vomiting in pregnancy.
   For allergic cough and allergic rhinitis, antihistamines are incorporated with other drugs like cough suppressants and nasal decongestants, vasoconstrictors respectively. Common cold is a viral infection. Antihistamines may provide symptomatic relief, which may not be rewarding completely.

**Contraindications**

Care is needed to use H₁ receptor blockers in infants, neonates and patients with urinary retention, glaucoma and prostatic hypertrophy.

**Drug Interactions**

1. Astemizole when used with antifungal ketoconazole may produce cardiac arrhythmias.
2. Antihistamines enhance the sedative effects of alcohol, opioid analgesics and benzodiazepines.

**DRUGS USED FOR MOTION SICKNESS**

Travel by air, land or sea may cause disequilibria in labyrinthine function which produces vomiting. Motion sickness cannot be cured and can only be prevented. Drugs used for motion sickness are:

1. Promethazine
2. Dimenhydrinate
3. Buclizine
4. Cyclizine
5. Scopolamine—given either as tablets or transdermal patches
   Promethazine 25 mg is given orally 40-60 min before undertaking journey.
SEROTONERGIC AGONISTS AND ANTAGONISTS

• 5-HYDROXYTRYPTAMINE
• 5-HT AGONISTS
• 5-HT ANTAGONISTS
• DRUGS USED IN MIGRAINE
• KININS

5-HYDROXYTRYPTAMINE (5-HT) (SEROTONIN)

Salient Features

5-Hydroxytryptamine is a naturally occurring indole ethylamine, present in plants, animals and venomous stings. This autacoid is abundantly present in human enterochromafin cells, platelets and raphe nuclei in brain. 5-HT is believed to be a neurotransmitter in certain parts of central nervous system. It is known to have a neurophysiological role in mood, sleep, appetite, temperature regulation, perception of pain, regulation of blood pressure and vomiting. 5-HT is a precursor of melatonin hormone. 5-HT is implicated in the etiology of many diseases, which includes mental depression, anxiety and migraine.

Molecular cloning study has identified numerous 5-HT receptors, suggesting a diverse physiological role to the autacoid (Table 10.1). However, the exact role of 5-HT on various organ systems is ill defined as yet.

Table 10.1: 5-HT—multiple receptors and their subtypes

<table>
<thead>
<tr>
<th>5-HT₁</th>
<th>5-HT₂</th>
<th>5-HT₃</th>
<th>5-HT₄</th>
<th>5-HT₅</th>
<th>5-HT₆/7</th>
</tr>
</thead>
<tbody>
<tr>
<td>As many as 25 subtypes of receptors known</td>
<td>5-HT₁A</td>
<td>5-HT₁B</td>
<td>5-HT₁C</td>
<td>5-HT₁D</td>
<td>5-HT₁E, 5-HT₁F</td>
</tr>
<tr>
<td>CNS and GIT ganglia</td>
<td>Platelet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT₂A</td>
<td>5-HT₂B</td>
<td></td>
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<td></td>
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<tr>
<td>5-HT₂C</td>
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<tr>
<td>uncertain</td>
<td></td>
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<td></td>
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<tr>
<td>5-HT₅A</td>
<td></td>
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<tr>
<td>5-HT₅B</td>
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</table>

5-HT AGONISTS

Therapeutically used 5-HT agonists are sumatriptan, zolmitriptan, buspirone, cisapride, renzapride. Fluoxetine-like drugs are selective serotonin reuptake inhibitors commonly used in the treatment of mental depression.

Sumatriptan is a 5-HT₁D agonist, most effective in the acute attack of migraine. Hence, it used as a drug of choice to relieve an attack of migraine. Sumatriptan produces constriction of intracranial blood vessels. It is administered by mouth, subcutaneously or intravenously and its plasma half-life is 2 hours.

Heaviness in the head, pressure in the head and feeling of warmth are the main transient and dose-related adverse reactions of sumatriptan. Pain, stinging and burning at the site of the injection may be seen. Cardiotoxicity and coronary vasoconstriction have been reported on sumatriptan administration. Therefore, sumatriptan is contraindicated in ischemic heart disease. It should not be used in uncontrolled hypertensive patients and with ergot alkaloids.
Buspirone is a 5-HT$_{1A}$ partial agonist and more selectively used as non-sedative antianxiety agent.

Fluoxetine and others that act like fluoxetine modulate 5-HT neuronal effects by inhibiting selectively, the neuronal reuptake of 5-HT in central nervous system. These drugs are used as antidepressants.

**5-HT ANTAGONISTS**

Therapeutically used 5-HT receptor blockers vary widely in their pharmacological properties. 5-HT receptor antagonists are mainly used as antiemetic, antipruritic and in the prophylaxis of migraine. These include the following:

1. Cyproheptadine
2. Ketanserin
3. Ritanserin
4. Methysergide
5. 5-HT$_3$ receptor antagonists: Ondansetron

Other drugs like risperidone and clozapine used as antipsychotic drugs also block 5-HT receptors, which contribute to their therapeutic effect.

**Cyproheptadine**

Cyproheptadine is an anti-5-HT as well as antihistaminic agent. It blocks 5-HT$_{2A}$ and H$_1$ receptors competitively. Cyproheptadine is also a weak anticholinergic agent. It is an appetite stimulant and, hence, on chronic administration increases body weight. The common indication for cyproheptadine is allergic pruritus. It is believed that cyproheptadine increases growth in children. Drowsiness and weight gain are reported side effects of cyproheptadine therapy.

**Methysergide**

Methysergide is an ergot alkaloid and a congener of lysergic acid diethylamide (LSD). It has both agonistic and antagonistic actions on different subtypes of 5-HT receptors, 5-HT$_{2A}$ and 5-HT$_{2C}$ in particular. Hence, it blocks as well mimics the central actions of 5-HT. Methysergide is a weak vasoconstrictor and oxytocic. This is often used in the prophylaxis of migraine and other vascular headache. To combat diarrhoea in carcinoid syndrome, methysergide is useful.

Confusion, psychosis, hallucination, exacerbation of angina pectoris, inflammatory fibrosis and enhanced release of growth hormone have been observed as methysergide adverse drug reactions.

Methysergide should not be used in valvular heart diseases and pulmonary as well as collagen diseases.

**DRUGS USED IN MIGRAINE**

Migraine is a neurovascular headache which may be unilateral or bilateral with or without aura. Aura is a prodromal symptom that precedes an attack of migraine. Aura may consist
of visual and sensory symptoms. Traditionally, intracranial vasoconstriction is thought to be responsible for migraine aura and extracranial vasodilatation for the headache. Now, it is believed that vascular events occur secondary to neurogenic changes. The liberation of 5-HT, histamine, kinin and neuropeptides and prostaglandins play an etiological role in migraine. Drugs used in migraine attack are aspirin, paracetamol, antihistamines, anti-5-HT drugs, 5-HT1D receptor agonists, vasoconstrictors and dopamine antagonists. If the attack is not relieved by aspirin, alternatively, ergotamine can be used. However, the drug of choice to treat acute attack of migraine is sumatriptan.

There are many drugs used for the prophylaxis of migraine. These agents have a wide range of actions with agonism or antagonism of 5-HT or interfere with platelet aggregation, calcium-blocking activity or beta-adrenergic receptor blockade. Drugs commonly recommended are propranolol, methysergide, flunarizine, clonidine, cyproheptadine and indoramin.

**Prostaglandins**

Prostaglandins are derived from 20-carbon polyunsaturated fatty acid, arachidonic acid, along with thromboxanes and leukotrienes. Prostaglandins are involved in many different physiologic and pathologic functions.

*Synthesis of Prostaglandins*

Many tissues synthesize a wide range of prostaglandins. Platelet mainly generates thromboxanes, whereas endothelial cell primarily synthesize prostacyclin. The pathway of prostaglandin synthesis is shown in Figure 10.1.

The active metabolites of arachidonic acid are collectively known as “eicosanoids”.

*Actions of Eicosanoids*

Prostaglandins are ubiquitously distributed throughout the body. Various prostaglandins produce qualitatively and quantitatively different biological functions. No other autacoids produce diverse functions than do prostaglandins.

Prostaglandins E and I2 produce vasodilatation. PGI2 inhibits platelet aggregation. Leukotrienes C4 and D4 reduce blood pressure.

PGE2 relaxes the bronchial smooth muscle and has a variable effect, whereas LTC4 and LTD4 (formerly known as SRS-A, i.e. slow-reacting substance-A) constrict bronchioles.

PGF2α has oxytocic action on uterine smooth muscles and are known to play a role in male fertility. Prostaglandins are abundantly present in seminal fluid.

LTB4 is a powerful chemotactic factor and generates oxygen radicals. The metabolites of arachidonic acid are potent mediators of inflammation.

PGE2 is said to be an immunosuppressant and prolongs several skin allografts.

On gastrointestinal system, PGE and F analogues promote contraction of longitudinal muscle and relax the circular muscle. These autacoids induce cramps, reflux of bile and diarrhoea.

Virtually, prostaglandins can be synthesized in all tissues in response to various stimuli and produce a wide range of effects. However, each metabolite of arachidonic acid varies
in their effects and potency. The nature of action of prostaglandins will depend on the tissues, concentration and mutual antagonistic actions may be seen with various types of prostaglandins at different sites.

Synthetic analogues of prostaglandins with more specific effect, more stability and longer duration of action have been developed.

1. PGE\textsubscript{1} synthetic analogues:
   a. Alprostadil: A vasodilator and inhibits platelet aggregation and helps to maintain the patency of ductus arteriosus in neonates.
   b. Misoprostol: A cytoprotective agent of gastric mucosa and can be used along with non-steroidal anti-inflammatory drugs to reduce the gastric irritant action.
   c. Gemeprost: This is a uterine stimulant and can soften and dilate the cervix. This is used along with abortifacients, in particular mifepristone.

2. PGE\textsubscript{2} analogue:
   a. Dinoprostone: An uterine stimulant and can be administered to induce labour as well as termination of pregnancy. Excessive doses can cause uterine rupture.

3. PGF analogues:
   a. Dinoprost: This synthetic analogue of PGF\textsubscript{2\alpha} is instilled intra-amniotically for medical termination of pregnancy.
   b. Latanoprost: This is recommended for the topical treatment of glaucoma.
   c. Carboprost: It can be used as abortifacient.

4. PGI\textsubscript{2} analogue:
   a. Epoprostenol: Epoprostenol produces vasodilatation and prevents platelet aggregation. It is indicated in renal dialysis to prevent clot in extracorporeal circulation and peripheral vascular diseases.
Adverse Reaction of Prostaglandins

Headache, diarrhoea, hypotension, dizziness, flushing, nausea, vomiting, tachycardia, apnoea, fever and uterine rupture are the few adverse reactions produced by various types of prostaglandins.

Therapeutic Uses

Various synthetic analogues of prostaglandin are used to inhibit gastric acid secretion, protect the gastric mucosa and also in the induction of labour. Prostaglandins are also used as abortifacients. Glaucoma, impotence and peripheral vascular diseases can be treated with suitable prostaglandins.

Contraindications

Pregnancy.

KININS

Kinins are locally acting autacoids that produce pain, vasodilatation, increase capillary permeability and also promote synthesis of prostaglandins. Kinins are synthesized from kininogen (Fig. 10.2).

![Kininogen Diagram](image)

**Fig. 10.2:** Kininogen

Bradykinin acts on two types of receptor B₁ and B₂ and is known to play a role in renal function, blood pressure regulation and inflammation. Bradykinin augments the release of PGI₂ as well as nitric oxide from endothelium.

Aspirin-like non-steroidal anti-inflammatory drugs antagonise the action of bradykinin.
Antitussives (Cough Suppressants)

Agents that suppress cough are known as ‘antitussives’. Cough is a useful physiological mechanism serving to clear the respiratory passage of foreign material and excess secretion. Therefore, cough should not be suppressed indiscriminately.

Cough may be:

a. Productive
b. Unproductive (dry cough).

Productive cough is useful. Unproductive cough when exhaustive is dangerous, especially patients undergoing eye surgery. The decision to treat cough or not is by no means easy. However, antitussive administration is based on severity, chronicity and cause of cough. Productive cough is usually associated with chronic bronchitis, bronchiectasis and cystic fibrosis. Here in addition to specific measures to control cough, expectorants and mucolytics are indicated. Cough may be the only or first symptom in bronchial asthma or allergy. In such cases, appropriate drugs are to be used. It is well recognised that there is substantial voluntary control of cough and where possible this needs to be strengthened.
Classification of Cough Suppressants

Antitussives are classified based on their site of action.

1. Central cough suppressants
   - **Opioid antitussives:**
     - Codeine, pholcodeine, oxycodone, methadone, ethylmorphine, noscapine
   - **Non-opioid cough suppressants**
     - Dextromethorphan, carbetapentine, caramiphen, glaucine, sedative antihistaminics (H₁ blockers)

2. Peripheral cough suppressants
   - Local anesthetics
     - Benzonatate (acts by central actions also)
     - Dornase-alpha
     - Terpin hydrate
   - As add-on drugs, mucolytics have been used with cough suppressants.

Mechanism of Action

Antitussives act by several mechanisms, which include the following:
1. Suppress the cough centre
2. Increase the threshold of the peripheral reflexogenous zones
3. Interrrupt the tussal impulses in the afferent limb of the reflex
4. Increase mucokinetics: Enhance the mucociliary movement of the respiratory mucus and facilitates bronchial drainage to remove the offending material.
5. Inhibit conduction along the motor pathways.

An antihistaminic antitussive acts as antiallergic, sedative and suppressant of cough centre.

**Codeine as Antitussive**

Linctus codeine is a cough suppressant widely used. Codeine is an opium alkaloid, analgesic, antitussive agent. Codeine is a central cough suppressant and it is incorporated into various analgesic antitussive mixtures, liquids and other formulations. Respiratory depression, constipation and interference with mucociliary movement are the main drawbacks of codeine.

The major concern of continued use of codeine is drug dependence. Addiction liability with codeine is substantial. Hence, codeine should be given for short time.

*Dose:* 15-45 mg/day.

**Dextromethorphan**

Dextromethorphan is a non-analgesic, non-addictive, non-respiratory depressant central, long acting, antitussive. This is a d-isomer of levorphenol but does not act on opioid receptor. Unlike codeine, dextromethorphan does not inhibit ciliary movement in the respiratory mucosa.

*Dose:* 15-30 mg 3-4 times a day. Gastrointestinal side effects are few and infrequent at the recommended dosage level.
Noscapine
Noscapine is a natural antitussive, an opium alkaloid. It is a non-analgesic, non-sedative, mild bronchodilator, respiratory stimulant antitussive.

Dose: 15-30 mg 4 times a day.

Benzonatate
Benzonatate is chemically related to procaine. This cough suppressant acts by both central and peripheral effects. Benzonatate is known to suppress the stretch receptors of the lungs. Many cough mixtures incorporate benzonatate as one of the ingredients.

Expectorants
As the name suggests, expectorants help in the removal of excess secretion present in the airway. Various substances including some plant products have been used as expectorants. The commonly used expectorants are:

1. Vascine
2. Vascicine
3. Syrup of ipecac
4. Iodides
5. Guaiphenesin
6. Squill
7. Creosote
8. Volatile oil
9. Tincture of benzoate
10. Acetates and bicarbonates
11. Terpin hydrate
12. Glycerol guaicolate

Expectorants are widely used in the adjuvant therapy of both allergic and non-allergic cough with other cough suppressants and antiallergic drugs. More commonly, syrup of ipecac is used as both expectorant and emetic.

Mucolytics
Mucolytics decrease the viscosity of mucus probably by splitting the disulphide bonds in mucus proteins. Glandular lysosomal enzymes are liberated by the administration of mucolytics. Thus, liberated lysosomal enzymes split the mucopolysaccharides of mucosal secretion. Generally, mucolytics are used with other drugs. However, mucolytic monodrug therapy can also be used without any reservations. The widely used mucolytics are:

1. Bromhexine
2. Acetylcysteine
3. Carbocysteine
4. Methylcysteine
5. Stepronin
6. Dornase-alpha
Bromhexine

Bromhexine is an orally effective mucokinetic agent, obtained from adathodic acid derived from the plant *Adhathoda vasica*. The mucolytic action of bromhexine is due to the depolymerization of mucosal proteins. In turn, bromhexine reduces the viscosity of mucus. Bromhexine is either indicated alone or with expectorants and other cough suppressants.

Acetylcysteine

Acetylcysteine is a mucolytic and used as an antidote for acute paracetamol poisoning too. This drug splits the disulfide bonds of mucus proteins. Acetylcysteine is to be given with a bronchodilator since it is known to cause bronchospasm. Hemoptyisis, rashes, pruritus and angioedema are the fewer frequent side effects produced by acetylcysteine.

Hyperbaric Oxygen

High-pressure oxygen is therapeutically indicated in many clinical conditions. Decompression sickness, diving accidents and gas emboli are often treated by 1 atmosphere hyperbaric oxygen. Furthermore, in carbon monoxide poisoning 2 atmospheres oxygen is used for the rapid conversion of carboxyhemoglobin to oxyhemoglobin. In addition, for anaerobic infections, peripheral arterial insufficiency, radiation necrosis, crush injuries and compromised skin grafts hyperbaric oxygen is found to be useful.

DRUGS FOR BRONCHIAL ASTHMA

Bronchial asthma is defined as a chronic inflammatory disorder with airway hyper-responsiveness, involving episodes of wheeze or breathlessness. A genetic predisposition of bronchial asthma has been recognised. The presence of cough may be the only symptom at the early stages of bronchial inflammation. Mucosal edema, hypoxia, hypercapnoea, hypertrophy of the basement membrane and mucosal glands have been associated with bronchoconstriction in asthmatic patients.

Bronchi remain hyperreactive to various stimuli like physical irritant—atmospheric dust, infection, exercise and psychological impact—stress. A host of endogenous substances play a significant role in the pathophysiology of bronchial asthma. Histamine, bradykinin, leukotrienes and platelet-activating factors are the major intermediate mediators of bronchial asthma. Hence, the drugs therapy is aimed at alleviating the actions of various asthma inducing endogenous mediators.

Clinically, bronchial asthma has been described as extrinsic or intrinsic and associated with chronic obstructive pulmonary diseases. Extrinsic bronchial asthma is also known as “allergic asthma” generally caused by pollen, dust, mite, weather, stress and drugs. Exercise can also induce bronchial asthma. Intrinsic bronchial asthma is caused by a wide variety of immunological mechanisms, which are not yet elucidated beyond comprehension. Currently, there is no curative treatment for intrinsic bronchial asthma. However, modern medicine offers an effective symptomatic relief to asthmatic patients without jeopardising their lifestyle.

The therapeutic strategy for the management of bronchial asthma aims at restricting the bronchial response by inducing dilatation of bronchi. Further, it also emphasizes that antigen
exposure should be avoided. Here, correction of hypoxemia and reduction of likelihood of airway obstruction resumes more clinical importance.

**Classification of Drugs used in Bronchial Asthma**

Drugs indicated in bronchial asthma include the following groups:

1. **Sympathomimetic bronchodilators:**
   - A. **Selective β₂ receptor agonists:** Salbutamol, terbutaline, salmeterol, fenoterol, pirbuterol, bitolterol
   - B. **Other adrenergic drugs:** Adrenaline, isoprenaline (not preferred nowadays)

2. **Methylyxanthines:** Aminophylline, theophylline

3. **Antimuscarinic bronchodilators:** Ipratropium, oxitropium, tiotropium

4. **Corticosteroids:** Subdivided into two groups based on route of administration:
   - A. **Inhalational corticosteroids:** Beclomethasone, budesonide, fluticasone, flunisolide, triamcinolone
   - B. **Oral and parenteral corticosteroids:** Prednisolone, dexamethasone, betamethasone, hydrocortisone, triamcinolone

5. **Drugs for prophylaxis of asthma:** Cromolyn sodium (disodium cromoglycate), nedocromil, ketotifen

6. **Newer drugs:**
   - A. **Leukotriene synthesis inhibitor:** Zileuton
   - B. **Leukotriene receptor antagonists:** Montelukast, zafirlukast
   - C. **Platelet-activating factor antagonists:** Apafant, ginkgolides

7. **Miscellaneous:** Methotreaxate, cyclosporine, gold, magnesium, mucolytics, expectorants, H₁ receptor blockers, oxygen and antibiotics.

**Selective β₂ Agonists**

Commonly, salbutamol, terbutaline or salmeterol have been used as bronchodilators in bronchial asthma. These act by the following mechanisms:

1. Preferentially stimulate bronchial β₂ receptors and increase cAMP concentration, which relaxes the bronchial smooth muscle.
2. Inhibit leukotriene release
3. Inhibit phospholipase A₂ enzyme
4. Enhance mucociliary function
5. Reduce microvascular permeability

**Routes of Administration**

Selective β₂ agonists are administered in bronchial asthma by inhalation, nebulisation, oral and parenteral routes. Metered dose inhalers are convenient dosage forms to achieve local action without pronounced systemic side effects. However, repeated inhalation of these drugs can cause cardiovascular adverse effects readily. The device and technique of inhalation of β₂ agonists is cumbersome, especially for young asthmatic patients.
Adverse Effects
Skeletal muscle tremor, tachycardia, reduced $P_{O_2}$, muscle cramps and hyperkalemia have been commonly observed. Hyperglycemia as well as pulmonary edema may also be seen with $\beta_2$ agonists.

Therapeutic Uses
1. Acute as well as chronic bronchial asthma
2. Acute severe bronchial asthma (status asthmaticus)
3. As uterine relaxant to arrest premature labour.

Contraindications
Caution is necessary for the administration of $\beta_2$ agonists in hyperthyroidism, acute myocardial infarction and cardiac arrhythmias.

Methylxanthines
Methylxanthines are the derivatives of xanthine alkaloid caffeine. Aminophylline and theophylline have an important role in the management of bronchial asthma, especially as valuable adjuncts in prolonged attack of asthma.

Mechanism of Action
Methylxanthines are direct bronchodilators. These act by several ways, which include:
1. Inhibit phosphodiesterase enzyme and increase the cAMP concentration which dilates bronchi
2. Increase diaphragmatic contractions
3. Antagonise bronchial adenosine receptors
4. Cause translocation of calcium to promote dilatation.
Aminophylline can be administered by all routes except by intramuscular route. The pharmacokinetics of methylxanthines is influenced by concurrent medication, diet, disease states, smoking and age of the patient. Therefore, it is essential to monitor plasma concentration of theophylline to avoid toxicity.

Therapeutic Uses
Methylxanthines are used in the management of bronchial asthma, chronic obstructive pulmonary diseases and neonatal apnoea.

Adverse Effects
Gastrointestinal side effects include mucosal irritation. Metabolic acidosis, central nervous system stimulation, convulsions and depression also have been reported. Intravenous aminophylline can cause cardiac arrhythmia and hypotension. Hence, aminophylline must be given as slow infusion. Sudden deaths have been reported after rapid intravenous administration of aminophylline.
**Drug Interactions**

1. Macrolide antibiotics like erythromycin decrease clearance of theophylline. To avoid toxicity, dose needs to be reduced. This interaction may not be seen with newer macrolides.
2. Combination of theophylline and imipenem may show increased incidences of seizures.

**Antimuscarinics**

Drugs that block muscarinic receptors and induce bronchodilatation are used in bronchial asthma along with other drugs. Currently, these are given as add-on drugs and invariably administered by inhalation. Some of the examples are ipratropium, oxitropium and tiotropium. These are the atropine analogs given by inhalation for asthma and in selected cases of chronic obstructive pulmonary diseases.

**Corticosteroids**

Hydrocortisone and various synthetic glucocorticoids have been indicated for the management of bronchial asthma. It is common to use corticosteroids as reserve drugs for bronchial asthma. Corticosteroids are given in asthma by inhalation, oral and parenteral routes particularly by intravenous route in severe bronchial asthma. These include:

A. *Inhalational corticosteroids:* Beclomethasone, budesonide, fluticasone, flunisolide, triamcinolone

B. *Oral corticosteroids:* Prednisolone, prednisone, betamethasone, dexamethasone, triamcinolone

C. *Intravenous corticosteroids:* Hydrocortisone hemisuccinate, dexamethasone

**Mechanism of Action**

Corticosteroids relieve bronchial asthma by several mechanisms. However, main mechanisms include suppression of inflammation. These drugs act by:

1. Anti-inflammatory effects
2. Immunosuppressant action
3. Promote action of catecholamines
4. Reverse the resistance developed on prolonged exposure to $\beta_2$ stimulants.

**Adverse Effects**

Inhalation of corticosteroids may cause oropharyngeal candidiasis due to local immunosuppressant effects. Hence, patients using inhalational steroids must be advised to rinse oral cavity with water three times after each inhalation of the corticosteroid.

Oral corticosteroids should not be withdrawn abruptly. It is advised to taper the dose gradually and withdraw. This will avoid steroid withdrawal syndrome as well as exacerbation of bronchial asthma. Oral corticosteroid therapy is to be instituted for short term only to overcome steroid-dependent state in patients. Steroid-dependent asthma demands corticosteroid therapy for undue length of time, which is likely to bring many more clinical complications. Therefore, corticosteroids are given in asthma only when required and withdrawn at the earliest time possible. A short rescue course is preferred at the hour of need.
Drugs Used for Prophylaxis of Bronchial Asthma

In chronic bronchial asthma, every effort must be undertaken to prevent the onset of asthmatic episodes. This may be achieved by many means—avoiding asthma precipitating factors like dust exposure, smoking, pollens and intake of drugs. Drugs that are mainly used for the prophylaxis of bronchial asthma are:

1. Cromolyn sodium
2. Nedocromil

All these drugs are commonly referred to as ‘mast cell stabilisers’ although ketotifen does possess antihistaminic action.

Mechanism of Action

Cromolyn sodium-like drugs by definition act like antiallergic drugs in the following ways:
1. Stabilise the mast cell membrane
2. Inhibit the release of inflammatory mediators
3. Inhibit intracellular Ca^{2+} movement
4. Antagonise substance-P
5. Act directly on airway neuronal regulatory mechanisms.

Hence, mast cell stabilisers should not be given during an attack of asthma. More importantly, the beneficial effect of cromolyn sodium may be manifested after 3-4 weeks of continuous administration.

Cromolyn sodium is always administered by inhalation. Ketotifen is available in oral form, especially suitable for school-going asthmatic children.

Therapeutic Uses

1. Bronchial asthma
2. Chronic allergic conjunctivitis
3. Food allergy
4. Chronic allergic rhinitis: Seasonal and perennial
5. Mastocytosis.

Adverse Effects

Inhalation of cromolyn sodium during attack may worsen the condition. Cough, joint pain and unpleasant taste have also been reported.

Ketotifen produces drowsiness, dry mouth, dizziness, increased appetite and weight gain, especially in pediatric patients.

Inhalation corticosteroids, antimuscarinic agents and selective β_{2} agonists have been used to prevent attacks of bronchial asthma.

Newer Antiasthmatic Drugs

This list of new antiasthmatics is ever expanding. Nevertheless, the following agents have been already in use:

1. Leukotriene synthesis inhibitors: Zileuton
2. Leukotriene receptor antagonists: Zafirlukast, montelukast
Drugs Acting on Respiratory System

Drugs for Acute Bronchial Asthma
Generally, acute bronchial asthma is managed well with inhalational $\beta_2$ selective bronchodilators. Salbutamol (100 $\mu$g/puff) or salmeterol (25 $\mu$g/puff) may be used.

Status Asthmaticus
This is a state of medical emergency. Prompt, effective, safer drug therapy must be given without delay. The measures to control status asthmaticus are as follows:

a. Salbutamol nebulization
b. Intravenous hydrocortisone hemisuccinate
c. Intravenous aminophylline as infusion
d. Oxygen supplementation
e. Antibiotic therapy for controlling infection
f. Intravenous fluid therapy
g. Ipratropium inhalation if required.

Exercise and Antiasthmatic Drugs
It is believed traditionally in India that by doing yogic exercises, one can control the severity of bronchial asthma. It is also possible that yoga can prevent the onset of asthmatic attack and improves the lifestyle of the asthmatic patient. It is pertinent to say that these observations do not apply to all. As contrast to this, exercise may induce asthma. Stress of any kind is one of the risk factors that can aggravate asthma. Exercise-induced asthma is not difficult to address with drugs. Prophylactic administration of mast cell stabilisers would suffice the need. Nevertheless, inhalation of selective $\beta_2$ agonists may be used. However, an exercise programme of asthmatic patients needs to be kept at optimum level to avoid overexertion.
Drugs Acting on Gastrointestinal System

• DIGESTANTS
• EMETICS
• ANTIEMETICS
  • CLASSIFICATION
  • PROKINETIC AGENTS
  • 5-HT, RECEPTOR ANTAGONISTS
  • NEUROLEPTIC ANTIEMETICS
  • H1 RECEPTOR BLOCKERS AS ANTIEMETICS
  • DRUGS USED IN MOTION SICKNESS
  • DRUGS FOR EMESIS INDUCED BY ANTICANCER DRUGS AND RADIATION
  • DRUGS FOR VOMITING IN PREGNANCY
  • ANTIEMETICS FOR POSTOPERATIVE VOMITING

DIGESTANTS
Drugs that promote the process of digestion in the gut are known as digestants. The examples include hydrochloric acid, pepsin, pancreatic enzymes and bile salts.

Carminatives
Carminatives are the agents that expel the gas collected in the alimentary tract either as belching or flatus. These provide relief from abdominal discomfort and stimulate appetite. Various carminatives act by virtue of their mild irritant action on gastric mucosa and by causing relaxation of gastric sphincter.

A wide variety of substances are used as carminatives.
• Compound tincture of cardamom
• Tincture of ginger
• Camphor
• Coriander
• Peppermint oil
• Cloves, nutmeg, fennel
• Carbon dioxide
Appetizers
Any agent that stimulates appetite is used to restore the impaired food intake in many clinical conditions. It is common to use bitters like quinine, tincture of orange and lemon as appetizers. Ethyl alcohol beverages also act as appetizers. However, the danger of addiction caused by alcohol intake precludes its use as appetizer.

Cyproheptadine is an antihistaminic and antiserotonin agent and is employed as appetite stimulant.

Antiflatulents
As the name suggests, antiflatulents relieve the symptoms of excess gas collection in the alimentary tract, for example, simethicone. Simethicone by defoaming action relieves flatulence and is commonly given along with antacids.

Anorexiants (anorectics, appetite suppressants, drugs used for obesity)
A wide variety of drugs are used to suppress appetite, especially when obesity is due to excessive food intake. Anorexiants act on central nervous system to stimulate the ‘satiety center’, which reduces the food intake. Fenfluramine, dexfenfluramine, dexamphetamine and phenmetrazine have become obsolete as anorexiants. Bulk-forming agents like methylcellulose have been used as adjunct drugs to reduce obesity.

Recently, a gastric lipase inhibitor—orlistat and a 5-HT and norepinephrine reuptake inhibitor—sibutramine, have been recommended for obesity. Initially, these drugs can be given for 12 weeks. If the weight reduction after 3 months of therapy is less than 5%, drug therapy must be discontinued.

Drugs for Obesity
The management of obesity does not rely on drug therapy. Dietary modification, behavioral modification and regular exercise programmes are the important modalities of obesity treatment. Drugs are only used as adjuncts.

EMETICS
Emetics are the drugs that induce vomiting. These include:
A. Local emetics: Act by gastric mucosal irritation.
   Copper sulfate, hypertonic saline, syrup of ipecac.
B. Central emetics: Stimulate vomiting center/chemoreceptor trigger zone in brain.
   Apomorphine
C. Others: Estrogen, digoxin, nitrogen mustards.

Apomorphine and syrup of ipecac are commonly used emetics in various drug poisoning conditions to remove the unabsorbed poison from the gut. Ipecac is preferred in young children. Local emetics when administered at subemetic doses can act as expectorants. Syrup of ipecac is chiefly used for this purpose.
ANTIEMETICS

Antiemetics are usually administered to produce relief from nausea and vomiting. Vomiting is a protective function that removes unsuitable materials from the stomach. Different types of stimuli induce vomiting—distention of visera, unequal stimulation of labyrinth, tactile pharyngeal stimulation, increased intracranial pressure, pain and psychogenic factors which involve sight, memory and smell. Since vomiting is a protective function, it should not be suppressed indiscriminately.

The stimulation of vomiting center is by four inputs:

- Afferent vagal rich in 5-HT\(_3\) receptors
- Vestibular system—muscarinic cholinergic receptors and with high concentration of histamine
- Higher centers—psychogenic
- Chemoreceptor trigger zone (CTZ) located outside the blood-brain barrier (BBB) rich in 5-HT\(_3\) and dopaminergic (D\(_2\)) receptors.

Besides gastric irritation, peripheral irritation, food poisoning, hepatic and pancreatic diseases can cause vomiting. Emesis is also observed with radiation therapy, anticancer drug therapy, cardiac diseases—acute myocardial infarction, Ménière’s disease, vertigo, migraine and uncontrolled diabetes mellitus.

Classification

The classification of antiemetics is based on their mode of action:
1. **Prokinetic agents**: Metoclopramide, domperidone, cisapride, renzapride
2. **5-HT\(_3\) receptor antagonists**: Ondansetron, tropisetron, granisetron
3. **H\(_1\) receptor blockers**: Promethazine, buclizine, cyclizine, doxylamine, diphenhydramine, dimenhydrinate, cinnarizine
4. **Anticholinergics**: Scopolamine
5. **Neuroleptic antidopaminergics**: Chlorpromazine, haloperidol, prochlorperazine
6. **Miscellaneous**: Lorazepam, pyridoxine, glucocorticoids, benzaquinamide

**Prokinetic Agents**

Drugs that augment esophageal and gastric motility and hence tend to speed gastric emptying are called **prokinetic agents**. The action of prokinetic agents on gastrointestinal tract depends on the preexisting tone of the gut. These drugs tend to increase the tone of lower esophageal sphincter and are useful as antiemetics.

**Metoclopramide**

It is a prokinetic, antiemetic agent. It is an antidopaminergic agent and is believed to block 5-HT\(_3\) receptors as well. Metoclopramide relaxes the pyloric sphincter thereby enhancing the gastric emptying besides increasing the tone of lower esophageal sphincter. By virtue of antidopaminergic action in central nervous system, metoclopramide increases prolactin release. Metoclopramide is given by mouth in a dose of 10-30 mg/d preferably before meals.
Metoclopramide has been used in many clinical conditions, which include:

- Prevention of nausea and vomiting of cancer chemotherapy
- Postoperative vomiting
- Gastroesophageal reflux disease
- Acute or chronic gastroparesis

Metoclopramide can produce sedation, diarrhoea, muscle spasm, confusion, hyperprolactinemia and menstrual disorders as adverse effects. On long-term use, parkinsonian symptoms and tardive dyskinesia may be seen with metoclopramide therapy, especially in elders.

Metoclopramide may not be preferred as antiemetic in motion sickness as the other drugs are safer and effective. This drug can be combined with other antiemetics for the management of cancer chemotherapy-induced vomiting. However, metoclopramide should not be combined with neuroleptics as it causes parkinsonism.

**Cisapride**

Cisapride is a commonly used, potent prokinetic agent. It acts by promoting the release of acetylcholine from the myenteric plexus. There are evidences to believe that cisapride is a 5-HT4 receptor agonist. It can be used in place of metoclopramide in gastroparesis. The advantage of cisapride is that it does not cross blood-brain barrier and is devoid of any central adverse effects. Further, unlike other prokinetics, cisapride can improve motility in chronic functional constipation.

**Domperidone**

This is primarily a peripheral dopmaine antagonist with prokinetic action and, hence, used in gastroesophageal reflux disease. Domperidone cannot cross blood-brain barrier. Hence, it is comparatively free from sedation and dystonic reactions unlike metoclopramide. Domperidone is preferred as antiemetic in patients with parkinsonism who are on dopaminergic drug treatment where metoclopramide is contraindicated.

Hyperprolactinemia, galactorrhoea, and gynecomastia are the few adverse effects seen with domperidone.

**5-HT3 Receptor Antagonists**

The stimulation of chemoreceptor trigger zone (CTZ) and gastrointestinal 5-HT3 receptors causes emesis. Therefore, drugs, which selectively block 5-HT3 receptors, are used as antiemetics in many clinical conditions. 5-HT3 receptor antagonists are the agents of choice for the management of cytotoxic drug-induced vomiting, especially due to cisplatin therapy.

**Ondansetron**

It is a 5-HT3 receptor antagonist antiemetic. This is the drug of choice to manage cisplatin-induced vomiting. It is generally administered by intravenous and oral routes. Its plasma half-life is 3-5 hours, undergoes extensive first pass metabolism. Adverse reactions to ondansetron are rare. However, headache and constipation are commonly observed with ondansetron.
Dronabinol

It is used in the treatment of anticancer drug induced-vomiting not responding to other drugs. Dronabinol is the principal psychoactive agent obtained from Cannabis sativa (Marijuana). It is an appetite stimulant. Combination antiemetic therapy with dronabinol and a neuroleptic antiemetic, for example, prochlorperazine, may result in synergistic therapeutic effect.

Euphoria, sedation, fatigue, confusion and palpitation are the few adverse effects of dronabinol. It is highly addictive; therefore, use of this drug must be restricted to the extent necessary.

Scopolamine

It is an anticholinergic antiemetic. It acts by decreasing the excitability of labyrinthine receptors and reducing the conduction of vestibular-cerebellar pathways. Scopolamine can be given orally or transdermal patches be used. Scopolamine is used as antiemetic in motion sickness. The transdermal patch has to be applied 6-8 hours before starting the journey. It is applied behind the pinna of external ear. Oral administration of scopolamine may induce amnesia, fatigue and rarely toxic psychosis.

Neuroleptic Antiemetics

The neuroleptic antiemetics are widely used in combating drug-induced vomiting, especially to counteract apomorphine-induced emesis. Chlorpromazine, perphenazine, triflupromazine, prochlorperazine and haloperidol are commonly used neuroleptic antiemetics. These drugs act by antagonising dopamine receptors in chemoreceptor trigger zone (CTZ).

Neuroleptic antiemetics and metoclopramide should not be used concomitantly, especially in elderly patients. The reason being: aggravation of extrapyramidal syndrome, therefore, this combination is to be avoided in geriatric patients.

H₁ Receptor Blockers as Antiemetics

Sedative H₁ receptor blockers have therapeutically useful antiemetic effects in motion sickness and vomiting caused by local emetics. Promethazine, doxylamine, cyclizine, diphenhydramine, dimenhydrinate, buclizine, cinnarizine and hydroxyzine are a few examples.

Evidently, promethazine-like drugs possess central antimuscarinic actions, which play a role in their antiemetic effects. These drugs are most effective if given before the onset of nausea and vomiting.

Drugs Used in Motion Sickness

Promethazine is the drug of choice for motion sickness. It is given in a dose of 25-75 mg orally at least 30 minutes before undertaking the journey. Sedation and dryness of mouth are the observed side effects with promethazine.

However, any H₁ receptor blocker can be used as antiemetic for the prevention of motion sickness. Scopolamine is rather preferred for sea-sickness. There is no hard and fast rule to use any particular drug for motion sickness.
Drugs for Emesis Induced by Anticancer Drugs and Radiation

A vast majority of anticancer drugs induce vomiting which demands prompt, effective antiemetic drug therapy.

Generally, a combination of metoclopramide, ondansetron and lorazepam with/without dexamethasone is often needed. However, there are no specific guidelines to select any particular antiemetic for this purpose. It is desirable to institute multiple antiemetic drug therapy as the vast clinical experience suggests this to attain relief.

Drugs for Vomiting in Pregnancy

In the initial stages, vomiting due to pregnancy need not be treated with drugs. Simple measures like avoiding repulsive foods, smell, switching over to frequent liquid meals would suffice. If the drug therapy is needed, an antiemetic, which is devoid of teratogenic effects, must be selected. Till today, no antiemetic drug is reported to be free from teratogenicity. There is no consensus as yet, about the selection of antiemetic drug for pregnant women. However, pyridoxine, doxylamine or any suitable H₁ receptor blockers have been indicated.

Antiemetics for Postoperative Vomiting

Vomiting is a common observation during postoperative period. An opioid analgesic used as preanaesthetic agent might cause vomiting. Besides, emesis may be seen as one of the postanesthetic complications. Modern anaesthetic techniques have minimized the extent of postoperative vomiting. Yet, antiemetic drug is very much needed.

It is common to employ a least toxic, safer antiemetic drug after surgery. Metoclopramide, prochlorperazine, chlorpromazine, domperidone or any 5-HT₃ antagonists like ondansetron may be given. Metoclopramide is to be avoided in elderly patients.
INTRODUCTION

The term acid peptic disease means that ulcer lesions found in the areas of alimentary tract exposed to acid and pepsin. This includes gastric and duodenal ulcers with the disorders of gastroesophageal reflux. The prevalence rate of this disease is 3-5% and occurs more often in male than female.

PATHOPHYSIOLOGY

The etiology of acid peptic disease is incompletely understood. In 80% of patients, colonization of *Helicobacter pylori* is implicated in the pathogenesis of peptic ulcer. Importantly, it is the imbalance between aggressive luminal factors—acid pepsin and defensive mucosal factors—mucus, bicarbonate and blood flow to the mucosa is the causative mechanism of peptic ulcer. Decreased mucosal resistance, hypersecretion of acid, bile reflux, gastritis, inflammatory changes, mental as well as physical stress, smoking, irritant drugs (NSAIDs), alcohol, genetic factors and environmental influence in part contribute to ulcer etiology. Thus, the etiology of peptic ulcer is probably multifactorial.

Goals of Antiulcer Therapy

The immediate goals of acid peptic disease management are to reduce clinical symptoms, to hasten healing and to prevent serious complications—hemorrhage, perforation and obstruction. In addition, dietary measures, avoidance of alcohol intake, irritant drugs, steroids and smoking is necessary. Furthermore, control of emotional factors like anxiety and stress is warranted.

CLASSIFICATION OF DRUGS USED IN ACID PEPTIC DISEASE

The advent of drug therapy in acid peptic disease has phenomenally reduced the surgery and the success rate is impressive. Drugs used in peptic ulcer act by virtue of promoting healing, reducing acidity and enhance defensive mechanisms. Accordingly, these drugs are classified based on their mechanism of action as mentioned below.

1. Antacids:

   - *Systemic antacids*: Sodium bicarbonate—which reaches the circulation and produces systemic alkalosis
- **Non-systemic antacids:**
  - *Aluminium salts:* Aluminium hydroxide, aluminium carbonate, aluminium dihydroxysodium carbonate
  - *Magnesium salts:* Magnesium trisilicate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium phosphate
  - *Calcium salts:* Calcium carbonate

2. **Mucosal protectives:** Sucralfate, colloidal bismuth salts, misoprostol
3. **H₂ receptor blockers:** Ranitidine, famotidine, cimetidine, roxatidine, nizatidine
4. **Proton pump inhibitors:** Omeprazole, lansoprazole, pantoprazole, rabeprazole
5. **Anticholinergics:** Pirenzepine, telenzepine, atropine
6. **Anti-*H. pylori* drugs:** Clarithromycin, amoxicillin, metronidazole, tetracycline
7. **Miscellaneous:** Amitriptyline, diazepam—to relieve mental stress.

### ANTACIDS

Gastric antacids are weak bases that react with hydrochloric acid. The direct acid neutralization by antacids elevates gastric pH. Antacids adsorb H⁺ and pepsin and provide relief from pain. Sometimes, antacids are given in combination with atropine to prolong the gastric emptying time, which increases the total buffering effect of antacids. Methylpolysiloxane—an antiflatulent and anti-hiccup agent is also used with antacids. Antacids should not be used routinely and on long-term basis. The antacid preparation must be free from any gastrointestinal side effects, palatable and should not cause rebound increase in acid secretion.

There is no standard antacids dose in terms of tablet or of syrup and at the same time, take as needed is clearly inadequate. Recommended liquid antacids may be taken 1 to 3 hours after meals and at bedtime. Caution must be exercised to avoid antacid abuse. Antacids do affect bowel motility and secretions. Alkaluria, nephrolithiasis on chronic use, constipation, diarrhoea, abdominal distention and flatulence are the general adverse effects of various antacids. Carbonate containing antacids produce belching. Transient metabolic alkalosis and hypophosphatemia have been observed with antacid therapy. Chronic antacid use may cause osteodystrophy, proximal myopathy and encephalopathy. Gastric antacids are used in:
- Peptic ulcer
- Hyperchlorhydria
- Reflux esophagitis—heartburn
- Zollinger-Ellison syndrome

### Drug Interactions with Antacids

Antacids are known to interact with many drugs. These agents alter the rate of absorption, bioavailability and in some cases renal elimination of concomitanoty used drugs. Antacids reduce the absorption of tetracyclines, phenothiazines, quinolones, digoxin, isoniazid, prednisone, ranitidine and fat-soluble vitamins. This interaction can be minimised by administering antacids and other drugs 2-3 hours apart. Calcium antacids when given with thiazide diuretics may cause hypercalcemia. Sucralfate should not be given along with antacids.
Aluminium Salts as Antacids

The commonly used aluminium salts are—aluminium hydroxide, aluminium phosphate and basic aluminium phosphate. The main adverse effects observed with aluminium salts are constipation, hypophosphatemia and hypercalcemia due to increased bone resorption, which may lead to osteomalacia. The constipation produced by aluminium salts can be avoided by concomitant use of other diarrhoea-causing antacids, namely, magnesium salts to nullify each other’s unwanted effects. In fact, this is one of the bases for combination antacid therapy.

Magnesium Salts as Antacids

Magnesium trisilicate, magnesium oxide, magnesium citrate and magaldrate (aluminium magnesium hydroxide sulfate) are commonly used magnesium salts as antacids.

The general properties of magnesium salts are similar as other antacids. However, magnesium trisilicate reacts slowly with gastric acid and acts for longer time. For this reason, magnesium trisilicate is given with rapidly acting antacid so that buffering period is quite long. When rapid symptomatic relief is desired, magnesium trisilicate is not the agent of choice from antacid group. Magnesium salts produce laxative effect, which can be countered by giving aluminium salts together.

H₂ RECEPTOR BLOCKERS

Histamine is a powerful acid secretagogue. It stimulates gastric acid secretion by stimulating H₂ receptors present in parietal cells of gastric mucosa. Drugs, which block H₂ receptors, are useful in the treatment of peptic ulcer and other conditions of hyperacidity. H₂ receptor blockers inhibit both basal and nocturnal acid secretion. Administration of H₂ receptor blockers in peptic ulcer not only provides pain relief, but also promotes ulcer healing. Nevertheless, gastric ulcer tends to heal more slowly. Commonly used H₂ receptor blockers are—ranitidine, famotidine, roxatidine and nizatidine. Cimetidine was the first competitive H₂ receptor antagonist to be introduced, now least preferred. The reason being, adverse effects of cimetidine are more readily seen and this drug inhibits cytochrome family of enzymes leading to multiple drug interactions. Cimetidine is a weak antiandrogenic agent—causes gynecomastia.

Ranitidine is the more potent, less toxic and long-acting H₂ receptor blocker. The dose regimen of ranitidine is comparatively easier than cimetidine. It is given in a dose of 150 mg twice daily for 6-8 weeks in acid peptic disease. However, 300 mg once daily therapy is also used in clinical practice. Unlike cimetidine, ranitidine is neither an inhibitor of cytochrome P450 nor an antiandrogenic drug. It does not cross blood-brain barrier and free from the action of prolactin release.

Nizatidine and famotidine are similar to ranitidine in their pharmacological actions except in dose and duration of treatment. Famotidine is given in a dose of 20 mg twice daily. The dose of famotidine needs to be reduced in renal dysfunction. Nizatidine can be given as 300 mg once daily at night.
Therapeutic Uses of \( \text{H}_2 \) Receptor Blockers

\( \text{H}_2 \) receptor blockers are used in:

- Acid peptic disease
- Reflux esophagitis
- Zollinger-Ellison syndrome
- As preanesthetic medication in emergency surgery
- Stress ulceration
- Short bowel syndrome

\( \text{H}_2 \) receptor blockers can be combined with \( \text{H}_1 \) receptor blockers in the management of chronic urticaria.

Drug Interactions

Cimetidine inhibits cytochrome P450 enzymes in the liver and interferes with the metabolism of phenytoin, theophylline, calcium channel blockers, estrogens and many other drugs that are metabolized by the same enzymes. Cimetidine is known to increase the efficacy of oral pancreatic enzymes.

PROTON PUMP INHIBITORS

It is common to indicate drugs that inhibit \( \text{H}^-\text{K}^-\text{ATPase} \) of the stomach for ulcer resistant to \( \text{H}_2 \) receptor blocker therapy. Proton pump is the ultimate mediator of acid secretion. The presence of \( \text{H}^-\text{K}^-\text{ATPase} \) activity is the unique feature of gastric parietal cells. Proton pump inhibitors, which are widely used in therapeutics, are: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

Following oral administration, these drugs undergo degradation to liberate active metabolites, which irreversibly inhibit the \( \text{H}^-\text{K}^-\text{ATPase} \) enzyme. Proton pump inhibitors produce sustained antisecretory action. Usually, omeprazole is used in peptic ulcer with two anti-\( \text{H. pylori} \) drugs.

Headache, hypergastrinemia, achlorhydria, diarrhoea and skin rash are the adverse drug reactions caused by omeprazole-like drugs.

Omeprazole inhibits cytochrome P450 and interferes with the metabolism of diazepam, warfarin and phenytoin.

MUCOSAL PROTECTIVES

Drugs that enhance mucosal defensive mechanisms by cytoprotective action provide significant benefit in acid peptic diseases. Mucosal protectives commonly used are: sucralfate, colloidal bismuth compounds, prostaglandin analogs—misoprostol and carbenoxolone sodium.

Sucralfate

Sucralfate is a cytoprotective agent used in acid peptic disease. Chemically, sucralfate is a complex of polyaluminium hydroxide and sucrose octasulfate. On oral administration, it reacts with acid to form a viscid whitish yellow sticky gel that coats the ulcer sites. The coating of ulcer sites acts as a protective barrier against acid, bile and pepsin. In addition,
sucralfate stimulates mucus and bicarbonate secretion. Sucralfate is also known to stimulate prostaglandin production. Duodenal ulcer is more readily healed on sucralfate use. Sucralfate is unabsorbed and virtually devoid of side effects except for producing constipation. Within 2 hours of sucralfate administration, other drugs should not be given as this drug hinders their absorption. Sucralfate should not be given with antacids or any other antisecretory drugs either as it leads to reduction in efficacy.

**Bismuth Compounds**

A variety of bismuth compound formulations have been used to treat acid peptic diseases. Bismuth promotes ulcer healing through stimulation of mucosal bicarbonate and prostaglandin generation. These compounds have direct anti-*H. pylori* action. Bismuth salts do have astringent and anti-diarrhoeal actions. Bismuth subsalicylate and tripotassium dicitratobismuthate are the commonly employed and these have excellent safety profiles. However, blackening of feces and tongue is observed. Bismuth compounds should not be administered with tetracycline.

**Tripotassium dicitratobismuthate (Colloidal bismuth subcitrate)** is active against *H. pylori* and used in peptic ulcer in conjunction with metronidazole or with tetracycline or amoxicillin, the regimen known as “triple drug regimen” given for couple of weeks.

Since bismuth salts used in peptic ulcer are insoluble compounds, toxicity does not occur. However, if used for excess period at high doses may cause bismuth poisoning. Darkening or blackening of tongue and feces may occur during treatment.

**Misoprostol**

Misoprostol is a synthetic analog of PGE1. This agent promotes ulcer healing by stimulating mucus and bicarbonate secretion. Misoprostol is a modest acid secretion inhibitor. It is solely used as a prophylactic agent to prevent NSAID-induced ulcers.

Abdominal cramps and diarrhoea are seen as dose-related adverse effects of misoprostol. It should not be given in pregnancy, as it is a potential abortifacient.

Drug therapy of peptic ulcer has drastically reduced the surgical interventions. Invariably, triple drug therapy which constitutes a H2 blocker + proton pump inhibitor + anti-*H. pylori* drug, e.g., metronidazole or clarithromycin or amoxicillin would suffice to cure peptic ulcer. Ulcers that are refractory to medical therapy are now uncommon.

**PURGATIVES**

Purgatives are the drugs that promote defecation and indicated in functional constipation where there is no intestinal obstruction. These are also referred to as laxatives, evacuants, bowel movers, cathartics and aperients.

Purgatives include different groups of drugs, which act by different mechanisms and differ in the onset of action as well. Hence, some purgatives are administered in the night and some in the morning. The prolonged and habitual use of purgatives is unhealthy and must be discouraged. Chronic and indiscriminate use of purgatives may lead to irritable bowel syndrome and loss of normal colonic neuromuscular function.
Purgatives are classified into groups based on their mechanism of action into three main classes.

1. **Bulk purgatives**
   - Hydrogogue purgatives
     - Methylcellulose, psyllium, bran, ispaghula
   - Osmotic purgatives
     - Magnesium sulfate, sodium potassium tartrate, lactulose

2. **Stimulant or contact purgatives**
   - Bisacodyl, phenolphthalein, senna, cascara sagrada, sodium picosulfate

3. **Emollient (fecal softeners) purgatives**
   - Dioctyl sodium succinate (docusate), liquid paraffin, poloxamers

*Others*
- Castor oil, glycerine

Magnesium sulfate, ispaghula and methylcellulose are the commonly used bulk purgatives. Magnesium sulfate exerts its osmotic purgative action in the upper part of the small intestine. Cholecystokinin-stimulated intestinal motility is augmented by magnesium sulfate. Magnesium sulfate exerts its actions within 4 hours hence given as early morning purgative.

**Lactulose** is unabsorbed on oral administration and resistant to digestion. Lactulose undergoes metabolism by bacterial enzymes to liberate osmotically active components, which increase motility and secretion of intestine. Lactulose is helpful in hepatic encephalopathy since it reduces ammonia levels in the blood and given with neomycin.

**Bisacodyl** is a contact purgative. It can be given by mouth as well as rectum. Bisacodyl inhibits intestinal Na⁺-K⁺ ATPase, promotes water and electrolyte collection in the colonic lumen thereby increasing motility. The purgative action of bisacodyl can be seen after 6-8 hours of administration. Hence, bisacodyl is given before retiring at night. Abdominal cramps are commonly observed with bisacodyl.

**Liquid paraffin** is a mineral oil obtained from petroleum industry. It is a mixture of aliphatic hydrocarbons. It is a lubricant, fecal softener and reduces water and electrolyte absorption. Liquid paraffinoma, pruritus ani, wetting the undercloth, hypovitaminoses A, D, E and K are the side effects of liquid paraffin.

**Castor oil** is a vegetable oil obtained from the seeds of *Ricinus communis*. It acts as anionic surfactant as well as contact purgative. It should be administered early in the morning on an empty stomach. Castor oil may produce pelvic congestion in pregnant women. After-constipation is the main drawback of castor oil as a purgative.

**Therapeutic Uses of Purgatives**
Purgatives are indicated in the following conditions:
1. Painful disorders of anorectum
2. Immobilization after surgery
3. Disorders of spinal cord and injury
4. Prevention of straining at stools after myocardial infarction
5. Colonic inertia
6. Preparation of the large bowel for radiology and surgery.
Contraindications of Purgatives
Purgatives are contraindicated in:
1. Intestinal obstruction
2. Patients with undiagnosed acute abdomen
3. Colic
4. Appendicitis
5. Toxic colitis
6. Bowel perforation
7. Megacolon
8. Gastric distension.

ANTIDIARRHOEAL AGENTS
Antidiarrhoeal agents are of significant value to prevent the risk of dehydration in many clinical situations. Diarrhoea may be due to infection, inflammation, malabsorption syndrome, secretory disorders of intestine or nonspecific entity. If the cause is known, specific and supportive drug treatment can be readily instituted. The most effective component of treatment of diarrhoea regardless of origin is salt and water replacement. Oral rehydration solution must be given promptly. To control the symptoms in acute non-specific diarrhoea where the causative mechanism is not known, following drugs are used—loperamide, diphenoxylate, kaolin and pectin, berberine, paregoric and bismuth salts.

Loperamide
It is a rapidly acting, potent antidiarrhoeal agent. It is believed that loperamide acts on μ-opioid receptors but devoid of abuse potentiality. The dose of loperamide should not exceed 16 mg/day. Toxic megacolon is one of its adverse effects observed very rarely. Since there is no risk of dependence, loperamide is widely used.

IMPLICATIONS TO PHYSIOTHERAPY
Drugs acting on gastrointestinal system in general may not preclude exercise program. However, systematic, regular and simple exercise may increase the blood flow to gastrointestinal system and may augment the healing of ulcer with drug therapy and relieve functional constipation. It is also common to expect that regular exercise is helpful to maintain the motility of intestine. It is interesting to study how gastrointestinal drug effects are modulated by exercise programme.
INTRODUCTION

Chemotherapy is the treatment of infectious diseases using chemical substances—(*chemo*: chemical agents, *therapy*: treatment). The success of treatment of any infection depends on a number of variables involving the host, causative organisms and the drug. Nonetheless, one of the most important advances in therapeutics is the development of prophylactic and curative antimicrobial agents. Currently, the terms antibiotic and antimicrobial are used as interchangeable words though there is a difference between the two terms. An antibiotic is a substance obtained from microorganisms and act lethally against other pathogens. Antimicrobial agents are synthetic substances and act lethal to a wide varieties of microorganisms.

CHEMOPROPHYLAXIS

Ideally, the treatment of infection after identification of causative organism and results of sensitivity test is rational. However, this is not possible always. Empirical therapy is often necessary and in life-threatening infections one cannot wait for bacteriological investigation report. Administration of chemotherapeutic agents for the prevention of infective diseases is known as ‘chemoprophylaxis’. Chemoprophylactic regimens have proven therapeutic value in malaria, surgery, some types of cancer, cholera, tuberculosis, rheumatic fever and dental procedures. For surgical chemoprophylaxis, the antibiotics used must have proven efficacy against common pathogens. At the time of incision, the lethal concentration of antibiotic must be achieved. Usually, chemoprophylactic regimen must be least expensive and the shortest possible course of treatment is recommended.
General Principles
Pertinently, before designing a chemotherapeutic drug regimen, the following principles are to be considered. This is necessary to achieve much needed success.
1. Firstly, it is rational to consider and arrive at a decision whether the patient requires an antimicrobial therapy or not. Many viral infections are self-limiting and require optimum supportive therapy only.
2. Identification of causative organism and sensitivity tests is desirable. But, this is always time consuming and, hence, the treatment must be started on empirical basis, based on experience and clinical entity.
3. The site of infection and clinical features may indicate the nature and type of likely pathogens.
4. Single or combination chemotherapeutic agents are to be given at optimum doses by appropriate route for an adequate duration.
5. Chemotherapeutic dose regimen and duration should be completed without any variation. Otherwise treatment failure or relapse may be seen.
6. The selection of a chemotherapeutic agent based on bacterial culture and sensitivity tests is sound and rational.
7. Adjunctive measures like draining the abscess, antiinflammatory and analgesic drugs administration are to be undertaken.
8. Local epidemiological data about prevailing infectious diseases, monitoring the therapeutic response and cost of the therapy should be considered.

Generally, by third day of the use of rational antimicrobial agent, the severity of the infection will reduce. If by fifth day infection is not controlled, change in antibiotic therapy is warranted. Errors in drug dose and sensitivity tests, bacterial resistance, abscess, interactions, foreign bodies and superinfection have been the major reasons of chemotherapeutic treatment failure.

BACTERIAL RESISTANCE
The development of resistance to the action of chemotherapeutic agents by bacteria and other organism is a natural consequence. Bacterial resistance may be intrinsic or acquired or due to spontaneous and rapid genetic events. Resistance to drug action can only be delayed by prudent use of chemotherapeutic agents. It is of great clinical significance that treatment policies adopted should not increase the prevalence of bacterial resistance.

Bacteria Develop Resistance to Drugs by Several Mechanisms
1. Impermeability: An antibiotic fails to reach the target site, for example, quinolones, and aminoglycosides.
2. Enzymatic inactivation: Organisms elaborate enzymes to inactivate the antimicrobials, for example, β lactamases metabolize penicillins.
3. Efflux transport: Antimicrobials are effluxed by a process involving transport protein—for example, tetracyclines and vancomycin.
4. Altered target sites: Bacterial target sites may be altered so that antimicrobials fail to act, for example, enterococci develops resistance to ampicillin and vancomycin.
5. **Genetic mechanisms:** The changes that occur in the genomes of a wide variety of bacteria contribute substantially for the development of resistance. These changes may be the result following mechanisms.
   i. Mutation
   ii. Conjugation
   iii. Transduction
   iv. Transformation
   v. Transposition.

   These genetic mechanisms involve the transfer of “resistance factor” from one organism to the other. The transfer of factor for resistance may be accomplished by an extrachromosomal fragment called “plasmid”. Plasmids present in cytoplasm are capable of mobility and insertion into the genome of a wide variety of bacteria.

   More importantly, methods to minimize the development of bacterial resistance must be followed before starting prophylactic and curative chemotherapeutic treatment. It is true that development of bacterial resistance cannot be stopped completely. At the same time, a rational chemotherapeutic dose regimen can reduce the development of resistance. Invariably, combination chemotherapy is employed for the treatment as one of the ways to decrease the chances of development of resistance. Combination chemotherapy also increases the efficacy, antibacterial spectrum and curative rate and decreases the duration of treatment. However, multiple drug resistance is often encountered in clinics, which makes the treatment more complex and costly, as seen in tuberculosis, malaria, leprosy, cancer and infections of different etiology.

**SUPERINFECTION**

Chemotherapeutic agents alter normal microbial population in intestine, upper respiratory tract and genitourinary tracts. This is often potentially dangerous. Appearance of bacteriological and clinical evidence of a new infection during the chemotherapy of primary infection is defined as ‘superinfection’. Superinfection is due to suppression of normal microflora in the body. Superinfection is commonly caused by enterobacteriae, pseudomonas and fungi like *Candida*. Broad-spectrum antibiotics like tetracyclines, chloramphenicol and third generation cephalosporins produce antibiotic associated colitis. *Clostridium deficile* causes colitis, which can be treated by either metronidazole or vancomycin or both. Recently, probiotic formulations have been indicated to mitigate antibiotic-induced superinfections.

**General Mechanism of Action of Antibiotics**

Antibiotics act lethal to microorganisms by many ways. Generally, depending on their spectrum of antibacterial activity, antibiotics have been referred to as:

- Narrow-spectrum antibiotics
- Intermediate-spectrum antibiotics
- Broad-spectrum antibiotics

*Narrow-spectrum antibiotics* are effective only against gram-positive microorganisms, for example, penicillin-G, lincomycin, vancomycin, bacitracin and erythromycin.
Intermediate-spectrum antibiotics are effective against gram-positive and some of the gram-negative microorganisms. These are primarily useful in aerobic gram-negative bacilli infections, for example, aminoglycosides and polymyxins.

Broad-spectrum antibiotics are defined as agents that are effective against a wide variety of microorganisms including gram-positive, gram-negative, chlamydiae, rickettsiae, some protozoa and large polyviruses, for example, tetracyclines and chloramphenicol.

The mechanism of antibiotics involve the following:

a. Inhibition of bacterial cell wall synthesis
b. Alteration of cell permeability
c. Inhibition of protein synthesis
d. Inhibition of nucleic acid synthesis.

Bacterial Cell Wall Synthesis Inhibitors
Penicillins, cephalosporins, carbapenems, monobactams, cycloserine, vancomycin, bacitracin, teicoplanin

Antibiotics that alter Cell Permeability
Polymyxins, polyene antibiotics, azoles, nystatin, novobiocin

Antibiotics Act by Inhibition of Bacterial Protein Synthesis
Aminoglycosides, macrolides, tetracyclines, chloramphenicol

Antibiotics that Inhibit Nucleic Acid Synthesis
Rifampicin, fluoroquinolones, nalidixic acid, anticancer agents, anti-HIV drugs

ANTIMICROBIAL AGENTS

Rationale for Combination Chemotherapy
Multidrug regimens in the treatment of infectious conditions are very common. Often, combination chemotherapy is overused in clinical medicine. For the treatment of mixed infections, synergistic combination antibiotic therapy is useful in particular. The pharmacological basis for combination chemotherapy is manifold which includes the following:

- To reduce the development of bacterial resistance
- To increase the efficacy and cure rate
- To increase the antibacterial spectrum of activity
- To reduce the duration of treatment of infectious disease
- To reduce the toxicity of individual chemotherapeutic agent
- To achieve therapeutic synergy by the pharmacodynamic mechanism of action of various drugs.

However, combination chemotherapeutic regimens undoubtedly increase the cost of disease management. Multiple drug therapy does not offer complete solution for the development of bacterial resistance. Recently, reports on resistance to multidrug therapy in cancer, AIDS and other infectious conditions are coming at rapid pace. It is the judicious,
optimal, appropriate and rationale use of multi-drug regimen by clinicians that can decrease the prevalence of-resistant microorganisms. Importantly, frequent misuse of chemotherapeutic dose regimen needs to be curbed.

SULPHONAMIDES AND COTRIMOXAZOLE

Sulphonamides

Currently, sulphonamides occupy a small place in the treatment of infectious diseases. These are bacteriostatic synthetic antifolate drugs. Structurally, sulphonamides are the derivatives of paraminobenzene sulphonamide known as sulphanilamide.

Sulphonamides are classified into six main classes on duration of action and rate of elimination:
1. Short acting: Sulphadiazine, sulphafurazole, sulphadimidine
2. Intermediate acting: Sulphamethoxazole
3. Long acting: Sulphadimethoxine, sulphamethoxypyramidine
4. Ultra long acting: Sulphadoxine, sulphametopyrazine
5. Topical sulphonamides: Sulphacetamide, silver sulphadiazine, mafenide
6. Antiinflammatory and antiulcerative colitis: Sulphasalazine

All sulphonamides act by same mechanism except mafenide, which seems to have different bacteriostatic action. Mafenide is active in presence of pus unlike other sulphonamides. Sulphonamides are the analogues of para-aminobenzoic acid and produce antifolate action. This is to say that sulphonamides act by inhibiting bacterial folic acid synthesis and thereby arrest their growth and multiplication. However, resistance is common to antimicrobial action of sulphonamides. Hence, these have limited therapeutic value in the chemotherapy of infectious diseases.

Therapeutic Uses

Sulphonamides are used in the following infections:
1. Urinary tract infections: Usually cotrimoxazole is preferred.
2. Nocardiosis: Sulphisoxazole or sulphadiazine is used.
3. Toxoplasmosis: Combination of sulphadiazine and pyrimethamine is recommended.

Topical sulphonamides like sulphacetamides are used in the management of eye infections. Silver sulphadiazine is employed topically to reduce bacterial colonization in wounds including burns. Mafenide is also used to dress burn wounds.

Adverse Effects

Relatively common adverse effects of sulphonamides are nausea, vomiting, diarrhoea, hypersensitivity reaction (sulpha reaction), nephrotoxicity and blood dyscrasias. Often, hypersensitivity reactions to sulphonamides are the source of concern. Pruritus, fever, photosensitivity, reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis are often fatal. Crystallization of some of the acetylated metabolites of sulphonamides in the urine occurs causing crystalluria, hematuria, oliguria and anuria. The risk of crystalluria can be reduced by the administration of fluids to maintain high urinary output. If there is a need, alkalinisation of urine by giving sodium bicarbonate is recommended to reduce crystalluria.
Agranulocysis and aplastic anaemia and acute hemolytic anaemia have been produced by sulphonamides.

**Contraindications**
1. Hypersensitivity reaction to sulphonamides
2. Severe renal and hepatic failure
3. Systemic lupus erythematosus
4. Women prior to delivery
5. Nursing mother
6. Patients with glucose-6-phosphate dehydrogenase deficiency.

**Drug Interactions**
1. Sulphonamide + procaine: No antimicrobial action—antagonism
2. Sulphonamide + warfarin: Potentiates the action of anticoagulant
3. Sulphonamide + phenytoin: Competition for plasma protein-binding sites and increases the plasma level of phenytoin
4. Sulphonamide + oral antidiabetics—sulphonylurea compounds: Potentiation of hypoglycemia

**Cotrimoxazole**
Cotrimoxazole is a mixture of two antifolate drugs trimethoprim and sulphamethoxazole. This combination is developed to increase the antibacterial spectrum of activity and to attain therapeutic synergy by their mechanism of action. Cotrimoxazole blocks folic acid synthesis at two steps, which is often referred to as “sequential blockade” as depicted in Figure 13.1. Cotrimoxazole is bactericidal and blocks the bacterial folic acid synthesis. Consequently, no DNA synthesis eventually causes the death of bacteria.

**Antibacterial Spectrum**
Cotrimoxazole is active against a wide variety of microorganisms. However, most of these organisms have now become-resistant to cotrimoxazole. *Neisseria meningitidis, Streptococci,*

![Fig. 13.1: Sequential blockade](image-url)
Enterobacteria, Chlamydiae, Salmonella typhi, Shigella, Pneumocystis carinii, Hemophilus influenzae and Proteus species are susceptible to antimicrobial action of cotrimoxazole.

Trimethoprim is not only similar to sulphamethoxazole in its antibacterial spectrum of activity but also resembles in its kinetic properties. Plasma half-life, the pattern of distribution is by and large same for both the drugs. These drugs are combined at the proportion of 1:5, i.e. trimethoprim 80 mg and sulphamethoxazole 400 mg. Commercially, double strength cotrimoxazole, trimethoprim 160 mg + sulphamethoxazole 800 mg is also available. For serious infections, cotrimoxazole can be given by intravenous route; otherwise, oral administration would suffice the need.

**Adverse Effects**

Most commonly, cotrimoxazole causes nausea, vomiting and skin rash. Headache, fatigue, glossitis and stomatitis have also been observed. Allergic reactions can occur, especially in patients who are sulphonamides sensitivity. Stevens-Johnson syndrome and toxic epidermal necrolysis may be seen. Cholestatic jaundice, hypoprothrombinemia, hemolytic anaemia, thrombocytopenia, hair loss and methaemoglobinemia are also reported with cotrimoxazole. Patients with AIDS are particularly vulnerable to cotrimoxazole toxicity.

**Therapeutic Uses**

In the past, cotrimoxazole was used commonly in all routine infections seen in hospital. Now, resistance to cotrimoxazole is most significant. Nevertheless, cotrimoxazole is used in the following infectious diseases:

- Acute, chronic and recurrent urinary tract infections
- Respiratory tract infections: Bronchitis and pneumocystis pneumonia in AIDS.
- Typhoid fever and shigellosis: Cotrimoxazole appears to be effective in the management of Salmonella typhi carrier state.
- Septicemia: Usually given with other antimicrobials
- Gonorrhea
- Meningitis due to H. influenzae
- Nocardiosis, histoplasmosis and prophylaxis of traveler’s diarrhoea, bacillary dysentery, biliary surgery and for the prevention of infection in acute leukemia.

**Contraindications**

Cotrimoxazole should not be administered to patients who are allergic to sulphonamides. It should be avoided during pregnancy. In severe hepatic and renal failure cotrimoxazole is contraindicated.

**FLUOROQUINOLONES**

Fluoroquinolones are broad-spectrum synthetic antibacterial agents. These are the derivatives of urinary antiseptic nalidixic acid. The list of fluoroquinolones that are widely used is expanding rapidly, currently used are:

- Ciprofloxacin
- Gatifloxacin
- Ofloxacin
- Pefloxacin
- Gemfloxacin
- Sparfloxacin
Pharmacology for Physiotherapist

<table>
<thead>
<tr>
<th>Norfloxacin</th>
<th>Levofloxacin</th>
<th>Trovafloxacin</th>
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<td>Enoxacin</td>
<td>Lomefloxacin</td>
<td>Rufloxacin</td>
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**Antibacterial Spectrum**

Fluoroquinolones are very active against gram-negative bacilli. Cocci including *Enterobacteriae*, *Haemophillus influenzae*, *Moraxella*, *Pseudomonas aeruginosa*, *Streptococci*, *Mycobacteriae*, *Salmonella*, *Mycoplasma*, *Rickettsiae* and *Plasmodium falciparum* are also susceptible to fluoroquinolones.

**Mechanism of Action**

Fluoroquinolones are bactericidal drugs and act by inhibiting bacterial DNA gyrase enzyme. As a result, bacterial DNA synthesis cannot occur.

**Ciprofloxacin**

Ciprofloxacin is a fluoroquinolone antimicrobial agent useful in a wide variety of infections. This is an inhibitor of bacteria DNA synthesis and hence bactericidal. Ciprofloxacin can be given intravenously when needed. Generally, it is administered by oral route. Eye drops preparations of ciprofloxacin are also available. Organisms-resistant to other antimicrobials may well respond to ciprofloxacin. Therefore, ciprofloxacin is used in a wide range of infectious diseases.

**Therapeutic Uses**

Ciprofloxacin is used commonly in complicated and uncomplicated urinary tract infections. Lower respiratory tract infections and infection of skin, bone, joints and infectious diarrhoea as well. Other uses include:

- Prostatitis: Tissue penetration of fluoroquinolones is good, hence, used for infections of deep organs.
- Pharyngeal and rectal gonococcal infections
- Typhoid fever
- Neutropenia-associated infections
- Cystic fibrosis associated with *Pseudomonas aeruginosa* infections
- Animal bites and sting
- Tuberculosis and leprosy
- Malaria
- Cellulitis and recommended for all complicated infectious conditions.

**Adverse Effects**

In general, fluoroquinolones are well tolerated. Adverse effects are seldom observed, which requires discontinuation of therapy.

- Flatulence, dyspepsia, stomatitis, headache, dizziness, insomnia, tendonitis, tendon rupture, facial edema, swelling of joints with cartilage erosion, especially in children below 8 years, hypersensitivity reactions, skin rash and superinfection have been reported as adverse effects of ciprofloxacin and other fluoroquinolones.
Contraindications

Ciprofloxacin should not be used with other fluoroquinolones. All fluoroquinolones are contraindicated in pregnancy. Children and nursing mothers should not use ciprofloxacin. Joint cartilage erosion is the source of concern in children aged below 8 years on fluoroquinolones administration.

Drug Interactions

1. Ciprofloxacin + theophylline: Ciprofloxacin decreases the clearance of theophylline and is likely to aggravate central nervous system toxicities of theophylline seizures in particular. Fluoroquinolones may be neurotoxic on their own. Hence, care is mandatory.
2. Ciprofloxacin probably inhibits the metabolism of oral anticoagulant warfarin and increases bleeding tendencies.
3. Ciprofloxacin + NSAIDs like naproxen and fenbufen: Central nervous system toxicities of ciprofloxacin are increased.
5. Antacids and sucralfate reduce the oral absorption of ciprofloxacin.

Ofloxacin

Ofloxacin resembles ciprofloxacin in its pharmacological properties and uses. Nevertheless, oral bioavailability of ofloxacin is very high > 95% of administered dose. Hence, ofloxacin is preferred in the treatment of tuberculosis and leprosy. It appears to be more active in Chlamydia trachomatis. It is administered by mouth and by intravenous route where necessary. Eye drop preparations are also available. The optical isomer (S-) of ofloxacin is levofloxacin has twice the activity of the racemate.

Lomefloxacin

Lomefloxacin is similar to that of ciprofloxacin in its actions and uses. It is a long-acting fluoroquinolones, hence, given once daily by mouth. Ophthalmic topical solution of lomefloxacin is used for bacterial conjunctivitis. Unlike ciprofloxacin, lomefloxacin, does not appear to interact significantly with theophylline.
INTRODUCTION

Beta-lactam antibiotics constitute a group of chemotherapeutic agents that share structure and mechanism of action. This class of antibiotics includes penicillins, cephalosporins, carbapenems and monobactams. Beta-lactam ring is attached to the structure of all these antibiotics and hence the name. These antibiotics are frequently prescribed and have prophylactic and curative value in many infectious conditions. However, the development of bacterial resistance to beta-lactam antibiotics remains as a challenge.

CLASSIFICATION

Currently, four groups of beta-lactam antibiotics have been used, namely:
1. Penicillins
   a. Natural
   b. Semisynthetic penicillins
2. Cephalosporins: Subdivided into four generations based on their antibacterial spectrum and clinical uses.
3. Carbapenems: Imipenem, Meropenem
4. Monobactams: Aztreonam, Carumonam

PENICILLINS

Alexander Fleming discovered penicillin as an antibiotic. Later, penicillin was developed as a chemotherapeutic agent by a systematic study in military patients and introduced to public use after the Second World War. Even today, penicillin enjoys a wide clinical application and, in fact, penicillin therapy is very much cost effective hence affordable. Modern man’s requirement of penicillin is steadily increasing and no let out. The term ‘penicillins’ generically denotes the entire natural and semisynthetic penicillins.

Penicillin is obtained from *Penicillium chrysogenum* or *Penicillium notatum*. The natural penicillin is otherwise known as *penicillin-G* or *benzyl penicillin*. Today, benzyl penicillin has a unique reputation of being an economical and affective antibiotic for a number of infectious diseases.

The structure of penicillin consists of three important components:
1. Thiazolidine ring
2. Beta-lactam ring
3. A side chain
The basic nucleus of penicillin is known as 6-aminopenicillanic acid. Various derivatives of 6-aminopenicillanic acid have been introduced as semisynthetic penicillins, which offer many clinical advantages over penicillin-G.

**Classification of Penicillins**

1. **Natural penicillin**
   a. Benzyl penicillin (Penicillin-G)
   b. Phenoxymethyl penicillin (Penicillin-V)

2. **Semisynthetic penicillins**

3. **Beta-lactamase-resistant penicillins** (Isoxazolyl penicillins)
   Methicillin, cloxacillin, dicloxacillin, flucoxacillin, nafcillin

4. **Extended spectrum penicillins**
   a. *Aminopenicillins*: Ampicillin, amoxycillin, hetacillin, pivampicillin, bacampicillin, metampicillin
   b. *Carboxypenicillins*: Carbenicillin, ticarcillin
   c. *Others*: Mezlocillin, piperacillin, azlocillin.

**Mechanism of Action**

Penicillins are bacterial cell wall synthesis inhibitors. The action of penicillin is more intense on growing and dividing bacteria. Penicillin is a bactericidal antibiotic.

Bacterial cell wall is essential for normal growth and development. Peptidoglycans are the building blocks of bacterial cell wall and provide mechanical stability. Penicillin inhibits bacterial cell wall synthesis by arresting the generation of peptidoglycans. All the beta-lactam antibiotics inhibit “transpeptidase” to prevent cross-linking of peptidoglycans. Besides, penicillin promotes “autolysis” of bacteria by causing the loss of inhibitor of autolysins. All bacteria have proteins called “penicillin-binding proteins” with which antibiotic binds to kill the bacteria. However, the number and the affinity of penicillin-binding proteins vary from one type of bacterium to the other. For this reason, beta-lactam antibiotics cannot kill the bacteria.

**Penicillin-G (Benzyl Penicillin)**

Benzyl penicillin is a short-acting parenteral penicillin. It is effective against gram-+ve and –ve cocci, pneumococci, meningococci, gonococci, spirochetes, neisseria, *Bacillus anthrax*, clostridia, *Treponema pallidum*, borrelia, listeria, *Corynobaeterium diphtheriae* and actinomycetes. However, many of the above microbes now reported from many countries to be resistant to penicillin.

The oral bioavailability of penicillin-G is poor. It is always given by intramuscular, intravenous and occasionally intrathecally. The plasma half-life of penicillin-G is 30 minutes. Major part of the administered dose of benzyl penicillin is excreted unchanged in urine. Penicillin is excreted by active renal tubular secretory mechanisms. Hence, drugs that are excreted by same active tubular secretion can compete with penicillin and delay the rate of penicillin elimination. Probenecid competes with penicillin for renal secretion and thus prolongs the action of penicillin. Many a time, probenecid is given with various penicillin preparations to increase the duration of action of the antibiotic.
Repository Preparations of Benzyl Penicillin

Since, as such the duration of action of benzyl penicillin is short and given parenterally, it is cumbersome to give benzyl penicillin once in two hours at the time of need. Therefore, depot preparations of penicillin-G have been developed.

These include:
1. Procaine penicillin
2. Benzathine penicillin.

Procaine penicillin is a suspension of procaine and penicillin-G complex, which is poorly soluble. Procaine penicillin is always given by intramuscular route. Virtually, the injection is painless. Since, procaine is released at the site of injection slowly to produce local anaesthetic action. A standard dose of procaine penicillin can act up to 24-48 hours.

Benzathine penicillin is a long-acting preparation of penicillin-G, which acts for 32 days after 1.2 mega unit intramuscular dose. This preparation should not be used for acute and severe infection. The distinct advantages of these preparations are it avoids repeated injections, local trauma is reduced and importantly, reduces the cost.

Therapeutic Uses

Benzyl penicillin has been used to combat a wide variety of infections particularly those caused by pneumococci, streptococci, gonococci, neisseria, actinomycetes. Gas gangrene, pneumonia, pharyngitis, necrotizing enterocolitis, orodental and peridental infections, gonorrhea, syphilis, gingivostomatitis, tetanus, leptospirosis, endocarditis, insect bite and stings and toxic shock syndrome have been treated with various preparations of penicillins.

Prophylactic uses of penicillin include the following:
1. Recurrence of rheumatic fever
2. Diphtheria for asymptomatic carriers
3. Pharyngitis and dental procedures
4. Syphilis
5. Streptococcal pyogenes infection
6. Gonorrhoea
7. Patients with deep burn
8. Surgical procedures in patients with valvular heart diseases.

Adverse Effects

Penicillin is apparently a safe antibiotic except for the fact that it can produce fatal hypersensitivity response. Penicillin hypersensitivity reactions can be seen with any preparation of penicillins. The metabolic products of penicillins appear to have potential hapten antigenic activity. The penicilloyl moiety of penicillin is the most powerful antigen known.

Penicillin hypersensitivity reactions can occur with any dosage and in fact, unpredictable. The most common life-threatening manifestations of penicillin hypersensitivity are angioedema and anaphylaxis. All types of skin rashes have been observed. Late reactions like serum sickness may also be produced by penicillin.
The management of penicillin hypersensitivity reactions demand evaluation of patient’s history of allergy to penicillin with other life-saving measures. Patients with the history of penicillin allergy should be treated with other antibiotic. Prior to administration of penicillin to the patient, skin testing for penicillin allergy should be done to avoid any fatal outcome. Necessary care should be taken and adrenaline must be kept ready to encounter anaphylaxis caused by penicillin.

Besides allergy, penicillin can produce adverse reactions like bleeding abnormalities and convulsions, especially on intrathecal administration.

During the treatment of syphilis with penicillin “Jarisch-Herxheimer” reaction has been observed. Probably, Jarisch-Herxheimer reaction is due to the liberation of endotoxins from dead spirochetes. Jarisch-Herxheimer reaction can be treated by analgesics and penicillin need not be discontinued.

**Drug Interactions**

1. Penicillin + Probenecid: Prolongation of penicillin action
2. Penicillin + Aspirin: Increased plasma steady state concentration of penicillin

Generally, penicillin should not be combined with bacteriostatic antibiotics like tetracycline and chloramphenicol.

**Penicillin-V (Phenoxymethyl Penicillin)**

It is an orally affective penicillin unlike penicillin-G. It is resistant to degradation by gastric acid. Penicillin-V is more completely absorbed from gastrointestinal tract. Phenoxymethyl penicillin is used in the treatment of mild to moderate infection and not for chronic, severe and deep-seated infections. Specifically, this preparation is used for Lyme disease of early pregnancy and young children. Penicillin-V is usually well tolerated and occasionally may cause diarrhoea.

**Ampicillin**

Ampicillin is a semisynthetic aminopenicillin with wider antimicrobial spectrum of activity when compared to benzyl penicillin. Ampicillin produces bactericidal action for both gram-positive and gram-negative organisms. *Haemophilus influenzae, Listeria monocytogenes, Streptococci viridans, Enterococci, E. coli, Proteus mirabilis, Salmonella typhi, Shigella, N. gonorrhoeae* exhibit varying degree of response to ampicillin. Most of these species are now being reported to be resistant to aminopenicillins.

The common route of ampicillin administration is oral because it is stable in gastric acid. Presence of food interferes with ampicillin absorption. Renal function impairment markedly prolongs the action of ampicillin and the dose adjustment is required under this condition. Ampicillin enjoys enterohepatic circulation and excreted in faeces.

Skin rashes are among the most common side effects of ampicillin. Patients with infectious mononucleosis develop maculopapular rash with ampicillin. Ampicillin induces diarrhoea due to suppression of intestinal microflora and is commonly seen in paediatric patients. Pseudomembranous colitis has also been reported as adverse affect of ampicillin.

Ampicillin is used in the treatment of a variety of infections due to susceptible organisms. These include biliary tract infections, bronchitis, endocarditis, gastroenteritis, gonorrhoea,
listeriosis, meningitis, otitis media, typhoid and paratyphoid, pneumonia, septicemia and urinary tract infections.

Ampicillin is used to treat beta-lactamase producing infections with sulbactam, a beta-lactamase enzyme inhibitor. Care is necessary when ampicillin is administered at high doses to a woman on contraceptive pill. There are reports of increased adverse effects of the pill. Ampicillin may prolong the bleeding time when administered with anticoagulants. There has been concern about ampicillin caused exacerbation of symptoms of myasthenia gravis and ampicillin rash prevalence rate in HIV patients.

**Amoxycillin**

Amoxycillin is an aminopenicillin bactericidal antibiotic. It bears similarities with ampicillin in its antibacterial spectrum of activity, therapeutic uses and drug interactions. Nevertheless, amoxycillin is more active against *Helicobacter pylori* and *Salomonella* species but less active against *Shigella* than ampicillin.

Amoxycillin is orally effective, resistant to gastric acid and more rapidly absorbed than ampicillin. Presence of food does not appear to interfere with amoxycillin unlike ampicillin and about 60% of amoxycillin dose is excreted unchanged in urine.

Amoxycillin is given with beta-lactamase inhibitor clavulanic acid to widen its antibacterial spectrum of activity. The incidence of diarrhoea is less in paediatric patients than ampicillin. Amoxycillin can be preferred to treat upper respiratory tract infection to ampicillin since it attains high concentration in the upper respiratory tract. Skin rash is less observed with amoxycillin although it is not free from this adverse effect.

**Beta-lactamase-resistant Penicillins**

Methicillin, flucloxacillin, cloxacillin, dicloxacillin, nafcillin.

These penicillins are indicated against staphylococci, which are-resistant to penicillin-G. It is advantageous to combine beta-lactamase-resistant penicillins with ampicillin or other antibiotics, especially to combat mixed bacterial infections. Methicillin is always administered by intravenous route. Cloxacillin and others can be given by mouth. The mechanism of action and adverse reactions of penicillinase-resistant penicillins are same as benzyl penicillin. However, methicillin-resistant *Staphylococcus aureus* is common now.

**Antipseudomonas Penicillins**

Carbenicillin, ticarcillin, pipercillin, azlocillin

Generally, antipseudomonas penicillins are given with aminoglycoside antibiotics. The pharmacology of these penicillins is same as other penicillin. However, these penicillins have extended spectrum of antibacterial activity and usually administered by intravenous route.

**CEPHALOSPORINS**

The cephalosporins are semisynthetic beta-lactam antibacterials derived from cephalosporin-C a natural product of *Cephalosporium acremonium*. The chemical structure of cephalosporins is very closely related to penicillin, bearing the active nucleus called 7-amino cephalosporanic
acid. These are bactericidal and inhibit cell wall synthesis like penicillin. Cephalosporins are classified into four generations based on the general features of their antimicrobial activity.

**Classification of Cephalosporins**

1. **First generation:** Cefalothin, cefradine, cefazolin, cefadroxil, cefalexin
2. **Second generation:** Cefamandole, cefonicid, cefuroxime, ceforanide
3. **Third generation:** Cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime
4. **Fourth generation:** Cefepime, cefpirome.

Cefamycins are the derivatives of cefamycin-C bearing 7-methoxy instead of 7-amino group in the basic nucleus of cephalosporanic acid. Cefamycins have great stability for beta-lactamase. The examples include cefoxitin, cefotetan and cefbuperazone.

Cephalosporins have high therapeutic/toxic ratio and effective in a wide variety of infections. Cephalosporins from I to IV generation show widening antibacterial spectrum to gram-negative organisms, loss of efficacy against gram-positive organisms, greater efficacy against-resistant organisms and increased cost. Nevertheless, III generation cephalosporins use is justified because of their high potency, greater efficacy and low toxicity.

Mechanism of action of cephalosporins is similar to that of penicillin. These antibiotics inhibit bacterial cell wall synthesis. The enzyme transpeptidase is inhibited by cephalosporins and cross-linking of peptidoglycans cannot occur. Additionally, bacterial murein hydrolase—an autolysing enzyme activity is augmented by cephalosporins.

**First Generation Cephalosporins**

Cefalothin, Cefazolin, Cefalexin, Cefadroxil

These are initial agents, which are more active against gram-positive organisms and primarily used as prophylactic agents before surgery. Cefalexin and cefadroxil are orally effective which are rarely the drugs of choice for any infection. However, orally effective first generation cephalosporins may be used for urinary tract infection.

**Second Generation Cephalosporins**

Cefuroxime, Cefaclor, Cefonicid, Ceforanide

Second generation cephalosporins are more active against gram-negative organisms including *Neisseria* and *Haemophilus meningitides*. Cefuroxime axetil is orally effective, more potent because it has greater affinity to bacterial cell proteins. Cefaclor can be used in otitis media and *Haemophilus influenzae* infections.

**Third Generation Cephalosporins**

Ceftriaxone, Ceftazidime, Cefotaxime, Cefixime, Ceftizoxime, Cefoperazone

Third generation cephalosporins have been shown to be more active against gram-negative organisms, more stable against beta-lactamase and bind strongly with cell proteins to produce more potent antibacterial action. However, these are less active against gram-positive organisms. These have clinical value in various severe infections caused by bacterial strains-resistant to other generations, penicillins and aminoglycoside antibiotics. These are recommended to tract sepsis of unknown cause.
Fourth Generation Cephalosporins
Cefepime, Cefpirome

Cefepime and cefpirome are more-resistant to beta-lactamase activity and effective against *Pseudomonas, Enterobacteria, Staphylococcus aureus*. Cerebrospinal penetration is good with fourth generation cephalosporins and used to treat nosocomial infections.

**Therapeutic Uses of Cephalosporins** *(Table 13.1)*

<table>
<thead>
<tr>
<th>I generation</th>
<th>II generation</th>
<th>III generation</th>
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<tr>
<td>Lymphadenitis</td>
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<td>Decubitus ulcer</td>
<td>Chancroid</td>
</tr>
<tr>
<td></td>
<td>Pelvic inflammatory diseases</td>
<td>Pelvic inflammatory diseases</td>
</tr>
<tr>
<td></td>
<td>Gonorrhea</td>
<td>Gonorrhea</td>
</tr>
<tr>
<td></td>
<td>Lyme disease</td>
<td>Lyme disease</td>
</tr>
</tbody>
</table>

**Adverse Reactions**

Cephalosporins are well-tolerated antibiotics. However, hypersensitivity reactions have been reported. Skin rash, rarely fever, eosinophilia, leukopenia, thrombocytopenia, anaemia, bleeding, diarrhoea, reversible cholestatic jaundice, headache, and convolutions can appear on cephalosporins administration. Superinfection is reported with II and III generation cephalosporins.

**Drug Interactions**

1. Cephalosporins + Aminoglycoside antibiotics: Nephrotoxicity is increased
2. Cephalosporins + Alcohol: Acute alcohol intolerance, disulfiram-like reaction is produced
3. Cephalosporins + Warfarin: Action of warfarin is increased
MACROLIDES

MACROLIDE GROUP OF ANTIBIOTICS

Macrolide group of antibiotics have a common macrocyclic lactone ring attached to sugar. All the macrolide antibiotics have similar antibacterial spectrum of activity and low toxicity. These antibiotics act by inhibiting bacterial protein synthesis and known to have post-antibiotic effect. This is to say that even the antibiotic concentration drops much below the minimum inhibitory concentration antimicrobial activity persists.

Currently Used Macrolides

Erythromycin, azithromycin, clarithromycin, roxithromycin, oleandomycin, josamycin.

Antibacterial Spectrum

Erythromycin group of antibiotics is active against gram-positive cocci, bacilli, *Mycoplasma, Bordetella pertussis, Spirochetes, N. meningitidis*, Anthrax, Clostridia, tetanus, *C. diphtheriae, Moraxella catarrhalis, Legionella* and also *Toxoplasma gondii*. Clarithromycin is effective against *Mycobacterium avium* complex and *Helicobacter pylori*.

Erythromycin

Erythromycin is a macrolide antibiotic used in a wide variety of infections caused by susceptible microorganisms. This antibiotic is used as an alternative to penicillin for penicillin allergic patients. It is an inhibitor of bacterial protein synthesis and essentially bacteriostatic antibiotic. Erythromycin binds to 50S ribosome, leading to inhibition of translocation reaction in bacterial protein synthesis. Erythromycin can be administered by topical, oral and parenteral routes but not by intramuscular route, which is painful.

Adverse Effects

Erythromycin is well tolerated and serious adverse reactions are rare. Erythromycin estolate preparation is particularly linked with hepatotoxicity. Epigastric distress, nausea, vomiting and diarrhoea may also be seen with erythromycin therapy. Jaundice, pruritus and skin rash may be seen as hypersensitivity reactions to erythromycin.

Therapeutic Uses

Erythromycin has been used in a wide variety of infectious diseases, which include:

1. Bronchitis
2. Severe campylobacter enteritis
3. Chancroid
4. Diphtheria
5. Legionella infections
6. Neonatal conjunctivitis
7. Pertussis (Whooping cough)
8. Bacterial pneumonia
9. Sinusitis
10. Trench fever
11. As an alternative for penicillin allergic individuals in anthrax actinomycetes, leptospirosis, otitis media, pharyngitis and rheumatic fever
12. Acne.

Drug Interactions
Erythromycin has the potential to interact with a large number of drugs. Erythromycin and other macrolides inhibit drug metabolizing P450 group enzymes—CYP1A2 and CYP3A4.

1. Erythromycin + Terfenadine
   Erythromycin + Astemizole
   Erythromycin + Cisapride
   \{ ventricular arrhythmias \}
2. Erythromycin + Penicillins
   Erythromycin + Cephalosporins
   Erythromycin + Gentamicin
3. Erythromycin + Theophylline—clearance is reduced and toxicity may be precipitated.
4. Erythromycin + Chloroquine—enhanced antiplasmodial action of chloroquine is reported.

Clarithromycin
Clarithromycin is a macrolide antibiotic with similar actions and uses of erythromycin. This antibiotic has antitubercular, antileprotic actions and used against Helicobacter pylori in peptic ulcer. Clarithromycin is less likely to interact with other drugs unlike erythromycin. It is given by mouth or by intravenous administration. Clarithromycin undergoes extensive first pass metabolism. Adverse effects of clarithromycin are usually mild and infrequent. Taste disturbances, stomatitis, glossitis and tooth discoloration have been reported. Clarithromycin is used in leprosy, tuberculosis, respiratory tract infections, skin and soft tissue infections. To eradicate Helicobacter pylori, clarithromycin is given along with other antiulcer drugs in peptic ulcer. Clarithromycin is contraindicated in pregnancy.

Azithromycin
Azithromycin is a long-acting macrolide antibiotic with extensive tissue distribution. It is effective against Mycobacterium avium, H. influenzae, Moraxella, Chlamydia trachomatis, Toxoplasma gondii and Plasmodium falciparum. Azithromycin is administered by mouth before meals. The duration of the treatment is usually for 3 days. Headache, skin rash and dizziness may occur with azithromycin administration. Azithromycin may be used to treat lower respiratory tract infections. In hepatic and renal dysfunction states, azithromycin should not be used.
AMINOGLYCOSIDES

AMINOGLYCOSIDE ANTIBIOTICS
Aminoglycoside antibiotics comprise a group of bactericidal drugs that share chemical, antimicrobial, pharmacological and toxic characteristics. Generally, these antibiotics are reserved for serious infections. Aminoglycosides are large polycations that cannot cross biological barriers readily; hence, always given parenterally and are excreted unchanged in urine. Widely used aminoglycoside antibiotics include:

- Amikacin
- Kanamycin
- Paromomycin
- Framycetin
- Neomycin
- Sisomycin
- Gentamicin
- Netilmicin
- Streptomycin
- Astromycin
- Mirinomycin
- Tobramycin

The mechanism of action of aminoglycoside antibiotics is complex and still being explored. Aminoglycosides act by interfering with bacterial protein synthesis. They are rapidly acting bactericidal drugs. These antibiotics are known to exert i) concentration-dependent action and ii) post-antibiotic effect, the significance of which is relevant to clinical outcome. The duration of action of aminoglycosides depends on antibiotic concentration as well as post-antibiotic effect. Based on these, once daily preparations of aminoglycosides are being marketed. Post-antibiotic effect means that residual bactericidal level after the reduction of minimal inhibitory concentration of antibiotic in vivo. Intravenous, intramuscular, intrathecal and intratympanic routes are usually employed to administer aminoglycosides.

Antibacterial Spectrum
Gentamicin group of antibiotics are effective against gram-negative bacilli, *Staphyloccocus aureus*, *Streptococcus epidermidis*, *Pseudomonas aeruginosa*, *Proteus*, *E. coli*, *Klebsiella* and *Serratia*. Most gram-positive bacteria and anaerobic microorganisms are naturally-resistant to aminoglycosides.

Adverse Effects
Aminoglycoside antibiotics are poorly tolerated; produce both reversible and irreversible toxicities, which make administration difficult and complicate chemotherapeutic regimen. All aminoglycosides are known to produce ototoxicity, nephrotoxicity and disrupt motor end plate function.

Ototoxicity
Progressive accumulation of aminoglycosides in perilymph and endolymphs damages cochlear and vestibular branches of 8th cranial nerve. Tinnitus (ringing in ear), hearing loss, impaired gait, dizziness and vertigo are the manifestation of ototoxicity caused by aminoglycosides. Largely, these manifestations are irreversible and seem to be due to the loss of hair cells.

Nephrotoxicity
Renal toxicities produced by aminoglycosides are reversible and mild. Glomerular filtration is reduced by aminoglycosides, which may contribute for nephrotoxicity since excretion
of antibiotic is reduced. Many drugs aggravate nephrotoxicity caused by aminoglycosides, cyclosporin an immunosuppressant in particular.

**Motor End Plate Blockade**

Aminoglycosides inhibit the release of acetylcholine at presynaptic sites and blocks the neuromuscular junction. Neomycin is more potent in blocking motor end plate.

Besides hypersensitivity reactions, nausea, vomiting, peripheral neuropathy, convulsions and mental depression have been reported on aminoglycoside administration. Hypomagnesemia and tetratogenicity also have been observed with aminoglycosides.

**Therapeutic Uses**

Invariably, aminoglycoside antibiotics are used in combination with other antibiotics, for example, penicillins to treat severe systemic infections, which include:

1. Bacterial endocarditis
2. Urinary tract infection
3. Brucellosis
4. Cystic fibrosis
5. Pneumonia (nosocomial)
6. Meningitis
7. Peritonitis
8. Intra-abdominal infection
9. Tularemia
10. Plague
11. Cat scratch disease
12. Bone infection
13. Hepatic coma
14. Bladder irrigation
15. Infected burns
16. Pelvic inflammatory diseases
17. As ‘intestinal antiseptics’ before bowel surgery to be given by oral route
18. Eye infections
19. Mixed aerobic-anaerobic infection
20. Skin infections

**Drug interactions**

1. Gentamicin + carbenicillin: This combination is used against pseudomonas infection for which both are administered intravenously. Before administering, the solutions of the antibiotics should not be mixed. Carbenicillin along with gentamicin forms a complex, which sticks to infusion tube and action is nullified. Hence, antibiotics should be given separately to avoid admixture incompatibility.

2. Aminoglycosides + vancomycin
   Aminoglycosides + cisplatin \( \rightarrow \) increased nephrotoxicity
3. Aminoglycosides + ethacrynic acid
   Aminoglycosides + furosemide  \{ enhanced ototoxicity \}
4. Aminoglycosides + methoxyflurane
   Aminoglycosides + neuromuscular blockers  \{ respiratory muscle paralysis may occur \}
   Aminoglycosides + other general anesthetics

**Commonly Used Aminoglycosides** (Table 13.2)

<table>
<thead>
<tr>
<th>Aminoglycoside</th>
<th>USES</th>
<th>Routes</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streptomycin</strong></td>
<td>Antitubercular</td>
<td>Intramuscular</td>
<td>Vestibular toxicity is more</td>
</tr>
<tr>
<td><strong>Gentamicin</strong></td>
<td>Infected burns</td>
<td>Intravenous</td>
<td>Intravenous</td>
</tr>
<tr>
<td><strong>Amikacin</strong></td>
<td>Semisynthetic</td>
<td>Intramuscular</td>
<td>Cochlear toxicity (auditory)</td>
</tr>
<tr>
<td><strong>Neomycin</strong></td>
<td>Infection of skin, eye and ear</td>
<td>Intramuscular</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td><strong>Kanamycin</strong></td>
<td>Second line drug in tuberculosis</td>
<td>Intravenous</td>
<td>Cochlear toxicity</td>
</tr>
</tbody>
</table>

- **USES**
  - Antitubercular
  - Infected burns
  - Semisynthetic
  - Infection of skin, eye and ear
  - Second line drug in tuberculosis

- **Route of administration**
  - Intramuscular
  - Intravenous
  - Topical

- **Toxicity**
  - Vestibular toxicity is more
  - Intravenous
  - Cochlear toxicity
  - Hypersensitivity
LINCOMYCINS

Lincomycins are bacteriostatic antibiotics and have limited use because of their toxicity. These antibiotics act by inhibiting bacterial protein synthesis. The antibacterial spectrum of activity closely resembles macrolide antibiotics. However, clindamycin is highly effective against the anaerobic microbe *Bacteroides fragilis*. Clindamycin and lincomycin both are commonly administered by mouth. Intramuscular and intravenous routes may also be employed. Mainly these drugs are used in acute and chronic osteomyelitis, caused by staphylococci. Clindamycin is an agent of first choice in *Bacteroides fragilis*, joint infections and intra-abdominal sepsis. Lincomycin is also used to combat many hospital-acquired infections. Diarrhoea, fatal colitis, jaundice and granulocytopenia are the concerning adverse effects of lincomycins.
INTRODUCTION

As the name suggests, the antibiotics, which are effective against gram-positive, gram-negative bacteria, large polyviruses, chlamydiae, rickettsiae and some protozoans are called broad-spectrum antibiotics. Tetracyclines and chloramphenicol are the traditional broad-spectrum antibiotics. However, in the literal sense, any antimicrobial, which is effective against a wide variety of microorganisms, can be referred to as broad-spectrum antimicrobial agent. For example, broad-spectrum penicillins, fluoroquinolones and third generation cephalosporins.

TETRACYCLINES

Tetracyclines are a group of antibiotics having four cyclic rings in their structure. Tetracyclines in the broader sense, share similar properties—bacteriostatic, bacterial protein synthesis inhibitors, broad-spectrum of antibacterial activity with antichlamydial, antirickettsial and antiprotozoal actions.

The commonly employed tetracyclines are further grouped into three classes based on their duration of action:
1. **Short acting** (t1/2: 6-9 hrs): Chlortetracycline, oxytetracycline, tetracycline
2. **Intermediate acting** (t1/2: 12-14 hrs): Demeclocycline, methacycline
3. **Long acting** (t1/2: 11-26 hrs): Doxycycline, minocycline

**Antibacterial Spectrum**

Tetracyclines have broad-spectrum of antibacterial activity which includes gram-positive, gram-negative bacteria, chlamydiae, rickettsiae, mycoplasma, spirochetes, some mycobacteria and protozoa. However, fungi, yeasts and viruses remain-resistant to tetracyclines.

**Mechanism of Action**

Tetracyclines bind to 30S ribosome and arrest bacterial protein synthesis. The cell growth is retarded. Bacteria absorb tetracyclines by active transport but mammalian cells do not appear to absorb tetracyclines actively. Hence, tetracyclines seem to be selective in their action.

**Resistance**

Generally, bacteria develop resistance to tetracyclines by plasmid-mediated mechanisms, often inducible and increased efflux of tetracycline. 

*Proteus, Pseudomonas aeruginosa, E. coli, other Enterobacteriae, Staphylococci and N. gonorrhoeae* develop resistance to tetracyclines by cellular efflux activity.
Pharmacokinetics
Tetracyclines, doxycycline and minocycline are absorbed well when given by mouth. Doxycycline is a lipid-soluble agent and hence tissue penetration is greater than other tetracyclines. Oral absorption of tetracyclines is markedly interrupted by milk, food and antacids. Tetracyclines are widely distributed inside the body and enjoy entero-hepatic circulation. Tissue deposition of these antibiotics is well known in bone and teeth. Tetracyclines appear in milk and saliva and mainly excreted in urine and feces.

Adverse Effects
Epigastric distress, esophagitis, diarrhoea, pancreatitis, pseudomembranous colitis—antibiotic therapy associated colitis due to suppression of intestinal microflora, superinfection, phototoxicity, nails pigmentation, hepatotoxicity, renal toxicity, permanent discolouration of teeth and bone and hypersensitivity reactions.

Outdated tetracyclines, if taken produce Fanconi’s-like syndrome characterized by vomiting, polyuria, polydypsia, proteinuria, acidosis and fever. Excessive doses of tetracyclines can produce fatty degeneration of the liver and prolong blood coagulation possibly by chelating with calcium.

Therapeutic Uses
Tetracyclines are used in the following infectious conditions. Doxycycline can be used in patients with renal failure.
1. Rickettsial infections: Typhus fever, spotted fever, trench fever, Q fever
2. Chlamydial diseases: Conjunctivitis, psitticosis, trachoma
3. Sinusitis: Acute sinusitis
4. Periodontal diseases: Both topical and systemic tetracyclines are used
5. Cholera
6. Pelvic inflammatory disease
7. Severe acne rosacea
8. Granuloma inguinale
9. Syphilis
10. Bronchitis
11. Neonatal gonococcal conjunctivitis
12. Anthrax
13. Infected animal bite
14. Mycoplasma pneumoniae
15. Nongonococcal urethritis
16. Brucellosis with rifampicin and streptomycin
17. Plague with streptomycin
18. In tularemia as an alternate to streptomycin
19. Falciparum malaria
20. Meliodosis
21. Actinomycosis
22. Amoebiasis
Contraindications
1. Tetracyclines are contraindicated for children aged below 12 years because it stains the teeth and bone permanently.
2. Hypersensitivity to tetracyclines
3. Systemic lupus erythematosus
4. Pregnancy
5. In hepatic and renal failure caution is necessary

Drug Interactions
1. Antacids, iron preparations, sucralfate, milk and other dairy products inhibit oral absorption of tetracyclines.
2. Oral contraceptive pill efficacy may be decreased by tetracyclines.
3. Tetracyclines and penicillins should not be used together, because of possible antagonism of action
4. Tetracyclines increase the action of oral anticoagulants
5. Methotrexate toxicity may be increased by tetracyclines
6. Tetracycline when with retinoids increased incidence of benign intracranial hypertension has been observed.

CHLORAMPHENICOL
Chloramphenicol is a broad-spectrum antibiotic. This antibiotic has been used particularly in typhoid and other Salmonella infections. However, its use is limited by its toxicity. Hence, chloramphenicol is reserved for serious infections.

Antibacterial Spectrum
Chloramphenicol has broad-spectrum of antimicrobial activity. Both gram-positive and gram-negative bacteria as well as some other organisms like Hemophilus influenzae, E. coli, Legionella, pasteurella, Vibrio cholerae, Klebsiella, Proteus mirabilis, Shigella, Yersinia, Leptospira, Actinomyces, Neisseria meningitides, B. fragilis and Fusobacterium are amenable to chloramphenicol action.

Mechanism of Action
Chloramphenicol is a bacteriostatic agent which acts by inhibiting bacterial protein synthesis. It binds to 50S ribosome and is known to inhibit peptide bond formation.

Resistance
Acquired resistance has been widely reported. Bacteria elaborate acetyltransferase enzyme to inactivate chloramphenicol and thus become-resistant. Ribosomal mutation and cell permeability changes contribute for the development of chloramphenicol resistance.

Pharmacokinetics
Chloramphenicol is readily absorbed by oral route. It is widely distributed in the body and reaches central nervous system at the concentration of about 50% of blood concentration.
It crosses the placenta and appears in milk and aqueous humor of the eye. It is excreted in urine and bile. The plasma half-life of chloramphenicol is 1.5 to 4 hours.

**Adverse Effects**
Chloramphenicol causes alarming adverse effects even at recommended doses and sometimes fatal too, because it inhibits mitochondrial protein synthesis. The most common adverse effects are on haemopoietic system. A dose-related bone marrow depression leading to pancytopenia, thrombocytopenia and leukopenia is common. Secondly, an idiosyncratic haemological toxicity, which is not related to dose, is observed with chloramphenicol. The main feature of this adversity is aplastic anaemia, which demands discontinuation of chloramphenicol.

Following the administration of chloramphenicol to premature baby or newborn, a toxic manifestation characterized by cyanosis, vomiting, hypothermia, ashen colour and circulatory collapse leading to death known as “grey baby syndrome” is widely reported. Therefore, chloramphenicol should never be given to newborns.

If the patient is deficient of G-6-phosphate dehydrogenase enzyme, chloramphenicol produces haemolytic anaemia.

Fever and hypersensitivity reactions are also reported. Chloramphenicol is a fetotoxic drug.

**Therapeutic Uses**
Currently, chloramphenicol is reserved for serious infections in which other safer effective antimicrobial agents fail to produce therapeutic benefit. Nonetheless, chloramphenicol may be used in conditions like:
1. Typhoid fever
2. Bacterial meningitis
3. Anaerobic infections—*B. fragilis*
4. Rickettsiae.

Importantly, care is needed particularly to avoid fatal toxicities produced by chloramphenicol administration. However, this risk is not a contraindication for chloramphenicol in life-threatening infections.

**Contraindications**
1. Neonates and infants
2. Hypersensitivity
3. Pre-existing bone marrow depression.

**Drug Interactions**
1. Rifampicin reduces the plasma half-life of chloramphenicol
2. Chloramphenicol may reduce the efficacy of oral contraceptive pill
3. Chloramphenicol + alcohol—antabuse-like reactions may be seen.
POLYMYXINS

Polymyxins are basic polypeptide antibiotics, which are bactericidal used as topical antimicrobial drugs only. Polymyxins that are used commonly are:

- Bacitracin
- Tyrothricin
- Gramicidin
- Polymyxin-B

Polymyxins act by altering the bacterial membrane permeability and cause leakage of small molecules. Eventually, the bacteria die. These antibiotics do not interact with gram-positive microorganism cell membrane and resistance to polymyxins is rare.

Therapeutic Uses

Bacitracin is used topically with neomycin or corticosteroids in the treatment of local infections. Polymyxin-B is also employed to treat infection of skin, ear and eyes with other drugs.

Adverse Effects

Polymyxins when administered systemically produce dose-related major adverse effects on kidneys and nervous systems. Therefore, these are not to be given by systemic routes. Application of polymyxins to large areas of broken skin should be avoided.

GLYCOPEPTIDE ANTIBIOTICS

- Vancomycin
- Ramoplanin
- Teicoplanin
- Avoparclin

Vancomycin

Vancomycin is a bactericidal glycopeptide antibiotic. It is a bacterial cell wall synthesis inhibitor. Further, it is also known to inhibit bacterial RNA synthesis. Notably, it is an agent of choice to treat methicillin-resistant _Staphylococcus aureus_ (MRSA) infection and antibiotics-associated colitis caused by _Clostridium difficile_. Vancomycin is given by intravenous, intrathecal as well as oral route in pseudomembranous colitis. It can also be applied topically.

Vancomycin infusion is accompanied with ‘red neck or red man syndrome’ characterized by flushing, erythema, skin rash and shock-like syndrome with hypotension. It can cause irreversible hearing loss. Ototoxicity may be aggravated with concurrent use of aminoglycosides, loop diuretics and polymyxins. Hypersensitivity reactions and nephrotoxicity also occur with vancomycin. Vancomycin should be discontinued in patients who develop tinnitus.

NEWER ANTIBIOTICS

- Streptogramins
- Oxazolidinones

Streptogramins

Streptogramins are also known as synergists, which are generally used in multidrug-resistant infectious diseases, including methicillin-resistant _Staphylococcus aureus_ and vancomycin-resistant enterococci. Currently, the following streptogramins are used:
• Pristinamycin
• Quinupristin/Dalfopristin
• Virginiamycin

Streptogramins act by inhibiting bacterial protein synthesis. Quinupristin/dalfopristin are the semisynthetic derivatives of pristinamycin are given always together. Streptogramins are reserved for serious infections. Nausea, vomiting, myalgia, arthralgia, skin rash and pain at injection site are reported on administration of streptogramins.

**Oxazolidinones: Linezolid**

Oxazolidinones are useful in infections of skin and respiratory tract caused by multidrug-resistant microorganisms. These antibiotics can also be used in vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus*. These antibiotics act by inhibiting bacterial protein synthesis and bacteriostatic.

Linezolid inhibits monoaminoxidases and have potential interaction with adrenergic and serotonergic agonists. Linezolid is used in various multidrug-resistant infections and given by mouth. Diarrhoea, vomiting, headache, metallic taste, insomnia and reversible bone marrow suppression have been observed as linezolid adverse effects. Caution is necessary to use linezolid with other bone marrow suppressive drugs.
INTRODUCTION
Tuberculosis is a chronic infectious disease and an important cause of mortality and morbidity. Human tuberculosis is caused by *Mycobacterium tuberculosis* or *Mycobacterium africanum*. In AIDS patients as an opportunistic infection atypical tuberculosis is produced by *Mycobacterium kansasii* or *Mycobacterium avium*. Tuberculosis occurs ubiquitously and prevalence rate is on the rise largely due to AIDS virus infection. Lung is the first organ generally affected by tuberculosis. Infection is usually due to inhalation of infected droplet nuclei of the microorganism. Miliary type of tuberculosis is seen when the acid-fast bacilli disseminate into blood and tissues. Tuberculous meningitis, renal tuberculosis and skeletal tuberculous infection may be the result of dissemination of the organism. Virtually, any organ of the body may be involved. Drugs used in chemotherapy of tuberculosis are:

1. First line drugs: Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin
2. Second line drugs: Ofloxacin, ciprofloxacin, levofloxacin, ethionamide, cycloserine, amikacin, kanamycin, capreomycin

FIRST LINE ANTITUBERCULAR DRUGS
Antitubercular drugs are conveniently grouped into first line and second line drugs. First line drugs are the first choice agents, which have greater efficacy in all forms of tuberculosis with negotiable toxicity and good success rate. These include isoniazid, ethambutol, streptomycin, rifampin (rifampicin) and pyrazinamide.

Isoniazid (isonicotinic acid hydrazide—INH)
The most commonly used antitubercular drug worldwide in all forms of the disease is isoniazid. This is one of the most active drug and structurally similar to pyridoxine. Isoniazid acts against both intracellular and extracellular bacilli and the bactericidal action is remarkably selective to tuberculous bacilli.

The mechanism of action of isoniazid is complex. The basic action of isoniazid is to inhibit the biosynthesis of mycolic acids, an important constituent of bacterial cell wall. It is also known to inhibit desaturated enzyme of the bacteria. Mycolic acids are unique to mycobacterium, thus isoniazid antibacterial action is limited to these species.

Isoniazid is rapidly absorbed when given by mouth and readily distributed into body tissues. Acetylation is the major metabolic pathway of isoniazid. Acetylated products of isoniazid are excreted in urine. There is genetic heterogeneity with regard to the rate of acetylation of isoniazid. The human population shows bimodal variation in the rate of isoniazid metabolism. Accordingly, slow acetylators and rapid acetylators have been well recognized. Eskimos, Japanese and Chinese rapidly acetylate isoniazid. Slow isoniazid acetylators are North African Caucasians, Negroes, Indians, Jews and Scandinavians. For slow acetylators, isoniazid dosage can be reduced to avoid hepatotoxicity. It is needless to say that isoniazid dosage has to be titrated based on rate of acetylation to maximize efficacy and minimize toxicity.
Adverse Effects
Prominent adverse reactions produced by isoniazid are skin rash, fever, peripheral neuritis, jaundice, insomnia, restlessness, hyperglycemia, lymphadenopathy and hypersensitivity reactions. Isoniazid may precipitate convulsions in epileptic patients.

Pyridoxine is given along with isoniazid to avoid peripheral neuritis. Neuropathy is more frequently seen in slow acetylators with diabetes mellitus.

Isoniazid is contraindicated in epilepsy, hypersensitivity, porphyria and chronic alcoholism. Precaution is necessary for isoniazid therapy in diabetes mellitus.

Drug Interactions
1. Isoniazid + alcohol: The rate of isoniazid metabolism is increased.
2. Antacids reduce isoniazid oral bioavailability by reducing absorption.
3. Phenytoin toxicity is increased by isoniazid.

Rifampin (Rifampicin or Rifamycin)
Rifampin is a macrocyclic antitubercular and antileprotic antibiotic. It is bactericidal against a wide variety of microorganisms.

Antibacterial Spectrum
Rifampin is active against, Mycobacterium tuberculosis, Mycobacterium leprae, gram-positive staphylococci, gram-negative Neisseria meningitides, gonorrhoea, Haemophilus influenzae and legionella. It is also effective against Chlamydia trachomatis.

Rifampicin is having high sterilizing activity against Mycobacterium tuberculosis and leprae. It has the ability to eliminate semidormant and persistent organisms. However, resistance is observed in both tuberculosis and leprosy and to avoid resistance. Rifampicin is always given with other drugs.

Rifampicin is a nucleic acid synthesis inhibitor. It inhibits DNA-dependent RNA polymerase enzyme.

Rifampin is readily absorbed from gastrointestinal tract. Presence of food delays the absorption. It can cross placenta and appears in milk. Rifampicin is an enzyme inducer, stimulates its own metabolism. Desacetylrifampicin is excreted in bile and responsible for imparting harmless orange-red colour to urine and other body secretions.

Therapeutic Uses
Rifampin is usually given with other drugs in tuberculosis and leprosy to avoid the development of bacteria resistance and maximize the cure rate.

It is also used as a prophylactic agent in meningococcal meningitis. In brucellosis, chancroid chlamydial infections rifampicin has proven clinical value. Rifampicin is also effective in penicillin-resistant pneumococcal meningitis.

Adverse Effects
Rifampicin is a well-tolerated antibiotic and more commonly given intermittently. Yet, flue-like syndrome, cutaneous syndrome characterized by facial flushing, itching, rash and rarely
eye irritation, nausea and vomiting have been reported with rifampicin. Numbness, menstrual irregularities, jaundice, renal failure and hypersensitivity reactions have been observed with rifampicin.

Rifampicin is contraindicated in jaundice. It should not be given by intramuscular or subcutaneous route.

**Drug Interactions**

1. Rifampicin as an enzyme inducer decreases the efficacy of oral contraceptive pill. Hence, other forms of contraceptive measures to be advised to women of childbearing potential receiving rifampicin.
2. Since it increases the activity of hepatic drug metabolizing enzyme system, it alters the rate of concurrently administered drugs. Dosage adjustments of other drugs have to be considered to avoid uncertainties in either efficacy. Ketoconazole, steroids, digoxin, anticoagulants, protease inhibitors and reverse transcriptase inhibitors used in HIV dosage have to be modified with rifampicin combination therapy.

**Ethambutol**

Ethambutol is a first line antitubercular drug and effective against-resistant mycobacterium. It is used with other drugs to suppress emergence of bacterial resistance. Ethambutol is a bacteriostatic drug and acts by inhibiting the incorporation of mycolic acids into cell wall.

The most common adverse effect of ethambutol is optic neuritis with reduction in visual acuity. Green-red colour blindness may be seen. Pruritus, joint pain, metallic taste, teratogenicity, allergy and numbness and tingling sensation of fingers are the other adverse effects of ethambutol.

Ethambutol should not be used in children below eight years of age since young children fail to realize ethambutol-induced visual complications during early stages of therapy. It can precipitate the attacks of gout.

**Pyrazinamide**

Pyrazinamide is one of the primary drugs used in multidrug regimens for the treatment of tuberculosis. It is used in the initial 8 weeks of short course treatment. Often, reserved for retreatment regimens. Pyrazinamide is a bactericidal drug with maximum sterilizing activity.

The most common serious side effect of pyrazinamide is fulminating hepatitis. Hyperuricemia commonly occur with pyrazinamide therapy and precipitate gout. Toxic epidermal necrolysis cerebral edema, joint pain, fever and sideroblastic anaemia are also appear as adverse effects of pyrazinamide.

Pyrazinamide is contraindicated in patients with chronic liver disease and acute gout.

**Streptomycin**

Streptomycin is an aminoglycoside antibiotic and often used as a first line drug in the treatment of tuberculosis. It is not effective by oral route. Hence, always given by intramuscular injection in tuberculosis although painful and cumbersome. Streptomycin has similar antibacterial
spectrum of activity to that of gentamycin but *Pseudomonas aeruginosa* is-resistant, but effective against *Mycobacterium tuberculosis* in particular. It acts by inhibiting bacterial protein synthesis. Streptomycin is always given in combination with isoniazid, rifampicin and other drugs. Like other aminoglycosides, streptomycin is not absorbed across alimentary tract and, therefore, administered parenterally, more common intramuscularly. Ototoxicity, nephrotoxicity and neuromuscular junction adverse effects have also been observed with streptomycin. Drugs which are known to cause ototoxicity are not to be given with streptomycin for better toxicity profile. Besides, tuberculosis streptomycin is used in the treatment of plague, endocarditis and tuleremia.

**SECOND LINE DRUGS FOR TUBERCULOSIS**

Ethionamide, amikacin, capreomycin, cycloserine, kanamycin, ofloxacin, ciprofloxacin, levofloxacin

Generally, these drugs are used when the treatment fails or problematic with the first line drugs. Often, resistance and toxicity profile of first line drugs make way for the second line drugs administration in tuberculosis.

**Amikacin** is a semisynthetic aminoglycoside antibiotic and generally reserved for the treatment of severe infections. It is used along with other antimicrobials in many mycobacterium infections. It is generally given by intramuscular route. Amikacin is one of the commonly used drugs in multiple drug regimen for the treatment of *Mycobacterium avium* complex infections. Ototoxicity and nephrotoxicity have also been seen with amikacin. Auditory functions are more severely affected by amikacin than gentamicin.

**Cycloserine** is used as a part of multidrug regimen in the treatment of tuberculosis. It is used when resistance or toxicity to primary drugs has developed. Cycloserine is an inhibitor of bacterial cell wall synthesis. The common route of administration of cycloserine is oral. It readily crosses the placenta and appears in milk. Anxiety, confusion, suicidal tendencies, hyperreflexia, tremor and convulsions occur as adverse effects of cycloserine. Megaloblastic anaemia and heart failure have been occasionally reported with cycloserine therapy. Cycloserine is contraindicated in epilepsy, severe anxiety, psychoses and mental depression.

**Capreomycin** is a second line of bacteriostatic agent used in combination chemotherapeutic drug regimen for tuberculosis. It is administered by either intramuscular or intravenous route. Nitrogen retention, ototoxicity, nephrotoxicity, hypokalemia and hypersensitivity reaction are the adverse effects of capreomycin. This drug should not be used with other ototoxic and nephrotoxic drugs.

**Kanamycin** has been used in the multidrug regimen for tuberculosis as a second line drug. It is an aminoglycoside antibiotic with actions similar to gentamicin. Kanamycin is usually administered by intramuscular route. It is also an ototoxic and nephrotoxic agent. Malabsorption syndrome is reported with kanamycin therapy. Kanamycin should not be given orally in gastric ulcer patients.

**CHEMOPROPHYLAXIS FOR TUBERCULOSIS**

Tuberculosis is a curable infectious disease. The prevalence of tuberculosis worldwide is causing concern. The introduction of rifampicin with rapid bactericidal activity has changed the modalities of tuberculosis treatment. There are various chemotherapeutic dose regimens
Chemotherapy

that reduce the duration, development of resistance and cost of treatment. However, the choice of regimen depends on epidemiological data on resistance, availability of drug and medical supervision. Many countries have defined their own treatment protocols and have been formulating guidelines at regular time intervals to fight this disease.

Chemoprophylaxis for tuberculosis is recommended to prevent the spread of disease through the community. It should not be given as routine treatment. Prophylaxis is recommended for patients with asymptomatic tuberculosis infection to prevent the occurrence of acute tuberculosis and also AIDS patients. Isoniazid administration for 9 months is the preferred regimen for chemoprophylaxis of tuberculosis. Rifampicin and pyrazinamide-induced hepatitis precludes their use for the chemoprophylaxis of tuberculosis.
INTRODUCTION
Leprosy is caused by *Mycobacterium leprae*. It is a chronic disease that affects skin, peripheral nervous system and other tissues. The clinical manifestations of leprosy are due to deficient cell-mediated immunity. Keeping this in view, leprosy is referred to as either multibacillary or paucibacillary. Multibacillary as the name suggests, presents a large population of bacteria and is generally due to severe deficiency of cellular immunity. Paucibacillary leprosy results when cellular immunity is partially deficient. Antileprotic drug treatment regimens depend largely on clinical types of leprosy.

TYPES OF LEPROSY
Mainly, there are five clinical types of leprosy which include:
1. **Lepromatous leprosy**: Desseminate type, anergic, multiple skin lesions with anaesthesia, multibacillary
2. **Tuberculoid leprosy**: Single or few lesions, hair growth affected, lepromin test positive, paucibacillary
3. **Borderline leprosy**: Dimorphous, both tuberculoid and lepromatous lesions present.
4. **Borderline tuberculoid leprosy**
5. **Borderline lepromatous leprosy**: For these, lesions variable, may be no sensory loss, hypopigmented macules are present.

ANTILEPROTIC DRUGS
Leprosy is treated by multidrug therapy and the exact regimen employed is primarily determined by bacillary load. Importantly, the outlook of patients has been remarkably altered by successful chemotherapy. As with treatment of tuberculosis, the combination chemotherapy is essential to:
1. Reduce the survival of any drug-resistant strains
2. Increase efficacy and the cure rate and
3. Minimize the development of bacterial resistance as well as individual drug toxicity.

The duration and the efficacy of drug treatment is based on factors which include the type of leprosy and bacterial index. Generally, here the WHO guidelines have been followed to make the patient non-infectious at first and to reduce the severity of the disease. The principal aims of antileprotic drug treatment are to:
1. Render the patient non-infectious
2. Prevent bacterial multiplication
3. Avoid/treat lepra reactions and
4. Promote the healing of lesions and ulcers.
It is common that to eradicate bacteria from mucous membrane, skin and nerves, it will take years with prompt care and medical aid. Drugs used in leprosy are:

1. **Antileprotic drugs**: Dapsone, rifampicin, clofazimine, sulfadoxine, ethionamide, ofloxacin thiacetazone
2. **Drugs used in lepra reactions**: Aspirin, thalidomide, chloroquine, prednisolone, metronidazole

**Dapsone**

Dapsone is a sulphone antileprotic drug used as a part of multidrug regimen in all forms of leprosy. It is an antifolate drug. Dapsone acts by inhibiting bacterial folic acid synthesis. Primarily, dapsone is bacteriostatic agent and given by mouth. It undergoes enterohepatic circulation and appears in milk. The most common regimen employed for leprosy constitutes daily administration of 100 mg of dapsone with other drugs like clofazimine and rifampicin which are given once a month. The duration of dapsone treatment varies with the clinical type of leprosy. It may vary from two years to 10 years or life long.

**Adverse Effects**

Most frequently, varying degrees of dose related hemolysis and methaemoglobinemia occur with dapsone therapy. Skin rash, hyperpigmentation, hypersensitivity reactions, peripheral neuropathy, and anorexia are other adverse effects of dapsone. At times, life-threatening “**dapsone syndrome**” may occur presenting fever, hepatitis, exfoliative dermatitis, lymphadenopathy and anaemia as clinical manifestations.

**Therapeutic Uses**

1. Dapsone is the drug of choice for all types of leprosy.
2. It is also used as antimalarial drug particularly in chloroquine-resistant malaria.
3. Dapsone can be used in various types of dermatoses.

**Clofazimine**

Clofazimine is a phenazine dye used as an antileprotic drug of multiple drug regimen employed for multibacillary leprosy. It also produces anti-inflammatory action, which is useful in type II lepra reaction. It is given by mouth after food to facilitate its absorption. Clofazimine is given daily 50 mg with dapsone and 300 mg single dose once in a month with rifampicin 600 mg. Clofazimine is not usually given in paucibacillary leprosy, unless dapsone toxicity becomes intolerable.

**Adverse Effects**

A dose related most common adverse effect of clofazimine is red to brown skin discoloration, especially on areas exposed to sunlight. Nausea, abdominal pain and diarrhoea have been reported on chronic administration of clofazimine, discoloration of hair, tears, sweat, sputum, breast milk, urine and faces may occur on clofazimine therapy.
In leprosy patients, reactive episodes may be seen on drug treatment. These are known as “lepra reactions”. There are two types of lepra reactions—lepra reaction-I or reversal reaction and type II reaction known as “erythema nodosum leprosum”.

Type I reaction occurs in first 6 months of drug treatment seen in borderline and tuberculoid leprotic patients. These reactions are regarded as delayed hypersensitivity manifestations. Neuritis, edema in face, hands and feet are commonly seen. The reversal reaction during leprosy treatment is generally treated with aspirin and other analgesics. In severe neuritis glucocorticoid administration will prevent permanent nerve damage.

Erythema nodosum leprosum is usually observed in lepromatous leprosy patients on drug treatment. This is thought to be the consequence of immune injury and reaction is due to type III hypersensitivity to toxins liberated following the death of bacteria. Erythema may be seen anywhere on the skin associated with fever, malaise, neuritis, orchitis, iridocyclitis, arthritis, proteinuria and lymphadenopathy. Antileprotic drug treatment must be continued to avoid resistance. Type II lepra reaction is managed with administration of thalidomide and clofazimine with glucocorticoids in severe reaction episodes.

**Paucibacillary Leprosy**

Drugs recommended for paucibacillary leprosy are rifampicin once monthly and dapsone daily for 6 months and to be continued till skin test negatively is achieved.

**Multibacillary Leprosy**

Three drugs regimen is recommended for multibacillary leprosy. The standard dose of rifampicin and clofazimine is given once in a month and dapsone with small dose of clofazimine daily for 12-14 months. Treatment is to be continued over years to prevent relapse. There are efforts worldwide for the elimination of leprosy as a public health problem. However, full control of leprosy throughout the world has not been attained yet.
CHEMOTHERAPY OF MALARIA

INTRODUCTION
Malaria is one of the most serious protozoan infections and now it is a global crisis. The infection is caused by any of the four species of *Plasmodium*.

- *Plasmodium falciparum*: Malignant malaria can be fatal
- *Plasmodium vivax*: Relapsing malaria
- *Plasmodium ovale*: Less common type, ovale tertian
- *Plasmodium malariae*: Quartan malaria

The life cycle of *Plasmodium* is complex. Mainly, *Plasmodium* life cycle consists of two phases: sexual phase (sporogony) and asexual phase (schizogony) (Table 13.3).

<table>
<thead>
<tr>
<th>Table 13.3: Life cycle of malarial parasite</th>
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<tbody>
<tr>
<td><strong>Mosquito</strong></td>
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<tr>
<td>Sporogony</td>
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<tr>
<td>Oocytes</td>
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<td>Sporozoites</td>
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</table>

The clinical manifestations of malaria are varied and non-specific. Fever, headache, fatigue, malaise, myalgia, sweating, shivering chill, anaemia, haemolysis, pulmonary edema, cerebral dysfunction including convulsions have been commonly seen with malarial infection. Identification of malarial parasite in blood sample confirms the diagnosis.

ANTIMALARIAL DRUGS
Drugs used in the treatment of malaria are classified into two types based on clinical and chemical nature.

**Clinical Classifications of Antimalarials**
1. Blood schizonticides (clinical curatives or suppressives): Chloroquine, quinine
2. Tissue schizonticides (causal prophylactics) (radical curatives): Pyrimethamine, primaquine
3. Gametocidal drugs: Chloroquine, quinine
4. Sporonticides: Chloroguanide, pyrimethamine

**Chemical Classification**
1. Cinchona alkaloids: Quinine
2. 4-aminoquinolines: Chloroquine, amodiaquine, hydroxychloroquine
3. 8-aminoquinolines: Primaquine, quinoclide
4. Acridines: Mepacrine
5. Diaminopyrimidines: Pyrimethamine, trimethoprim
6. Biguanides: Proguanil
7. Sesquiterpines (terpene lactones): Artemisinin derivatives: artesunate, artemether, arteether
8. Others: Mefloquine, dapsone, sulphadoxine, tetracycline, doxycycline, clindamycin, atovaquone

Since malaria is a serious and potentially fatal disease, falciparum malaria in particular, requires prompt and effective drug therapy. Treatment is usually started with a blood schizonticidal drug to suppress or attain clinical cure. This is usually followed with radical cure therapy with primaquine particularly for vivax malaria. Chloroquine is primarily used as blood schizonticidal drug to control clinical manifestations. If resistance to chloroquine is observed, drugs like artemisinin, dapsone, mefloquine, doxycycline, pyrimethamine with sulphadoxine or any other agents can be used.

**Chloroquine**

Chloroquine is a 4-aminoquinoline, blood schizonticidal, antimalarial drug. It is also an antirheumatic, antiinflammatory and antiamoebic agent. As antirheumatic, hydroxychloroquine is preferably used as it is long acting and appears to be less toxic.

**Chloroquine as Antimalarial Agent**

As antimalarial agent, chloroquine kills erythrocytic forms of *Plasmodium*. It acts as blood schizonticide, controls parasitemia and completely cures falciparum malaria. Chloroquine does not prevent relapse of vivax malaria. The patients become completely afebrile within 24 hours. However, resistance to chloroquine antimalarial action is reported worldwide in many countries. Chloroquine-resistant malaria is not easy to treat, although mefloquine, quinine and many other drugs offer rescue.

**Mechanism of Action**

The exact mechanism of action of chloroquine remains obscure. It is believed to act by inhibiting nucleic acid synthesis. Chloroquine increases the intracellular pH to inhibit lysosomal degradation.

More commonly, chloroquine is given by oral route. It has a large volume of distribution since it is sequestrated in liver, spleen, lung and kidney. The plasma half-life of chloroquine is more than 150 days.

**Adverse Effects**

Nausea, vomiting, headache, visual disturbances, irreversible retinopathy toxic myopathy, and peripheral neuropathy corneal opacities are the adverse effects of chloroquine. Chloroquine is not recognized as teratogenic and can be given during pregnancy although hearing and vision of neonate is at stake.

**Therapeutic Uses**

Chloroquine is a useful drug in:
1. Malaria
2. Hepatic amoebiasis
3. Photosensitivity reaction
4. Systemic lupus erythematosus

**Drug Interaction**

1. Chloroquine + metronidazole: Acute dystonic reactions are likely to occur
2. Chloroquine + amiodarone: Increased cardiac arrhythmias have been observed

**Primaquine**
Primaquine is 8-aminoquinolone antimalarial drug. It is a tissue schizonticide as well as gametocidal agent. Primaquine produces radical cure in vivax malaria. Since primaquine kills hepatic forms of *Plasmodium* both tissue schizonts and hypnozoites, it prevents relapse of vivax malaria. Primaquine has no other actions and should not be used for acute attack of malaria. Most commonly, primaquine is given by oral route.

Primaquine is an innocuous antimalarial agent. However, primaquine sensitivity in G-6-PD deficient individuals can cause mortality. In these subjects primaquine produces haemolytic anaemia. Large doses may cause methaemoglobinemia.

Primaquine is gametocidal against *Plasmodium falciparum*. Hence, it is also employed for falciparum malaria in view of keeping the patient non-infective. Primaquine prevents parasite transmission.

**Pyrimethamine**
Pyrimethamine is an antimalarial drug that belongs to diaminopyrimidine group. It is used in the prevention and to cure malarial infection. Pyrimethamine is given with sulphadoxine in chloroquine-resistant malaria. Pyrimethamine is an antifolate drug which acts by inhibiting dihydrofolate reductase enzyme and thereby blocks plasmodial DNA synthesis. Generally, pyrimethamine is given by mouth with sulphadoxine both in malaria and toxoplasmosis.

Nausea, vomiting, abdominal pain, skin rash, depression of haematopoiesis and thrombocytopenia have been observed as adverse effects of pyrimethamine.

Pyrimethamine should not be given to patients with megaloblastic anaemia due to deficiency of folic acid.

**Mefloquine**
Mefloquine is a blood schizonticidal antimalarial agent used in chloroquine-resistant malaria due to *Plasmodium falciparum*. It is administered only by oral route as single or two split doses. Mefloquine is well tolerated. The plasma half-life of mefloquine is 19-21 days. It enjoys extensive enterohepatic circulation. The major route of elimination is faeces.

Nausea, vomiting, insomnia, loss of balance, sensory and motor neuropathies, tremor, ataxia and emotional instability are the adverse effects of mefloquine.

Mefloquine is contraindicated in patients with psychosis and mental depression.

**Artemisinin**
Artemisinin is an alkaloid obtained from a Chinese plant Quinghaosu. It is a blood schizonticide antimalarial drug used in chloroquine-resistant malaria. It acts rapidly and
is commonly administered by oral route. Artemisinin and its derivatives artemether and sodium artesunate can also be used in both chloroquine sensitive and-resistant malaria. These drugs are well tolerated although there have been reports of mild gastrointestinal tract disturbances. The safety of artemisinin derivatives in pregnancy is yet to be elucidated.

**Quinine**

Quinine is obtained from cinchona bark. It is a rapidly acting antimalarial which kills blood schizonts. Quinine is a gametocidal drug. The exact mechanism of action of quinine is not yet elucidated. Quinine may interfere with lysosomal function and nucleic acid synthesis.

Quinine is used to treat chloroquine-resistant malaria and given intravenously in cerebral malaria. For the treatment of non-complicated malaria, quinine is given by mouth. The plasma half-life of quinine is 11 hours. Quinine crosses placenta and appears in bile, saliva and milk. Quinine has mild analgesic, antipyretic and oxytocic actions.

Administration of quinine may produce a wide variety of adverse effects. Hypoprothrombinemia, hypoglycemia, cinchonism (tinnitus, impaired hearing, vomiting), blurred vision, hemolysis, black water fever—haemoglobulinuria, sludging and hypersensitivity reactions are seen as quinine adverse effects.

Quinine is also used in the management of nocturnal leg cramps.

Quinine is contraindicated in conditions of hemolysis, optic neuritis, tinnitus and myasthenia gravis.

Quinine and mefloquine combination may cause convulsions. Arrhythmogenic drugs like amiodarone, astemizole and cisapride precipitate cardiac arrhythmia with quinine.

**Drugs Used in Acute Malaria**

1. **Falciparum malaria**
   a. Chloroquine: Total dose 1.5 g base. To start with 600 mg; after 6-8 hours 300 mg; 24 hours 300 mg and 48 hours 300 mg
   b. Chloroquine-resistant malaria:
      i. Quinine with pyrimethamine + sulphadoxine or doxycycline  
         Or
      ii. Mefloquine  
         Or
      iii. Atovaquane + proguanil
2. **Vivax malaria**
   a. Chloroquine: Total dose 1.5 g dose spread over 48 hours
   b. Primaquine: 45 mg to start (for radical cure) 15 mg/day for 6-14 days
3. **Prophylaxis of malaria**
   a. Chloroquine (300 mg dose once weekly start two weeks before and continue for 4 weeks after return from malarial endemic area)  
      Or
   b. Mefloquine  
      Or
   c. Pyrimethamine + Dapsone
INTRODUCTION

A large proportion of human populations in tropical regions have been affected by worm infection of different kinds. In developing countries, worm infestation is an important issue of public health. Improvement in public hygiene measures, awareness to avoid contamination of food preparations, and use of chemotherapeutic agents are the effective methods to control worm infestations.

The worms that cause infestations in man belong to the phylum platyhelminthes and nematoda. Hence, the name anthelmintic is given to designate drugs used in worm infestations.

DRUGS FOR ASCARIASIS (ROUNDWORM INFESTATION)

Pyrantel pamoate, albendazole, mebendazole, piperazine

Ascariasis is caused by Ascaris lumbricoides (roundworm). It is usually an infestation of small intestine. Anorexia, abdominal pain, and diarrhoea with nutritional deficiency are the major clinical features of roundworm infestation. Drug of choice to treat ascariasis is mebendazole or albendazole. Pyrantel pamoate is an alternative drug (Table 13.4).

ANCYLOSTOMIASIS (HOOKWORM INFESTATION)

Mebendazole, albendazole, pyrantel pamoate

Ancylostomiasis is caused by Ancylostoma duodenale and Necator americanus. Iron deficiency anaemia is usually associated with hookworm infestation. Abdominal pain, weight loss, and diarrhoea are the major clinical features of ancylostomiasis. Mebendazole or albendazole have been used as drug of choice to treat hookworm infestation.

TAENIASIS (TAPEWORM INFESTATION) AND CYSTICERCOSIS

Niclosamide, albendazole, praziquantel

Taeniasis is caused by either beef tapeworm Taenia saginata or pork tapeworm Taenia solium. Single dose of praziquantel is the treatment of choice for taeniasis.

Cysticercosis is a systemic infection caused by the larval form of Taenia solium. Invasion of brain by these larvae is known as neurocysticercosis. Praziquantel with prednisolone administration is the treatment of choice although albendazole has been used.
**Table 13.4**: Drugs used for various worm infestations

<table>
<thead>
<tr>
<th>Name of the worm</th>
<th>Agent of choice</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
<th>Alternate drug</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascariasis (roundworm)</td>
<td>Albendazole</td>
<td>Blocks glucose uptake</td>
<td>Headache, insomnia, epigastric discomfort Anorexia, nausea skin rash</td>
<td>Mebendazole</td>
<td>Treatment may be repeated after 2 weeks</td>
</tr>
<tr>
<td>Pyrantel pamoate</td>
<td>Induce worm muscle paralysis</td>
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<td></td>
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<tr>
<td>Enterobiasis (pinworm)</td>
<td>Mebendazole</td>
<td>Irreversible block of glucose uptake</td>
<td>Abdominal discomfort</td>
<td>Prazantel pamoate</td>
<td>Mebendazole is contraindicated in pregnancy. Repeat the dose after 4 weeks</td>
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</tr>
<tr>
<td>Ancylostomiasis (hookworm)</td>
<td>Albendazole</td>
<td>Blocks glucose uptake</td>
<td>Insomnia, headache</td>
<td>Mebendazole, pyrantel pamoate</td>
<td>Repeat the treatment after 6 weeks</td>
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<tr>
<td>Strongyloidiasis (threadworm)</td>
<td>Ivermectin</td>
<td>Augment GABA action to produce paralysis of worm</td>
<td>Pruritus, fever, muscle pain</td>
<td>Albendazole, thiabendazole, mebendazole</td>
<td>Ivermectin is also effective in onchocerciasis</td>
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<tr>
<td>Taeniasis (tapeworm)</td>
<td>Praziquantel</td>
<td>Interferes with influx of calcium sensitization of larva for phagocytosis, aldicidial effect</td>
<td>Vomiting, abdominal discomfort Lightheadedness, pruritus</td>
<td>Albendazole</td>
<td>Praziquantel is effective in cysticerciasis</td>
</tr>
<tr>
<td></td>
<td>Niclosamine</td>
<td>Inhibits mitochondrial oxidative phosphorylation</td>
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<tr>
<td>Filariasis (elephantiasis)</td>
<td>Diethyl-carbamazine</td>
<td>Sensitization of larva for phagocytosis, filaricidal effect</td>
<td>Headache, weakness, dizziness, drowsiness, hypersensitivity reactions</td>
<td>Ivermectin</td>
<td>Also used in tropical eosinophilia</td>
</tr>
</tbody>
</table>
ENTEROBIASIS (PINWORM INFESTATION)
Albendazole, pyrantel pamoate

Enterobiasis is common in children and caused by Enterobius vermicularis. Perianal itching is a common symptom of enterobiasis. Albendazole or mebendazole or pyrantal pamoate is used for enterobiasis.

FILARIASIS (ELEPHANTIASIS)
Diethylcarbamazine, ivermectin

Filarialiasis is the result of infection produced by Wuchereria bancrofti or Brugia malayi or Brugia timori. This is a mosquito-borne disease. Adult and immature worms produce inflammatory reactions in the lymphatic system with fever. The main clinical features are lymphoedema, elephantiasis, chyluria and hydrocele. Tropical eosinophilia characterized by cough, wheezing and eosinophilia is a clinical variant of bancroftian filariasis.

Diethylcarbamazine is the agent of choice to treat filariasis. Ivermectin is also used particularly in conditions associated with loiasis or onchocerciasis.

SCHISTOSOMIASIS
Praziquantel, niclosamide, metrifonate, oxamniquine

Schistosomiasis is an infection caused by S. mansoni, S. japonicum, and S. haematobium. Fever, fatal illness resembling serum sickness, granuloma deposition and fibrosis in lung, liver intestine, and urinary tract have been the clinical manifestations of schistosomiasis.

Praziquantel is effective against all species of schistosomes. Metrifonate or oxamniquine are used as alternative drugs.

STRONGYLOIDIASIS (THREADWORM INFESTATION)
Ivermectin, albendazole, thiabendazole, mebendazole

Strongyloidiasis is an infection of small intestine caused by Strongyloides stercoralis (threadworm). The larvae migrate to lungs and skin rash, pneumonitis, bronchospasm, colicky pain, diarrhoea, vomiting and weight loss are the clinical features of threadworm infestation.

Ivermectin is the best choice of drug for the treatment of strongyloidiasis. Thiabendazole, albendazole and mebendazole are also useful.
INTRODUCTION

In the past six decades, drug therapy for malignant diseases has remained as a real challenge to science. The nature and approach of drug treatment for cancer is rapidly changing with time. Now, most of the cancer diseases are being cured with drug treatment given with or without radiation therapy. Nevertheless, as yet for large varieties of neoplastic diseases, therapy remains unsuccessful. Multidrug resistance is a real problem. However, worldwide scientists are making an all out effort to reduce the development resistance to anticancer drugs. Much remains to come.

Cancer chemotherapy is more effective, when tumour growth rate is high. Therefore, if cancer is detected at early stages, drug treatment is more successful. Further, there is every need to elucidate the mechanisms involved in regulation of cell multiplication and apoptosis (programmed cell death) more comprehensively. If this is achieved, more accurate treatment strategies can be readily designed to contain malignant diseases.

What causes cancer? No convincing answer from science as yet. A plethora of factors seem to be involved in the genesis of cancer. Mutation that occur in protooncogenes, deletion of tumor suppressor genes, viral invasion, ionizing radiation, smoking, environmental pollution, high fat diet, UV (ultraviolet rays) radiation and lifestyle pattern contribute substantially for the origin of cancer. Unfortunately, the biochemistry of cancer and normal cell is same. This further adds to the misery produced by chemotherapy of cancer. Cancer chemotherapy usually involves administration of cytotoxic drugs. These drugs affect both cancer and normal cell without any difference. As a result, normal cell multiplication will be at stake. Accordingly, organ toxicity profiles of anticancer drugs are always high. In short, anticancer drugs are rarely selective in their cytotoxic action.

Anticancer drug treatment must aim at attaining cure and prevention of relapse. The popular belief is that 50% of cancers can be cured by the modalities of treatment available currently. To achieve this, early diagnosis of cancer is of immense value. Various modalities of treatments considered for cancer are—(1) chemotherapy, (2) radiation, (3) surgery, (4) immunotherpy, and (5) gene therapy.
The success of cancer chemotherapy depends on the type of tumour and its stage of development. Nonetheless, the cost of chemotherapy is pretty high and the socio-economical background of patients plays a decisive role in saving the life.

CLASSIFICATION

A wide variety of drugs have been used as anticancer agents. These are classified into the following groups.

1. Alkylating—DNA damaging drugs—subdivided into:
   a. Nitrogen mustard: Mechlorethamine, chlorambucil, cyclophosphamide, ifosfamide
   b. Alkylsulfonate: Busulphan
   c. Nitrosoureas: Carmustine, lomustine, semustine, streptozotocin, chlorozotocin
   d. Aziridines: Hexamethylmelamine, thiopeta
   e. Triazenes: Dacarbazine, Procarbazine
   f. Platinum-coordinated complexes: Cisplatin, carboplatin (non-classical alkylating agents)

2. Antimetabolites
   a. Folic acid antagonist: Methotrexate
   b. Purine antimetabolites: 6-mercaptopurine, thioguanine, pentostatin
   c. Pyrimidine antimetabolites: 5-fluorouracil, cytosine arabinoside

3. Antibiotics: Doxorubicin, daunorubicin, dactinomycin, plicamycin, bleomycin, mitomycin, idarubicin, epirubicin

4. Natural products:
   a. Alkaloids:
      i. Vinca alkaloids: Vincristine, vinblastine
      ii. Paclitaxel
      iii. Epipodophyllotoxins: Etoposide, teniposide
      iv. Homoharringtonine
   b. Enzyme: L-asparaginase
   c. Biological: Monoclonal antibodies, interferons, BCG vaccine, interleukins, tumour necrosis factor

5. Hormones
   a. Glucocorticoids: Prednisone, prednisolone
   b. Androgen: Testosterone
   c. Estrogen: Ethinyl estradiol

6. Hormone antagonists
   a. Antiestrogen: Tamoxifen
   b. Antiandrogen: Flutamide
   c. GnRH analogues: Leuprolide, goserelin, buserelin

7. Other drugs: Hydroxyurea, radioactive isotopes, octreotide, angiostatin, mitoxantrone, topotecan, irinotecan, endostatin, antisense oligonucleotides

8. Toxicity protectives: Mesna, biphosphonates, amifostine, dexrazoxane

GENERAL ADVERSE EFFECTS OF ANTICANCER DRUGS

Anticancer drugs affect all the tissues where cell division is fairly rapid. The action of anticancer drugs is not selective for cancer cell. Therefore, adverse effects produced by antineoplastic agents are quite alarming and may force the withdrawal although it is not possible to discontinue the therapy. Adverse effects seen with anticancer drugs are generally the extension of their therapeutic action.

Bone marrow, lymphoid tissue, gastrointestinal mucosa, skin, gonads and fetus are more vulnerable for anticancer drug toxicity.

The acute adverse reactions produced by anticancer agents are nausea and vomiting, sometimes very severe. Many cytotoxic drugs are irritants, extravasation produces local pain, irritation inflammation, ulceration and necrosis. Further, the incidence of anticancer drug-induced serious vomiting depends on drug (cisplatin, dacarbazine), route of administration, dose and treatment schedule. To control vomiting due to cancer chemotherapy, antiemetics like 5-HT3 antagonists like ondansetron and lorazepam, dexamethasone have been employed either alone or in combination. Anorexia, mucositis, tracheitis and stomatitis are also seen commonly.

Cytotoxicity—Myelosuppression

Anticancer drugs produce bone marrow suppression (myelosuppression), which often limits their doses. Leucopenia and thrombocytopenia are readily seen and for which intensive supportive care is essential. There are various means and methods to contain myelosuppression produced by anticancer drugs. The doses of drugs can be given keeping wide time interval such as “pulse therapy” is often employed to reduce cytotoxicity. Administration of colony-stimulating factors and erythropoietin is recommended to increase stem cell proliferation. Recovery from myelosuppression may take a few months. Busulphan and lomustine, vinblastine suppress bone marrow which may force discontinuation of treatment and/or adjustment of dose with changes in frequency of administration.

Tumour Lysis Syndrome

Rapid destruction of a large number of cells caused by anticancer drugs produce this syndrome. Hyperuricemia, acute renal failure, hyperkalemia, hyperphosphatemia and hypercalcemia are the features of tumour lysis syndrome. Administration of allopurinol, adequate hydration and alkalization of urine can prevent clinical symptoms of tumour lysis syndrome.

Immunosuppression

Many drugs used for cancer treatment have immunosuppresant action, for example, cyclophosphamide and methotrexate. Consequently, patient’s resistance to infection decreases giving rise to complications and second malignancies may occur. Aspergillosis, viral invasion and pneumonia due to Pneumocystis carinii may be seen after a few months.

Carcinogenicity

Following anticancer drug therapy, the patient may develop new neoplastic disease. This is known as “second malignancy”. Non-lymphoid leukemia and bladder cancer may be seen with procarbazine, lomustine, teniposide and cyclophosphamide therapy respectively.
Mutagenicity
Anticancer drugs by causing chromosomal breakage induce mutagenicity. Alkylating agents cause mutation and related changes more often than any other groups of anticancer drugs. Since most of the anticancer drugs are potentially mutagenic and teratogenic, they are contraindicated in pregnancy in the first trimester in particular.

Thromboembolism
Multidrug cancer chemotherapeutic treatment is not without cardiovascular adverse effects. Deep vein thrombosis, pulmonary embolism and stroke have been reported with fatal outcome. Evidently, cancer chemotherapy itself elevates coagulant activity in patients, which can be reduced by heparin and warfarin.

Megaloblastic anaemia is seen with hydroxyurea and cytarabine. High doses of cyclophosphamide may cause congestive cardiac failure. Angina pectoris may be produced by fluorouracil, which commonly progresses to myocardial infarction.

Organ Specific Toxicities
Some anticancer drugs produce organ specific toxicities suggesting that it is not related to their therapeutic action. Often, these adverse effects may be the result of hypersensitivity reactions. However, this needs more supporting evidence. Organ specific toxicities seen with anticancer drugs include the following.

Lung
Agents used in chemotherapy of cancer do produce lung injury. Pulmonary fibrosis is seen with bleomycin, busulphan, mitomycin and methotrexate.

Kidney
Nephrotoxicity is produced by methotrexate and cisplatin. Hence, these drugs are not to be recommended for use with other nephrotoxic drugs.

Urinary Bladder
Hemorrhagic cystitis has been recognised as cyclophosphamide and ifosfamide-induced organ toxicity. Busulphan, chlorambucil and mitomycin also affect urinary bladder function. MESNA is used to cover haemorrhagic cystitis produced by cyclophosphamide and ifosfamide.

Ototoxicity
Cisplatin causes ototoxicity. Therefore, combination of cisplatin with loop diuretics and aminoglycoside antibiotics is not recommended.

Liver
Azathioprine, asparaginase and plicamycin produce hepatotoxicity. Care is necessary when these agents are combined with other hepatotoxicity inducing drugs.
Nervous System
Many anticancer drugs produce neurotoxicity. Vincristine, asparaginase, methotrexate, cisplatin, chlorambucil and hydroxyurea are known to cause neuropathy and convulsions may be rare.

Skin
Hair loss (alopecia) is one of the common adverse effects of anticancer drugs. Regrowth of hair occurs after the treatment is over. Nithosoureas, paclitaxel, cyclophosphamide induce alopecia. Hyperpigmentation of skin is seen with alkylating agents and some anticancer antibiotics. Bleomycin produces hypersensitivity and hyperkeratotic skin lesions.

Gonads
Azoospermia, abortion, loss of libido and infertility have been observed with anticancer drugs. Chlorambucil is known to cause sterility.

Fetotoxicity
Women of reproductive phase must be advised to postpone the pregnancy till the anticancer drug regimen is completed. Alkylating agents and antimetabolites are teratogens. Spontaneous abortion and malformation of fetus is as high as 70% with cytotoxic drugs. Hence, termination of pregnancy is always suggested to women who receive radiation and/or chemotherapy for neoplastic diseases.

Heart
Doxorubicin and daunorubicin anthracycline anticancer antibiotics produce major dose-limiting cardiotoxicity. Cardiomyopathy produced by these antibiotics is often fatal.

Cyclophosphamide at high doses produces congestive cardiac failure and hemorrhagic cardiac necrosis.

Flurouracil is known to be associated with angina pectoris and myocardial infarction.

Pancreas
L-asparaginase produces pancreatitis and streptozotocin is diabetogenic.

Bone
It is reported that anticancer drugs produce a vascular necrosis of bone. Male cancer patients appear to be more susceptible for bone toxicities caused by anticancer drugs.

The aims of modern cancer treatment are many. One such aim is to attain cure and prevent suffering. Cytotoxic drugs are potentially toxic. To minimize the toxicity caused by anticancer drugs, various means and methods have been developed. Administration of drug doses in pulses, periodical evaluation for toxicity, modification of dose regimens and use of other drugs that prevent toxicities are established to reduce antineoplastic drug toxicity.
ALKYLATING AGENTS

Alkylating agents are capable of introducing alkyl groups into nucleophilic sites on other molecules through the formation of covalent bonds. These are antimitotic anticancer drugs, which cause DNA damage. Besides, alkylating agents are mutagenic, carcinogenic and immunosuppressants. Often alkylating agents are described as polyfunctional (nitrosoureas and busulphan) monofunctional and nonclassical types (procarbazine).

Mechanism of Action

The cytotoxic alkylating agents cross-link DNA, cause mispairing, chain scission and depurination eventually leading to cell death. On administration, alkylating agents liberate “carbonium” ions, which bind to 7-nitrogen of guanine residue of DNA thus leading to mispairing and chain scission causing cell death.

Nitrogen Mustards

Mechloethamine, chlorambucil, cyclophosphamide, ifosfamide

Nitrogen mustard alkylating agents have a wide spectrum of activity in lymphomas including Burkitt’s lymphoma, chronic leukemias, ovarian cancer sarcomas, neuroblastima, carcinoma of cervix and bladder and as antirejection drugs in transplantation surgery.

Oral cyclophosphamide is given in severe rheumatoid arthritis and childhood nephrosis. Mechloethamine is indicated in Hodgkin’s disease, chlorambucil in chronic lymphocytic leukemia by mouth.

Nitrogen mustard alkylating agents are capable of producing severe adverse effects. Bone marrow suppression, alopecia, amenorrhoea, inhibition of oogenesis, spermatogenesis, and sterility and induce second malignancies. Cyclophosphamide is a leukemogenic drug. Cyclophosphamide and ifosfamide produce haemorrhagic cystitis and their toxicity can be reduced by MESNA administration, maximum hydration and other supporting measures.

Nitrosoureas

Carmustine, lomustine, semustine, streptozotocin

Nitrosoureas are alkylating agents used in the treatment of brain tumours, multiple myeloma and-resistant Hodgkin’s lymphoma. These are also given in combination with other anticancer drugs for the management of solid tumours. Bone marrow depression is the most serious side effect of nitrosoureas. These are potentially carcinogenic, mutagenic and teratogenic.

Busulphan

Busulphan is an alkyl sulphonate bifunctional alkylating agent. It is well absorbed by oral route and drug of choice to treat chronic myeloid leukemia. Busulphan has selective bone marrow toxicity at therapeutic dose level, reduces granulocyte count. However, at larger doses cause severe bone marrow depression. Busulphan is also used prior to bone marrow transplantation. Hyperpigmentation, pulmonary fibrosis and gynecomastia are observed with busulphan therapy.
## Miscellaneous Alkylating Agents (Table 13.5)

### Table 13.5: Miscellaneous alkylating agents used in neoplastic diseases

<table>
<thead>
<tr>
<th>Name</th>
<th>Route of administration</th>
<th>Uses</th>
<th>Major adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiotepa</td>
<td>IV, IM, intralesional, intrathecal</td>
<td>Urinary bladder tumour to control effusions</td>
<td>Myelosuppression</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>IV</td>
<td>Metastatic melanoma sarcomas</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe emesis</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Oral</td>
<td>Hodgkin’s disease</td>
<td>Leukopenia</td>
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<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Neurotoxicity</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>IV</td>
<td>Islet carcinoma</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinoid syndrome</td>
<td>Diabetogenic</td>
</tr>
<tr>
<td>Chlorozotocin</td>
<td>IV</td>
<td>Pancreatic endocrine tumour</td>
<td>Toxic to kidney</td>
</tr>
</tbody>
</table>

## ANTIMETABOLITES

Antimetabolites are the structural analogues of physiologically occurring substances that compete with metabolites for various pathways of metabolism and produce deficiency of metabolites in a biological system. Antimetabolites have special place in producing remission in leukemias and solid tumours. Currently, three types of antimetabolites have been used which include:

1. **Folic acid antagonists:** Methotrexate, trimetrexate
2. **Purine antagonists:** 6-mercaptopurine, thioguanine, pentostatin, azathioprine
3. **Pyrimidine antimetabolites:** 5-fluorouracil, cytarbine (cytosine arabinoside).

### Folic Acid Antagonist

**Methotrexate**

Methotrexate is an antifolate, antineoplastic and immunosuppressant drug. Methotrexate acts by inhibiting dihydrofolate reductase. As a result, de novo synthesis of purines and pyrimidines ceases. Hence, no DNA synthesis occurs leading to cell death.

Methotrexate is used in choriocarcinoma, acute lymphoblastic leukemia, Burkitt’s lymphoma, breast carcinoma, osteogenic sarcoma and also in non-Hodgkin’s lymphoma. The nonneoplastic indications of methotrexate include psoriasis, rheumatoid arthritis and other cell-mediated immune diseases.

The common adverse effects of methotrexate are on the bone marrow, gastrointestinal tract, kidney and liver. Leucopenia, thrombocytopenia and anaemia may occur abruptly. Ulcers in the mouth, stomatitis, diarrhoea, hemorrhagic enteritis and intestinal perforation may occur. Hepatic fibrosis and cirrhosis caused by methotrexate is often a cause for death of patient. Renal tubular necrosis on high doses of methotrexate is common. Methotrexate induces megaloblastic anaemia. It may cause defective oogenesis and spermatogenesis and infertility.

Folinic acid (tetrahydrofolate) is always recommended to neutralize toxic effects of methotrexate on bone marrow. This is called ‘folinic acid rescue’ or ‘leucovorin rescue’.

Alkalization of urine must be maintained with adequate hydration to prevent methotrexate-caused renal tubular necrosis.

Methotrexate is a potent teratogen and should not be used in pregnancy.
Purine Anti-Metabolites
6-mercaptopurine, azathioprine, thioguanine, pentostatin

6-mercaptopurine
Mercaptopurine is a purine antimetabolite used generally with other drugs to induce remissions in acute lymphoblastic and myeloid leukemias. It produces delayed bone marrow depression and sometimes fatal hepatotoxicity. Allopurinol, an inhibitor of xanthine oxidase, enhances the toxicity of mercaptopurine, which can be reduced by decreasing the doses of mercaptopurine.

Azathioprine
Azathioprine is mainly used as an immunosuppressant in transplantation surgery, autoimmune diseases including myasthenia gravis. Azathioprine is given by mouth. Hepatotoxicity is reported with this purine antimetabolite and bone marrow toxicity is also seen. This drug should not be used in pregnancy. Azathioprine is known to have corticosteroid sparing effect.

Pyramidine Antimetabolites
Cytosine Arabinoside (cytarabine)
Cytarbine is used for induction of remission in acute myeloid leukemia. It acts by inhibiting DNA polymerase and prevents DNA chain elongation. Cytarabine is a potent myelosuppressant. Nausea, vomiting and stomatitis are the common adverse effects produced by cytarabine.

ANTICANCER ANTIBIOTICS
Anthracycline antibiotics, dactinomycin, bleomycin, plicamycin, mitomycin

Anthracycline Antibiotics
Doxorubicin (adriamycin), idarubicin, daunorubicin, epirubicin
Several anthracycline antibiotics are used in many types of neoplastic diseases. These are potent cytotoxic drugs. Cardiotoxicity has been a major adverse effect that limits the use of anthracycline antibiotics. Almost all these antibiotics produce some degree of cardiotoxicity. Therefore, anthracycline antibiotics are generally contraindicated in patients with heart disease.

Mechanism of Action
Doxorubicin-like antibiotics used in cancer act by several mechanisms. These antibiotics “intercalate” DNA and thus inhibit DNA synthesis as well as DNA-dependent RNA synthesis. In addition, anthracycline antibiotics generate free radicals, which cause tissue damage. Doxorubicin group of antibiotics is known to interfere with topo-isomerase II enzyme and arrest cell growth.
Therapeutic Uses

Anthracycline antibiotics have been used in a variety of neoplastic diseases with other drugs. Breast carcinoma, endometrial cancer, bladder cancer, oat cell carcinoma of lung, thyroid cancer, osteogenic sarcoma and neuroblastoma are a few among the various types of cancer for which doxorubicin group of antibiotics are indicated.

Adverse Effects

Primarily, anthracycline antibiotics like other antineoplastic drugs can cause bone marrow depression, which limits their dose. Nausea, vomiting, conjunctivitis, lachrymation and occasionally hypersensitivity reaction have been observed. Doxorubicin is a cardiotoxic drug, induces focal necrosis of cardiomyocytes, which may lead to congestive cardiac failure and arrhythmias. “Radiation recall” reactions can be caused by doxorubicin-like antibiotics. This can flare up dermatitis, vein sclerosis, hyperpigmentation of nailbeds and skin creases. These drugs impart intense red colour to urine.

Doxorubicin-induced cardiotoxicity is augmented by concomitant use of paclitaxel.

Bleomycin

Bleomycin is a mixture of bleomycin A2/B2 glycopeptides used as antineoplastic agent.

Mechanism of Action

Bleomycin is a DNA intercalating drug. On intercalation of nuclein acid, it causes single and double strand scission and fragmentation of DNA. It is also believed that bleomycin generates free radicals which damage tissues.

Bleomycin is always given parenterally by intravenous route. Intramuscular injection may be painful and may be given with 1% lignocaine. Bleomycin is a widely used anticancer antibiotic particularly in squamous cell carcinomas. It is used with other drugs in testicular cancer, cancer of cervix, oesophagus, skin, head and neck. With doxorubicin, vinblastine and dacrabazine, bleomycin (ABVD) is used in Hodgkin’s disease.

Hyperpyrexia, hypersensitivity, hyperpigmentation, hyperkeratosis, alopecia and stomatitis have been reported with bleomycin therapy as adverse effects. Bleomycin produces very little bone marrow suppression. Pulmonary fibrosis is a source of concern with bleomycin administration.

An increased incidence of pulmonary fibrosis has been reported in patients receiving bleomycin (as ABVD) and colony-stimulating factor given for neutropenia.

PLATINUM-COORDINATED COMPLEXES

Cisplatin

Cisplatin is a platinum-coordinated complex having a broad range of antineoplastic activity. This drug acts similar to alkylating agents.

Mechanism of Action

Cisplatin binds to DNA and produces “platinating effect” which results in cross-linking of DNA. Consequently, unwinding of DNA occurs.
Cisplatin is administered by intravenous infusion along with mannitol with hydration to avoid nephrotoxicity.

Cisplatin is of significant therapeutic value in the treatment of metastatic testicular cancer. It is given in combination with bleomycin, vinblastine and etoposide to produce cure in this condition. Cisplatin is also given with other drugs in the cancer of bladder, cervix, prostatic, lung and osteogenic sarcoma.

Severe nausea and vomiting, nephrotoxicity, ototoxicity (tinnitus: loss of hearing) and neurotoxicity have been observed with cisplatin therapy. Cisplatin causes myelosuppression. Cisplatin-induced renal tubules are invariably seen within two weeks in susceptible patients. Adequate hydration and use of osmotic diuretics can reduce the severity of nephrotoxicity. Peripheral neuropathy, loss of taste and seizures are the neurological toxic manifestations of cisplatin. Cisplatin is mutagenic, leukemogenic and teratogenic platinum derivative.

Generally, cisplatin is contraindicated in patients with renal and hearing impairment.

**ANTICANCER ALKALOIDS**

Vincristine, vinblastine, etoposide, teniposide, paclitaxel, docetaxel.

**Vinca Alkaloids**

Vinca alkaloids are obtained from the plant *Vinca rosea* and these are subdivided into two:

1. Natural vinca alkaloids: Vincristine, vinblastine
2. Semisynthetic vinca alkaloids: Vindesine, vinorelbine

**Vincristine**

Vincristine is a vinca alkaloid antineoplastic agent. It arrests the cell division in M-phase and acts as spindle poison. Vincristine depolymerises the microtubules, which constitute spindle in cell division. An antimitotic drug vincristine is mainly used in the combination chemotherapy of acute leukemia and Hodgkin’s disease. It can also be used in Burkitt’s lymphoma, Wilms’ tumour, neuroblastoma and sarcomas.

Vincristine is always administered by intravenous infusion in normal saline. Vincristine is more neurotoxic than myelotoxic unlike vinblastine. Vincristine impairs walking, causes convulsions, may rise blood pressure and constipation is common. Concomitant use of vincristine with bleomycin may cause Raynaud’s syndrome.

**Vinblastine**

Vinblastine is a natural vinca alkaloid used as antineoplastic agent particularly in Hodgkin’s lymphoma. Like vincristine, vinblastine arrests the cell division in metaphase acting as spindle poison.

Vinblastine is given by intravenous route. It is a useful anticancer drug in inoperable carcinomas of breast, bladder and kidney. Bone marrow depression, especially leucopenia, is the most common adverse effect of vinblastine. Vinblastine can produce headache, peripheral neuropathy and loss of deep tendon reflexes. It is also known to produce ischemic cardiac toxicity, hypertension, skin rash, alopecia, jaw pain, vertigo and partial deafness.
Paclitaxel

Paclitaxel is an alkaloid isolated from the bark of yew tree—*Taxus brevifolia*. The antineoplastic action of paclitaxel is due to its effect on mitotic spindles. Paclitaxel stabilizes the spindles (microtubules) and thereby disrupts cell division.

Paclitaxel is given by intravenous route and primarily used in the treatment of advanced ovarian cancer. It can also be used in breast cancer, non-small cell cancer of lung, AIDS-related Kaposi’s sarcoma and relapsed germ cell tumours.

Severe dose-limiting bone marrow depression is the main disturbing adverse effect of paclitaxel. Peripheral neuropathy produced by paclitaxel may also be severe and occasionally dose limiting. Further, paclitaxel provokes hypersensitivity reactions. Alopecia, arthralgia, myalgia, bradycardia, ECG changes and nail dystrophies have been reported as paclitaxel adverse effects.

Paclitaxel can cause chest pain and angioedema in patients already receiving corticosteroids and H₁ and H₂ receptor antagonists.

**HORMONES AND HORMONE ANTAGONISTS AS ANTICANCER DRUGS**

Glucocorticoids, estrogens, androgens and their antagonists, gonadotropin analogues and other drugs that modulate various hormone effects have been used as oncopharmacological agents. In particular, glucocorticoids are used in combination with antineoplastics in the treatment of malignant diseases like acute leukemias and lymphomas. Sex hormones and their antagonists play a critical role in the treatment of various types of cancer in male as well as female patients (Tables 13.6 and 13.7).

<table>
<thead>
<tr>
<th>Table 13.6: Hormones used in cancer chemotherapy</th>
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<tbody>
<tr>
<td><strong>Group</strong></td>
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<tr>
<td>Corticosteroids</td>
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<td>Estrogens</td>
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<td>Progestogens</td>
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<td>Androgens</td>
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<td>LHRH analogues</td>
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<th>Table 13.7: Hormone antagonists in cancer chemotherapy</th>
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<tr>
<td><strong>Group</strong></td>
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<tr>
<td>Corticosteroid antagonists</td>
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<td>Antiestrogens</td>
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<td></td>
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<tr>
<td>Antiandrogens</td>
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</table>
Prednisolone as Anticancer Drug

Synthetic corticosteroids particularly prednisolone is used with other anticancer drugs in leukemias and lymphomas. The rationale for prednisolone antineoplastic use is as follows:
1. Prednisolone induces lymphocyte apoptosis
2. Prevents growth
3. Immunosuppressant and antiinflammatory effects do contribute
4. Release of erythropoietin which may reduce bone marrow toxicities produced by drugs administered concurrently
5. Mild euphoric action may add to better feeling on the part of patient.

However, patients remain more prone for superinfection, hence, constant vigilance is mandatory.

Tamoxifen

Tamoxifen is an estrogen antagonist used both in chemoprophylaxis and the treatment of breast carcinoma. It is also used to stimulate ovulation in women with anovulatory infertility.

Tamoxifen acts by inhibiting transforming growth factor-beta (TGF-β) and insulin-like growth factor (TGF) in addition to estrogen antagonist action. Recently, it is said that tamoxifen induces apoptosis of cell. Tamoxifen is given orally and the plasma half-life is 7 days.

Tamoxifen appears to undergo enterohepatic circulation and slowly excreted in faeces.

The most common adverse effect of tamoxifen is “hot flushes”. Fluid retention, vaginal bleeding, dry skin, muscle cramps and increased tendency for thromboembolism are reported on tamoxifen therapy.

Tamoxifen increases the anticoagulant effect of warfarin and dopaminergic effect of bromocriptine.

HYDROXYUREA

Hydoxyurea is an analogue of urea used as antineoplastic drug in chronic myeloid leukemia refractory to busulphan and polycythemia vera. Hydroxyurea acts by inhibiting DNA synthesis. It inhibits ribonucleotide reductase enzyme.

Hydroxyurea is given by mouth as single dose in a day. It crosses blood-brain barrier, placenta and appears in milk. Hydroxyurea is also being tried in squamous cell carcinoma of head, neck, cervix and urethra.

Besides antineoplastic use, hydroxyurea is considered as a promising agent in the treatment of haemoglobinopathies, essential thrombocytosis and hypereosinophilic syndrome.

Megaloblastic anaemia and bone marrow depression are the main adverse effects of hydroxyurea. In addition, headache, gastrointestinal disturbances, hallucinations and convulsions have been reported with hydroxyurea.

Recently, hydroxyurea is given with didanosine to inhibit HIV replication in AIDS.

L-ASPARAGINASE

L-asparaginase is an enzyme which catalyses the degradation of L-asparagine to asparatic acid and ammonia. As antineoplastic agent, L-asparaginase is used in acute lymphoblastic
leukemia. The cells of acute lymphoblastic leukemia are dependent on exogenous L-asparagine. Administration of L-asparaginase hydrolyses L-asparagine into aspartic acid and ammonia and induces apoptosis of cancer cell.

L-asparaginase is administered by intravenous and intramuscularly along with vincristine and prednisolone in acute lymphoblastic leukemia on intradermal test dose.

Hypersensitivity reactions like anaphylaxis may be produced by L-asparaginase. However, if given with pegaspargase, hypersensitivity reactions occur at low intensity.

Pancreatitis, Parkinson’s-like syndrome, deficiency of protein C and S and antithrombin III and hyperammonemia are the other adverse effects of L-asparaginase.
INTRODUCTION

A wide variety of diseases are caused by viral infection. Virus is a small discrete infective agent and has no metabolic machinery of its own. Viruses are intracellular parasites and evade immune mechanisms. Many viral diseases resolve spontaneously. Not all viral infections are amenable to drugs. Mumps, poliomyelitis, rabies and rubella are not cured by drugs. However, antiviral drugs have prophylactic as well as therapeutic value in many viral infections. Further, where there is no definitive indications for antiviral drugs, non-specific symptomatic supportive treatment with drugs is all the more important rather essential.

REPLICATION OF VIRUSES

Viruses are composed of linear or helical nucleic acid core consisting of either DNA or RNA. Hence, these are referred to as DNA viruses or RNA viruses. Many viruses possess an outer cover called capsid and lipoprotein envelope, which is highly antigenic.

The steps involved in viral infection and replication are as follows:

- **Phase 1: Attachment and penetration**: The virus binds to a specific receptors of the host cell membrane and penetrates by a phagocytosis-like mechanism.
- **Phase 2: Uncoating**: The protein coat capsid undergoes lysis by viral enzymes liberating free viral DNA or RNA depending on the nature of viral genome.
- **Phase 3: Synthesis of viral components**: The genome of virus is duplicated on fusion with cell nucleus responding elements. As a result, viral regulatory and structural proteins are being synthesized. Viral DNA polymerase and reverse transcriptase enzyme of RNA virus are the key enzymes for viral protein synthesis.
- **Phase 4: Assembly of viral particle**: In this phase, viral components are assembled to form the mature virus particle.
- **Phase 5: Release of the virus**: The release of the virus from the host cell may be rapid and accompanied by host cell death. If the release of virus is slow by means of budding, the host cell may survive.

Antiviral drugs, theoretically, could interfere with any one or more phases of viral replication process. In fact, drugs can be fusion blockers that inhibit viral attachment with the cell. Some of the drugs act by blocking the enzymes like viral DNA polymerase, reverse transcriptase and proteases.
CLASSIFICATION OF ANTIVIRAL DRUGS

Antiviral drugs are classified by either based on their therapeutic use or mechanism of action. It is common to refer antiviral drugs by the following groups.

1. **Drug that cause fusion block: inhibit viral attachment and penetration**: Amantadine, rimantadine, immunoglobulins

2. **Viral DNA-dependent polymerase inhibitors**: Acyclovir, ganciclovir, valaciclovir, famciclovir, foscarinet, ribavirin (tribavirin)

3. **Reverse transcriptase enzyme inhibitors**: Zidovudine, stavudine, didanosine, lamivudine, zalcitabine, delavirdine, efavirenz, nevirapine

4. **Protease inhibitors**: Saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir

5. **Immune modulators**: Interferons—α (alpha), β (beta), γ (gamma)

6. **Topical antivirals**: Idoxuridine, trifluridine.

ANTIHERPES VIRUS AGENTS

Herpes simplex virus type 1 causes diseases of mouth, face, skin, esophagus and brain. Virus type 2 attacks genitals, rectum, skin, hands and meninges. Varicella zoster virus could be life-threatening virus. Drugs like acyclovir, ganciclovir, penciclovir and foscarinet have been widely used against herpes virus.

**Acyclovir**

Acyclovir is an antiherpes virus acyclic guanine nucleoside. The spectrum of activity of acyclovir is restricted to herpes virus. Following administration, acyclovir undergoes phosphorylation. Acyclovir triphosphate competetively inhibits viral DNA polymerase.

Acyclovir can be administered topically, orally and parenterally for a variety of herpes infections. Headache, nausea, vomiting, skin rash, fatigue, fever, increased hair loss and depression are the adverse effects produced by acyclovir. Topical application may produce irritation and burning.

Therapeutic uses of acyclovir include herpetic keratoconjunctivitis, other herpes virus infections and herpes varicella zoster. Prophylactically, acyclovir can be used in organ transplantation surgery accompanied with immunosuppressive treatment.

If acyclovir is given with cyclosporin, drug-induced nephrotoxicity may increase. With azidothymidine, acyclovir induces lethargy and somnolence. However, these drug interactions can be negotiated well within the ambit of multiple drugs dose regimen.

**RIBAVIRIN (TRIBAVIRIN)**

Ribavirin is a guanine analogue antiviral drug. Many viruses are inhibited by ribavirin. Susceptible viruses to ribavirin include herpes viruses, advenoviruses, proxyviruses and RNA viruses like lassavirus, measles and respiratory syncytial viruses. It is given as aerosol as well as tablets by oral route.

Ribavirin inhalation may cause deterioration of pulmonary function. Bacterial pneumonia, pneumothorax, hemolytic anaemia, skin rash and pruritus have been reported as adverse effects of ribavirin.

Ribavirin aerosol is commonly recommended for the treatment of respiratory syncytial virus infection. In chronic hepatitis-C ribavirin is given by mouth. Ribavirin is the agent of choice to treat lassa fever.
Ribavirin antagonizes zidovudine antiviral action. Pregnancy is a contraindication for ribavirin therapy since it is teratogenic in animals. Ribavirin should be avoided in patients with severe hepatic diseases including hepatic cirrhosis. Exacerbation of gout occurs with ribavirin administration.

**AMANTADINE**

Amantadine is an antiherpes zoster and antiinfluenza A antiviral agent. It is a weak dopamine agonist with some antimuscarinic action. Hence, used as antiparkinsonian drug in the early stages of disease where symptoms are mild.

Common side effects of amantadine are livedo reticularis, ankle edema, orthostatic hypotension, urinary retention, nightmares, headache, and insomnia.

Amantadine should not be used in patients with the history of epilepsy.

Amantadine may enhance the adverse effects of atropine-like drugs.

**INTERFERONS (INTERFERON—α, β AND γ)**

Virus infected cells produce interferons, to protect the uninfected cells of same species. Interferons have antiviral, antiproliferative and immunoregulatory activities. Interferons bind to cell surface proteins, activate several enzymes, which block viral development. It is well recognised that interferons have beneficial effect in infections caused by herpes simplex viruses, varicella zoster virus, cytomegalovirus, rhinovirus and papilloma viruses. Studies have revealed that interferons are also useful in hepatitis B and C virus infections.

Interferons are not absorbed by gastrointestinal tract. Therefore, generally administered by subcutaneous or intramuscular routes. Intravenous administration produces more rapid distribution and elimination.

**Adverse Effects**

Clinical experience with interferon α is rather vast than interferons β or γ. Adverse effects documented so far are observed with interferon alpha. Influenza-like symptoms, nausea, vomiting, diarrhoea, alopecia, skin rash, epistaxis, hypotension, myocardial infarction, stroke, pulmonary edema, hyperglycemia and thyroid function abnormalities have been reported following interferon therapy.

Interferon-α-2a is used in a wide range of diseases, which include;

- Hair cell leukemia, chronic myeloid leukemia, melanoma, carcinoid tumours, renal cell carcinoma and AIDS-related Kaposi’s sarcoma.
- Chronic active hepatitis B and C
- Age-related macular degeneration

Drugs that cause bone marrow suppression (most anticancer drugs) should not be given along with interferons.

Interferons are contraindicated in patients with psoriasis. These should be used with caution in patients with autoimmune disorders, epilepsy, depression and other psychotic disorders.
ANTI-AIDS DRUGS (DRUGS USED IN AIDS)

Acquired immunodeficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV) 1 and 2. The most common is HIV-1, which occurs worldwide. The second type HIV-2 infection is seen in Africa. AIDS virus is a retrovirus transmitted by sexual contact, blood and blood products, contaminated needles and from mother to fetus. The major effect of HIV virus is to cause progressive depletion of CD4 and T lymphocytes. The typical course of infection is followed by seroconversion development of antibodies. Fatigue, weight loss, recurrent fever, dementia, persistent infection and lymphadenopathy give rise to a condition called AIDS-related complex. In general AIDS is fatal. Therefore, therapeutic intervention is needed. Antiretroviral drugs, management of AIDS-related complex including the treatment of opportunistic infections are the modalities of AIDS treatment.

Classification of Anti-AIDS Drugs

Antiretroviral drugs used in AIDS are classified into the following groups based on their mechanism of action:

1. **Nucleoside reverse transcriptase inhibitors**: Zidovudine, lamivudine, didanosine, zalcitabine, stavudine, abacavir
2. **Nonnucleoside reverse transcriptase inhibitors**: Delavirdine, efavirenz, nevirapine
3. **Protease inhibitors**: Indinavir, saquinavir, nelfinavir, ritonavir, amprenavir
4. **Miscellaneous**: Peptide-20, integrase inhibitors, hydroxyurea, antisense oligonucleotides.

**Reverse Transcriptase Inhibitors (Zidovudine-like drugs)**

Zidovudine, lamivudine, didanosine, stavudine, abacavir, zalcitabine

Zidovudine group of drugs acts by inhibiting reverse transcriptase of HIV virus and prevents the spread of virus to uninfected cell. These drugs also inhibit vertical transmission of virus from mother to fetus.

Anaemia, leucopenia, neutropenia, bone marrow suppression and nephrotoxicity are produced by zidovudine group of drugs as adverse effects.

Currently, these drugs are used in combination with protease inhibitors.

**Protease Inhibitors**

Indinavir, amprenavir, ritonavir, nelfinavir, lopinavir, saquinavir

Protease inhibitors suppress viral replication. These drugs should not be used alone. Protease inhibitors have been linked with metabolic abnormalities. Indinavir-like drugs are known to increase cholesterol and triglycerides levels.

Abdominal obesity, skeletal muscle wasting, insulin resistance and diabetes mellitus may be produced by protease inhibitors. Indinavir can produce nephrolithiasis with flank pain.

The combination of antiretroviral drugs aims at minimizing toxicity, increasing efficacy and delaying the development of drug resistance. Generally, two nucleoside reverse transcriptase inhibitors are given with either an HIV protease inhibitor or nonnucleoside reverse transcriptase inhibitor. This combination is supposed to be highly active antiretroviral therapy. However, the effectiveness of anti-AIDS drug therapy is very much dependent on patient compliance with treatment. Any lapses in compliance results in increased virus load and development of resistance. To overcome compliance problems, simplified dose regimen remains as a main approach.
INTRODUCTION
Infections caused by fungi may be superficial affecting skin, hair, nails or mucous membrane or systemic affecting the whole body. Fungal infections may be local, invasive and disseminated. Some fungi cause disease in any individual acting as true pathogens. Other fungi like *Candida* and *Pneumocystis carinii* are opportunistic low pathogens which attack individuals with AIDS or show altered normal defense mechanisms for disease to occur. In immunocompromised patients, fungal infections are often rapidly progressive and needs to be treated promptly without delay.

CLASSIFICATION OF ANTIFUNGAL DRUGS

1. **Azole and triazole antifungals:**
   - **Azoles:**
     - Ketoconazole
     - Clotrimazole
     - Miconazole
   - **Triazoles:**
     - Fluconazole
     - Itraconazole
     - Terconazole

2. **Polyene antibiotics:** Amphotericin-B, Nystatin

3. **Other antibiotic:** Griseofulvin

4. **Topically used antifungals:** Clotrimazole, econazole, butaconazole, miconazole, terconazole, tioconazole, ciclopirox olamine, terbinafine, tolnaftate, benzoic acid + salicylic acid, undecylenic acid.

KETOCONAZOLE
Ketoconazole is a broad-spectrum azole antifungal agent given by mouth and also topically applied. This drug is known to act by altering the permeability of the fungal cell membrane. Ketoconazole interferes with ergosterol synthesis and produces fungistatic action.

Nausea, vomiting and abdominal pain are the gastrointestinal disturbances produced by ketoconazole which can be minimized by giving the drugs with food. Ketoconazole interferes with steroid synthesis and is known to produce gynecomastia, oligospermia, menstrual irregularities, and reversible hepatitis, allergic reactions and photophobia are rarely reported with ketoconazole.

Ketoconazole is used in superficial fungal infections of skin, hairs and nails and systemic fungal disease like blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis and paracoccidioidomycosis. It can be used prophylactically in immunocompromised patients.

Ketoconazole should not be used in patients with previous history of liver disease.
Pharmacology for Physiotherapist

Ketoconazole inhibits cytochrome P$_{450}$ isoenzyme CYP$_{3A4}$ and alters the rate of metabolism of many drugs. The risk of cardiac arrhythmias is there if ketoconazole is given with astemizole and cisapride. Hence, concurrent use of ketoconazole with these drugs should be avoided.

AMPHOTERICIN-B

Amphotericin-B is a polyene antifungal antibiotic. This antibiotic alters the permeability of fungal cell membrane to produce fungistatic or fungicidal action. It is effective against *Aspergillus*, species of *Blastomyces*, *Candida*, *Mucor*, *Coccidioides* and *Rhizopus*. Amphotericin-B is given intravenously in the treatment of severe systemic fungal infections like candidiasis, mucormycosis, fungal endocarditis, meningitis, peritonitis and respiratory tract infections. It can be used locally for superficial candidiasis.

Amphotericin-B infusion in conventional form is more toxic. Liposomal and different formulations have been developed to reduce toxicity. Headache, chills, fever, muscle and joint pains, gastrointestinal cramps, nephrotoxicity, anaemia, thrombocytopenia, hypertension, ventricular fibrillation, anaphylactoid reactions, hearing loss, peripheral neuropathy and convulsions are seen with amphotericin-B infusion.

Other drugs, which cause nephrotoxicity, aggravate amphotericin-B-induced renal adverse effects. Diuretics, which produce K$^+$ loss, should be avoided with amphotericin-B administration. Amphotericin-B inhibits the metabolism of zidovudine.

NYSTATIN

Nystatin is an antifungal polyene antibiotic used in the prophylaxis and treatment of candidiasis of the skin and mucous membrane. It has been given with antibiotics which suppress intestinal microflora to avoid superinfection, especially candidiasis. It is applied locally and given by mouth in the form of suspension.

Nystatin is well tolerated, occasionally nausea, vomiting and diarrhoea are observed as nystatin adverse effects.

GRISEOFULVIN

Griseofulvin is a fungistatic antibiotic. It inhibits fungal cell division by acting as a spindle poison. Griseofulvin is effective against dermatophytes, *Trichophyton* and *Microsporum* species. This antibiotic is given by mouth after food. Fatty meal enhances the absorption of griseofulvin. It is deposited in keratin-secreting cells of skin, hairs and nails. Therefore, it prevents the growth of fungi in these structures. Griseofulvin is used in the treatment of dermatophytes, which involve scalp, hairs, nails and skin.

Adverse effects produced by griseofulvin are mild and transient. Urticaria, headache, dry mouth and taste alteration and may precipitate systemic lupus erythematosus.

Griseofulvin should not be used in patients with liver disease and systemic lupus erythematosus.

Griseofulvin given with alcohol produces disulfiram-like action.
IMMUNOMODULATORS

INTRODUCTION
Specific immune response is a defensive mechanism to fight against many diseases. Disorders of immune system function are the basis of many human illnesses. In the past three decades, immunopharmacology has made significant advances in the treatment of disorders characterized by either depressed or exaggerated immunity. Primary immune response is effectively and easily modulated by drugs. Once the immunological memory is established, drugs are moderately effective. This is to say that not all immune responses are equally affected by drugs.

Many clinical disorders like autoimmune and inflammatory diseases are characterized by aberrant immune reactivity. Organ transplantation also requires suppression of undesirable immunological responses to maintain the function of transplanted organ. Drugs that are used for immuno-intervention therapy fall mainly into two categories:
- Immunosuppressants
- Immunostimulants

IMMUNOSUPPRESSANTS
Drugs that suppress immune response have been used in organ transplantation surgery and many chronic debilitating immune diseases. There are potential risk of infection of all types and lymphoma-related malignancies with immunosuppressive drug therapy. This precludes immunosuppressant drug treatment.

Classification of Immunosuppressants
Currently used immunosuppressants are classified into four groups:
1. **Specific immunosuppressants**: Cyclosporin, tacrolimus, mycophenolate mofetil, Rh (D) immune globulin
2. **Corticosteroids**: Prednisolone, prednisone
3. **Antibody reagents**: Antithymocyte globulin, Antilymphocyte immunoglobulin, monoclonal antibody—muromonab
4. **Nonspecific cytotoxics**: Azathioprine, rapamycin, cyclophosphamide, methotrexate
5. **Miscellaneous**: Thalidomide, methoxsalen.

Cyclosporin
Cyclosporin is a potent specific immunosuppressant. It acts on helper T-cells. Cyclosporin inhibits proliferation of T-cells and also activation of calcineurin. Inactivation of calcineurin decreases the generation various cytokines—interleukins 2, 3, 4, interferon α and tumour necrosis factor which take part in immune response. Cyclosporin is known to increase the production of transforming growth factor β, which inhibits interleukin-2.

Cyclosporin is given by oral route as liquid-filled capsules. It can be administered by intravenous route with ethanol. Cyclosporine is excreted in bile, faeces and urine.
Cyclosporin is used as antirejection drug in organ transplantation surgery. It is approved for kidney, liver, lung and heart transplantation surgery along with corticosteroids. Cyclosporin is also used in rheumatoid arthritis, psoriasis, arthropathy, uveitis and systemic lupus erythematosus.

Cyclosporin is also useful in nephrotic syndrome secondary to glomerular kidney disease and severe corticosteroid-dependent asthma.

The major adverse effect of cyclosporin therapy is nephrotoxicity which is related to plasma concentration of cyclosporin and usually reversible. Hypertension, hyperplasia of gums, hypertrichosis, tremor and burning sensation in the extremities are often reported. Cyclosporin can induce lymphoma and skin cancers.

During the treatment with cyclosporin, the use of vaccines should generally be avoided. Psoriatic patients who are on cyclosporin therapy should avoid excessive sun exposure and ultraviolet irradiation.

**Tacrolimus**

Tacrolimus is a macrolide immunosuppressant like cyclosporin. Tacrolimus inhibits calcineurin and lymphokine gene expression. Tacrolimus is more potent than cyclosporin. Tacrolimus is used in organ transplant surgery as antirejection drug. Topically, tacrolimus is used in atopic eczema. Tremor, headache, hyperkalemia, convulsion, frank diabetes mellitus and hypertropic cardiomyopathy have been observed as adverse effects of tacrolimus.

**IMMUNOSTIMULANTS**

A variety of natural adjuvants, cytokines and synthetic agents have been used as immunostimulants in many cancers and non-cancerous conditions including viral and fungal infections. Immunostimulants generally produce nonspecific stimulation of immune activity, which is explored for therapeutic benefit in a limited sense. Currently used immunostimulants are as follows:

**Natural Adjuvants**

1. **BCG vaccine**: Used in bladder cancer
2. **Immunoglobulins**: Indicated in a wide variety of disorders including idiopathic thrombo-cytopenic purpura
3. **Thymic factors**: They are being tried in bronchial asthma and allergic rhinitis

**Cytokines**

1. **Interferon-alpha**: In hairy cell leukemia
2. **Interleukin-2**: In multiple myeloma and AIDS
3. **Interleukin-6**.

**Synthetic Agents**

1. **Levimasole**: May be useful in Hodgkin’s lymphoma, rheumatoid arthritis, aphthous ulcer and colorectal cancer
2. **Isoprinosine**: Used in AIDS.
Drugs Acting on Endocrine System: Thyroid and Antithyroid Drugs

Thyroid Hormones

Hormones secreted from thyroid gland are:
- Thyroxine
- Thyronine
- Calcitonin (from parafollicular cells)

Thyroxine is crucial for normal growth and development, especially of the central nervous system. Thyroxine is the key hormone in the maintenance of energy metabolism homeostasis affecting the function of virtually all organ systems. Disorders of size, shape and function of thyroid gland is common. Hypothyroidism and hyperthyroidism both bring dramatic clinical manifestations. Iodine deficiency and congenital defects of thyroid gland can produce mental retardation and cretinism in children respectively. Endemic cretinism is due to iodine deficiency, which can be prevented by proper iodine intake.

Synthesis of Thyroxine

The normal daily output of thyroxine is about 70-90 μg. The synthesis of thyroxine involves the following steps:
- Uptake of iodine
- Iodide oxidation and organification
- Coupling process
- Proteolysis: release of hormones
The cells of the thyroid absorb iodide by active transport. Thyroid-stimulating hormone from anterior pituitary accelerates iodide trapping in thyroid. Thus, trapped iodide undergoes oxidation catalysed by peroxidase to elemental form of iodine. Tyrosine present in colloidal substance of thyroid follicular cells accept iodine leading to iodide organification. As a result of iodination of tyrosine, monoiodotyrosine and diiodotyrosine moieties are formed. Thyroid peroxidase enzyme also catalyses the coupling process that occurs between monoiodotyrosine and diiodotyrosine. Thyroxine is obtained by the coupling of two diiodotyrosine moieties. Release of thyroxine takes place by proteolysis.

**EFFECTS OF THYROID HORMONES**

Thyroxine is converted into active form thyronine (T₃) in the periphery, the major part of conversion occurs in the liver.

The exact mechanism of action of thyroid hormones is still to be elucidated completely. However, thyroxine and thyronine bind to receptors present in the plasma membrane, mitochondria and nucleus to produce effects like:

- Increase in the uptake of nutrients like glucose and amino acids
- Increased synthesis of RNA, subsequently leading to accelerated protein synthesis, enzyme activity and cellular activity.

Actions of thyroid hormones include the following:

- Stimulate Na⁺-K⁺-ATPase enzyme directly and increase ATP turnover which increase oxygen consumption responsible for “calorigenic” effects—increases basal metabolic rate (BMR)
- Optimal growth, development and functioning of all body tissues require thyroid hormones. Especially thyroid hormones are vital for the development of CNS at the early stages of human life.
- Thyroid hormones are regarded as ‘pluripotent’ suggesting their role in energy management and metabolic homeostasis.
- The widespread actions of thyroid hormones are secondary to calorigenic action. T₄ is essential for fertility, to regulate lipid metabolism and to potentiate the action of growth hormone on tissues.
- Larger doses of thyroid hormones increase heat production, cause cutaneous vasodilatation, decrease peripheral resistance and upregulation of β receptors in cardiac tissue as a result of which, tachycardia is seen.

**Comparison of Thyroid Hormones** (Table 14.1)

<table>
<thead>
<tr>
<th>Thyroxine (T₄)</th>
<th>Triiodothyronine (T₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural and synthetic</td>
<td>Synthetic and natural</td>
</tr>
<tr>
<td>Prohormone</td>
<td>Active form</td>
</tr>
<tr>
<td>10 times less potent than T₃, maximum effect seen within 10 days</td>
<td>More potent, maximum effect seen within 24 hours</td>
</tr>
<tr>
<td>Oral absorption: 65%</td>
<td>Oral absorption: 95%</td>
</tr>
<tr>
<td>Plasma half-life: 7 days</td>
<td>Plasma half-life: 36 hours</td>
</tr>
<tr>
<td>Preferred for long-term replacement therapy</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity high</td>
</tr>
</tbody>
</table>
PREPARATIONS OF THYROID HORMONES

- Sodium levothyroxine
- Thyroid extract from animal source
- Thyroglobulin
- Sodium levotriiodothyronine
- Liotrix (a combination of T₄ and T₃ used in myxedema coma)

DRUGS USED IN HYPOTHYROID STATES

Primary thyroid deficiency: Hormone replacement therapy:
- Cretinism: Childhood hypothyroid state. Deficiency may be there during intrauterine life and/or early neonatal life. Endemic cretinism is due to iodine deficiency.
- Myxoedema: Hypothyroid state of adulthood. Thyroxine is the drug of choice at a dose of 0.1-0.2 mg/day life long.
- Myxoedema coma: Intravenous administration of a combination of T₄ and T₃ (Liotrix) may be used to start with thereafter oral thyroxine therapy. Currently, along with thyroid hormones replacement hydrocortisone is also given as a supportive treatment.

Adverse Effects of Thyroxine

Palpitations, nervousness, diaphoresis, heat intolerance, headache and insomnia. Thyroxine overdosage may cause angina pectoris and related cardiac abnormalities. Polyphagia and emaciation can occur.

Thyroid preparations must be used with care in hypertensive patients.

Drug Interactions

- Thyroxine potentiates the actions of anticoagulants by increasing degradation of the vitamin K-dependent clotting factors.
- Thyroxine enhances the actions of adrenergic drugs as well as tricyclic antidepressants.
- Digitalisation of the patient increases thyroxine requirement.

Implications to Physiotherapy

Significantly, it is a matter of great interest how thyroxine replacement therapy helps or brings drug-induced complications during/after strenuous exercise programme. It is apt to undertake extreme care to avoid any imminent hormone-induced changes in skeletal muscle physiology during exercise.

ANTITHYROID DRUGS

Drugs used in the management of hyperthyroidism and carcinoma of thyroid are generally referred to as antithyroid agents. Invariably, antithyroid drugs are of immense clinical value in the preparation of patients for thyroid surgery.
CLASSIFICATION OF ANTITHYROID DRUGS

Antithyroid drugs are classified based on their mechanism of action into different groups:

- **Thyroxine synthesis inhibitors**: Propylthiouracil, methylthiouracil, carbimazole, methimazole
- **Inhibitors of peripheral conversion of T₄ to T₃**: Sodium ipodate, propylthiouracil, iopanoic acid, glucocorticoids
- **Thyroid cell-destroying agent**: Radioactive iodine (I³¹)
- **Iodide-trapping inhibitors (Ionic inhibitors)**: Thiocyanate, perchlorate
- **Miscellaneous**: Iodine and iodides, lithium, propranolol, Lugol’s solution.

PROPYLETHIOURACIL

Propylthiouracil is a thioamide antithyroid drug, generally used in the long-term suppression of hyperthyroidism in children and in selected patients of thyrotoxicosis. Propylthiouracil is an inhibitor of "thyroid peroxidase" enzyme thereby blocking oxidation of iodine into elemental iodine. Iodide organification is also inhibited along with disruption of coupling process of monoiodotyrosine and diiodotyrosine moieties. Thus, propylthiouracil inhibits the synthesis of thyroid hormones. It is evident that propylthiouracil has immunosuppressant effect which may be an additional advantage in use of this agent in chronic autoimmune thyroiditis (Hashimoto's thyroiditis). Propylthiouracil is preferred to treat elderly patients, patients with cardiac diseases and also pregnant women with hyperthyroidism.

Propylthiouracil produces granulocytopenia, agranulocytosis, pruritus and skin rash as main adverse effects. Rarely, systemic lupus erythematosus (SLE), lymphadenopathy and hypoprothrombinemia may also be seen.

METHIMAZOLE

Methimazole is a long acting, more potent thioamide antithyroid drug. Unlike propylthiouracil, methimazole is not an inhibitor of peripheral conversion of T₄ to T₃. Methimazole inhibits thyroid peroxidase and consequently blocks iodine organification and coupling process. Agranulocytosis is a less frequent adverse reaction of methimazole. Methimazole is contraindicated in pregnancy.

LUGOL’S IODINE

Lugol’s iodine is 5% iodine in 10% potassium iodide. It is used as antithyroid drug to decrease the size and vascularity of the hyperplasic thyroid gland. It is given by oral route continuously for 10–14 days prior to thyroid surgery to increase the consistency of the gland. This will make the surgical handling of thyroid gland easy. Lugol’s solution can also be used in the management of thyrotoxicosis.

RADIOACTIVE IODINE (I³¹)

Sodium iodide I³¹ is the only radioactive iodine isotope, which is commonly used as antithyroid drug. Oral administration of I³¹ given either in the form of oral solution or
capsule readily accumulates in thyroid. I$^{131}$ emits β-rays in the gland to destroy functional and regenerative capacity of thyroid cells. The dose of I$^{131}$ is expressed as millicuries (mCi). Radioactive iodine (I$^{131}$) is used in hyperthyroidism as well as thyroid carcinoma. I$^{131}$ has diagnostic use to assess thyroid cell function.

Adverse reactions of I$^{131}$ may be alarming which includes radiation thyroiditis and permanent hypothyroidism. Radiation thyroiditis may be painful which demands analgesic therapy.

Radioactive iodine is contraindicated in pregnancy, nursing mothers and young patients.

**DRUGS USED IN THYROTOXICOSIS**

Thyrotoxicosis may be a life-threatening metabolic crisis. Major clinical features of thyrotoxicosis include high fever, delerium, extreme palpitations, cardiac failure (high output failure), pulmonary edema, mania and coma. The management of thyrotoxicosis includes the administration of the following drugs with supportive care and fluid replacement:

- Aspirin and tepid sponging for fever
- Propranolol 1 mg/kg IV 8th hourly to control palpitations (Esmolol IV can also be used)
- Carbimazole
- Lugol’s solution
- Dexamethasone/prednisolone/hydrocortisone
- Suitable antibiotic therapy
- Oxygen
- Diuretic
- Sedative drugs if required
- Charcoal hemodialysis reverses the condition
INTRODUCTION

Clinical, genetical and various biochemical with immunological findings have recognised diabetes mellitus as a common endocrinal heterogeneous metabolic syndrome or disorder. Diabetes mellitus is characterised by either decreased or net loss of insulin effectiveness or insulin deficiency or both. Generally, when patient’s fasting blood glucose level is > 140 mg/dl and postprandial blood glucose level is > 200 mg/dl accompanied by polyuria, polydipsia, fatigue and azotemia, diabetes mellitus is well recognised. If hyperglycemia is not adequately controlled in patients with diabetes mellitus, long-term complications like neuropathy, nephropathy, retinopathy and vascular damages may be seen.

The etiology of diabetes mellitus is largely ill-defined. However, immune damage to the β-cells of the islets of Langerhans, viral infection and genetic causes have been implicated. It is now certain that diabetes mellitus is a polygenic disease with interwoven and interlocking complex etiological mechanisms.

TYPES OF DIABETES MELLITUS

In clinical medicine, types of diabetes mellitus have been described as mentioned below:

Type 1: Insulin-dependent diabetes mellitus (IDDM)

Type 2: Non-insulin-dependent diabetes mellitus (NIDDM)

Others: Gestational diabetes mellitus, drug-induced diabetes mellitus, pancreatic diseases causing diabetes mellitus.

Modalities of Treatment

There are different modalities of treatment of diabetes mellitus to reduce the morbidity and mortality and to achieve euglycemia in patients with different diabetic etiology.
• Diet therapy
• Drug therapy
• Exercise and education modality
• Gene therapy

Goals of Drug Treatment in Diabetes Mellitus
The major goals of all the treatment modalities of diabetes mellitus is to restore the known metabolic derangements, inhibit vascular, renal, retinal and neurological long-term complications and avoid ketoacidosis and hyperglycemia. At present, dietary and drug therapy with a well-defined exercise programme is the method of choice to control diabetes mellitus. Exercise enhances the insulin action, reduces the body weight and brings better lifestyle prognosis.

INSULIN
Insulin is a polypeptide hormone secreted from the β-cells of the islets of Langerhans of pancreas. Commercially available insulins are obtained from pig (porcine), cow (bovine), horse (equine) and recombinant DNA technology (human insulins). The daily output of insulin is approximately 25-30 units. Insulin secretion is a tightly regulated process, designed to provide a stable glucose level in blood in both fasting and feeding. Insulin is continuously released from the β-cells and augmented after food. Various nutrients, gastrointestinal hormones and autonomic neurotransmitters affect insulin release.

Glucose, ketone bodies, few amino acids and fatty acids, gastrin, secretin, enteroglucagon, cholecystokinin, sulfonylurea compounds, repaglinide, vagal stimulation and β₂ receptor stimulation stimulate insulin secretion.

Drugs like diazoxide, phenytoin, vinblastine, colchicine, somatostatin, glucagon, adrenergic α₂ stimulation and 5-hydroxytryptamine inhibit insulin secretion. Thus, a co-ordinated interplay of various endogenous substances and exogenous agents regulate insulin secretion.

Mechanism of Action
Insulin binds to its receptor on cell membrane and stimulates tyrosine kinase system to produce its effects.

Actions of Insulin
Insulin is the hormone that plays a vital role in fuel homeostasis. It is the hormone that controls uptake, storage and utilization of cellular nutrients—free fatty acids, amino acids and glucose in particular. The actions of insulin include:

• Activates glucose and ion transport
• Inhibits the catabolism of glycogen, proteins and fat—anabolic effect
• Has an effect on gene transcription
• Insulin does influence cell proliferation and differentiation which may take days to manifest.
On Liver
- Reduces hepatic glucose output
- Increases glycogen synthesis
- Inhibits gluconeogenesis
- Glycogenolysis is inhibited by insulin
- Hepatic glycogen phosphorylase is also inhibited by insulin

On Muscle
Glucose transport is augmented by insulin across muscle membrane. However, the biotransport of glucose precursors is inhibited. Insulin inhibits protein catabolism in the muscle.

On Adipose Tissue
Intracellular lipolysis is inhibited by insulin in adipose tissue. Insulin promotes glucose transport and inhibits cellular uptake of glucose precursors.

Route of Administration
Insulin is not effective by oral route. It is always given by subcutaneous route. Recently, insulin nasal spray and other types of inhaler formulations of insulin have been introduced to avoid injectable forms.

Preparations of Insulin
Commercially available insulin preparations differ in their source, purity, potency, onset of action, duration of action and immunogenicity besides safety and cost. Hence, insulin preparations are classified into three groups based on their duration of action:

I. Rapid and short acting insulins (act up to 16 hours)
   - Regular insulin or crystalline insulin or amorphous insulin or plain insulin or soluble insulin
   - Semilente insulin
   - Human semilente insulin

II. Intermediate acting insulins (duration of action up to 24 hours)
   - NPH insulin (Neutral Protamine Hagedorn’s)
   - Lente insulin
   - Human NPH, Human Lente insulin

III. Long-acting insulins (duration of action up to 36 hours)
   - Ultralente insulin
   - Protamine zinc insulin (PZI)
   - Insulin glargine (human insulin)

In addition, mixed insulin preparations are also available. New forms of insulin preparations as well as delivery systems have been designed and released to the market to overcome the disadvantages of conventional insulin preparations. Attempts have been made to develop oral, rectal and transdermal insulin preparations. Insulin nasal spray has been employed...
to control postprandial blood glucose level since it acts rapidly without alarming systemic adverse reactions.

**Adverse Effects of Insulin**

*Hypoglycemia*

Major risk of insulin administration is hypoglycemia accompanied with sweating, palpitations, hunger and paresthesias. Tremors, anxiety, confusion, weakness, loss of concentration and convulsions have been observed. If this is not treated promptly, fatality is certain. Therefore, all insulin-taking diabetics must take possible precautionary measures to avoid this. One simple method to avoid hypoglycemia is to carry some amount of easily ingested glucose and to be taken when the early signs of hypoglycemia set in. Hypoglycemic coma is generally treated with intravenous administration of 50% dextrose solution with other supportive measures.

*Insulin Lipoatrophy and Lipohypertrophy*

This is due to cutaneous erosion because of local injection of insulin. Both dissolution of fat at the site of injection and high fat deposition have been reported. It is supposed to be an immune response to impurities present in insulin preparation. Human insulins are less common to produce this side effect. Change in the site of injection is another way to avoid this complication. Insulin edema, insulin allergy and insulin hypokalemia are the other adverse reactions often seen.

**Insulin Resistance**

Resistance to the actions of insulin is common among obese type II diabetic patients. It is defined as a state in which patient requires more than 200 units of insulin/day. Insulin resistance is often self-limited. It is common to switch over to purified insulin preparations to stabilize the patient.

**Diabetic Coma**

This is a medical emergency. When blood sugar level exceeds 250 mg/dl and the levels of plasma ketone bodies rise, an alarming condition prevails because fatality may be seen. Prompt, effective and life-saving measures have to be undertaken without delay. Administration of regular insulin by intravenous route along with fluid and electrolyte replacement, oxygenation and antibiotic may serve the purpose well and save the life of the patient.

**ORAL ANTIDIABETIC DRUGS**

Generally, non-hormonal antidiabetic drugs are given by oral route unlike insulin. Different groups of drugs reduce blood sugar level in diabetic patients when given alone. These drugs can be taken with insulin to reduce its requirement in life-long management of diabetes mellitus.
Classification

Oral antidiabetic drugs are classified into the following groups based on their chemical nature and mechanism of action.

- **Sulfonylurea compounds:**
  - I Generation: Tolbutamide, Acetohexamide, Chlorpropamide
  - II Generation: Glibenclamide, Glipizide, Gliclazide
  - III Generation: Glimepiride
- **Biguanides:** Metformin, Phenformin
- **Insulin sensitizers:** Troglitazone, Pioglitazone, Rosiglitazone
- **α-glucosidase inhibitors:** Acarbose, Miglitol
- **Miscellaneous:** Repaglinide, Nateglinide, Guar gum

Sulfonylurea Compounds

Modern diabetologists prefer II or III generation sulfonylureas to I generation drugs. Reasons for this are: II and III generation drugs are more potent, safer and longer acting agents. Obviously, sulfonylureas are effective only in Type II diabetes mellitus since they require at least 30% functioning β-cells of islets of Langerhans. Hence, these drugs are not useful in Type 1 diabetes mellitus.

**Mechanism of Action**

Sulfonylureas and repaglinide-like drugs act by more or less similar mechanism, i.e. by stimulating insulin secretion from the pancreas. The action on β-cells involves blockade of ATP-sensitive K+ channels which trigger Ca2+ influx through its channels. An increase in cellular Ca2+ promotes insulin release to reduce blood glucose level. Further, extrapancreatic actions of sulfonylurea compounds have been considered for their hypoglycemic effects. However, this remains controversial. Though not clinically significant, extrapancreatic actions of sulfonylureas include: increased insulin receptor density at target sites and stimulation of synthesis of glucose transport proteins.

**Adverse Effects**

Although adverse reactions to sulfonylureas are infrequent, these may cause concern in elderly diabetic patients. Gastrointestinal disturbances like nausea, vomiting, anorexia, hypoglycemia particularly on missing the regular food consumption, cholestatic jaundice, skin rash, drug fever and hyponatremia have been observed.

**Therapeutic Uses**

Sulfonylureas are effective only in Type 2 diabetes mellitus. Initially, response to sulfonylureas may be quite satisfactory. However, as the time passes, progression of β-cell loss results in failure of sulfonylurea therapy. This may cause unacceptable level of hyperglycemia which essentially requires insulin administration. Chlorpropamide is also used in diabetes insipidus.
Drug Interactions

Chlorpropamide + Alcohol
- Peculiar type ‘flush’ which is genetically determined. Chlorpropamide has disulfiram-like action.
- Aspirin, clofibrate and sulfonamides displace sulfonylureas from the protein-binding sites to increase the actions. Insulin and sulfonylureas can be used together.

Contraindications
- Type 1 diabetes mellitus
- Pregnancy
- Lactating mother

Metformin
Metformin is an oral antidiabetic drug. Unlike sulfonylureas, metformin is a euglycemia agent. Metformin does not produce hypoglycemia, however, it tends to normalize glucose level in diabetic patient.

Mechanism of Action
Metformin acts by the following mechanisms:
- Reduces the absorption of glucose
- Promotes the action of insulin at tissue level
- Reduces the hepatic glucose output
- Inhibits gluconeogenesis
Metformin has the ability to reduce insulin resistance, hyperinsulinemia and known to minimize vascular complications observed in diabetic patients.

Therapeutic Uses
Metformin is used both in Type 1 and Type 2 diabetes mellitus with other drugs.

Adverse Effects
- Nausea, vomiting and diarrhoea
- Vitamin B\textsubscript{12} and folic acid deficiency
- Lactic acidosis is rare but common in patients who suffered from this before metformin administration.

Drug Interactions
- With alcohol, metformin increases the risk of lactic acidosis
- When administered with sulfonylureas, more effective—therapeutic synergy.
- Metformin reduces insulin requirement. Hence, therapeutic synergy and cost of hormonal therapy is rationalized.
Contraindications

- Congestive cardiac failure
- COPD
- Lactic acidosis
- Myocardial infarction
- Septicemia

INSULIN SENSITIZERS

Rosiglitazone, pioglitazone and troglitazone act by reducing insulin plasma level as well as decreasing blood sugar level. These are effective only in Type 2 diabetes mellitus by increasing the action of insulin in liver, muscle and adipose tissue. Insulin sensitizers are also known to reduce the severity of insulin resistance. However, clinical experience with insulin sensitizers is far less at present.

ALPHA-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors like acarbose and miglitol have been in use mainly to reduce postprandial blood sugar level. These drugs are administered before each meal to control rise in postprandial rise in glucose level. Side effects like nausea, vomiting and flatulence have been reported with the use of acarbose and miglitol.

ANTIDIABETIC DRUGS AND PHYSIOTHERAPY

All levels of exercise can be performed by people with Type I diabetes mellitus. More importantly, along with the exercise program the patient must do self-monitoring of blood sugar and the data of response to exercise. This will enable the patient safety in particular. Exercise may be useful in preventing or delaying the onset of Type II diabetes mellitus. Preparing the individuals with diabetes mellitus for a safe and enjoyable exercise program is as important as exercise itself. Aerobic exercise should be recommended. Proper hydration is also essential. Precautions should be taken when exercising in extremely hot or cold environments. High resistance exercise using weights is not acceptable for elderly diabetic patients. Moderate weight reduction exercise program for enhancing body strength is recommended to nearly all diabetic patients. It is pertinent that before beginning an exercise program, diabetic patients should undergo medical evaluation. The presence of macro- and microvascular complications may be worsened by the exercise program. Identification of areas of concern will allow the design of an individualized exercise program that can minimize the risk.

The presence of autonomic neuropathy may limit an individual exercise capacity and increase the risk of an adverse cardiovascular event during exercise. Significant peripheral neuropathy is an indication to limit weight-bearing exercise. Therefore, diabetic patients should be screened thoroughly before exercise is advised. It must also be realized that the benefit of exercise in improving the metabolic abnormalities of Type II diabetes mellitus is probably greatest with adequate drug treatment.
DRUGS AFFECTING CALCIUM METABOLISM

CALCIUM METABOLISM
Calcium is an essential electrolyte of the body. Human body contains about 1.2 kg of calcium, of which major part is deposited in the skeleton. Calcium homeostasis is regulated by the interplay of parathyroid hormone; calcitonin and vitamin D. Normally, plasma concentration is kept in range of 2.15 to 2.60 mmol/l. The richest dietary source of calcium is milk and milk products. Leafy vegetables, fortified flour and hard water contain significant amount of calcium. The human requirement of calcium varies with country and culture. Specific guidelines to determine human requirement of calcium are difficult to frame.

Calcium is essential for neurotransmission, muscle contraction, coagulation of blood, cardiac function and cell membrane permeability. Calcium mediates intracellular actions of many hormones.

Calcium is absorbed predominantly from small intestine by active transport and passive diffusion. Vitamin D₃ enhances the active transport of calcium. Excess amount of calcium is excreted in urine and feces. Minor amounts of calcium do appear in milk and sweat.

Calcium salts are used in the management of calcium deficiency states. The commonly used calcium salts are calcium gluconate, calcium gluceptate, calcium glycerophosphate and calcium lactate. Calcium salts in simple general deficiency states are given by mouth. The dose is dependent on patients’ requirements. In severe deficiency states intravenous calcium gluconate is given either as injection or as slow infusion.

Intravenous calcium is administered to reverse cardiac toxicity produced by hyperkalemia and as antidote for hypermagnesemia. In hyperphosphatemia, calcium acetate and calcium carbonate are given orally as phosphate-binding agents to reduce phosphate absorption. Calcium salts are also used as antacids but commonly produce rebound acid secretion.

Hypercalcemia
Hypercalcemia is more commonly due to vitamin D intoxication, primary hyperparathyroidism and malignant diseases. The common symptoms are thirst, polyuria, anorexia, constipation, fatigue, nausea, vomiting and cardiac arrhythmias. Convulsions are the major symptoms of hypercalcemia. Chronic hypercalcemia may produce interstitial nephritis and calcium calculi.

Severe hypercalcemia is treated with rehydration and infusion of normal saline, phosphate and diuretics, especially mannitol or furosemide. Gallium nitrate has been used in hypercalcemia associated with malignancies. Trisodium edetate can also be used to chelate calcium which reduces plasma level of calcium.

Hypocalcemia
Hypocalcemia may be due to decreased intestinal absorption of calcium, vitamin D deficiency-osteomalacia and chronic renal failure. Increased neuromuscular excitability, parasthesias, laryngospasm, carpopedal spasm, muscle cramps and tetany are the common symptoms of
hypocalcemia. Chronic hypocalcemia can lead to dental defects, cataract formation and mental retardation in children.

Hypocalcemia is effectively treated by intravenous administration of 10% calcium gluconate and vitamin D replacement. Convulsion due to tetany is promptly relieved by diazepam. Calcium chloride is more powerful gastric irritant. Calcium salts should not be administered by intramuscular and subcutaneous routes. This may lead to soft tissue calcification on excess administration. Intravenous administration of calcium salts should not cause extravasation (Table 14.2).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Effects</th>
<th>Therapeutic uses</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
<td>Promote calcium absorption and decrease excretion</td>
<td>Synthetic analogs used in tetany</td>
<td>Hypercalcemic hormone</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Acts in conjunction with parathormone</td>
<td>Rickets and osteomalacia</td>
<td>Now regarded as hormone and regulates cell differentiation</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Inhibits osteoclastic activity</td>
<td>Paget’s disease and hypercalcemia</td>
<td>Bone resorption is inhibited—hypocalcemic hormone</td>
</tr>
<tr>
<td>Biphosphonates</td>
<td>Anti-bone resorption</td>
<td>Hypercalcemia associated with malignancy Postmenopausal osteoporosis</td>
<td>Hypocalcemic agent</td>
</tr>
<tr>
<td>Pamidronate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etidronate</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Alendronate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallium nitrate</td>
<td>Inhibits bone resorption, promotes bone formation</td>
<td>Hypercalcemia states</td>
<td>As adjuvant in cancer chemotherapy</td>
</tr>
<tr>
<td>Ethylene diamine tetraacetic acid (EDTA)</td>
<td>Chelates calcium Hydroxyapatite</td>
<td>Calcium-induced cardiac arrhythmias, hypercalcemia associated with malignancy</td>
<td>Calcium chelating agent</td>
</tr>
</tbody>
</table>

**Drug Interaction**

1. Calcium + digoxin: Augmentation of effects of cardiac glycoside and can cause digoxin intoxication
2. Calcium + thiazide diuretics: Hypercalcemia
DRUGS ACTING ON ENDOCRINE SYSTEM

HORMONES OF THE ADRENAL CORTEX

• ADRENOCORTICOSTEROIDS
• CLASSIFICATION
• PHARMACODYNAMICS
• MECHANISM OF ACTION
• PHARMACOLOGICAL ACTIONS
• PHARMACOKINETICS
• ADVERSE EFFECTS
• THERAPEUTIC USES OF CORTICOSTEROIDS
• DRUG INTERACTIONS

ADRENOCORTICOSTEROIDS

Adrenal cortex is the organ of ‘par-excellence’ which maintains the homeostasis crucial for survival. Hormones secreted from adrenal cortex extend actions to almost every cell in the body. Adrenal cortex elaborates a number of hormones, which help the body to adapt well for changing environment, and endows the capacity to resist noxious stimuli.

CLASSIFICATION

Hormones secreted from adrenal cortex are steroidal in nature. Based on the source of corticosteroids, this class of therapeutic agents is grouped into:
- Natural hormones
- Synthetic corticosteroids

1. Natural steroidal hormones of adrenal cortex:
   - Glucocorticoids: Cortisol, Cortisone
   - Mineralocorticoids: Aldosterone
   - Adrenal sex steroids:
     - Androstenedione
     - Testosterone
     - Oestriol

2. Synthetic corticosteroids:
   - Prednisolone, prednisone, methylprednisolone
   - Triamcinolone, clobetasol, flucinolone
   - Betamethasone, dexamethasone
   - Beclomethasone, budesonide, fluticasone

PHARMACODYNAMICS

Mechanism of Action

Corticosteroids are known to act on intracellular steroid receptors. Steroids enter the target cell by diffusion and then form a complex with their cytosolic receptor protein. Steroid-receptor complex undergoes an irreversible activation process that results in its migration to the nucleus. In the nucleus this complex binds to specific DNA regions. As a result, stimulation or regression of gene transcription occurs which modifies protein synthesis. In this way, steroids enhance the production of a protein called ‘lipocortin’ which suppresses inflammation.
Pharmacological Actions

The pharmacological actions of steroids are generally an extension of their physiological effects. Corticosteroids are essential for homeostasis, to sustain stress and for the maintenance of life. The hormones of adrenal cortex based on their predominant physiological actions are referred to as:

- **Glucocorticoids**: Hydrocortisone and other widely used synthetic steroids
- **Mineralocorticoids**: Aldosterone, desoxycorticosterone

Glucocorticoids produce the following actions:
1. Metabolic actions
2. Antiinflammatory
3. Antiimmune (Immunosuppressant)
4. Antigrowth
5. Actions on blood
6. Other effects on bone and gastrointestinal system.

**Metabolic Actions**

Glucocorticoids produce antiinsulin effects on carbohydrate metabolism. Thus, they act as hyperglycemic hormones. Glucocorticoids inhibit glucose uptake and reduce utilisation and increase gluconeogenesis from amino acids. Excess of glucocorticoids produce glycosuria and may even cause diabetes.

Glucocorticoids increase the breakdown of proteins into amino acids and at higher doses cause negative nitrogen balance. Chronic administration of high doses of glucocorticoids produces steroid myopathy, thinning of skin and consequently weakness.

Hydrocortison-like drugs act directly on triglycerides to promote their breakdown and enhance lipolysis. Glucocorticoids when administered at higher doses for prolonged period cause ‘Cushing’s Syndrome’—one of the major characteristic features of this syndrome is peculiar redistribution of body fat from periphery to neck and other parts of trunk. The deposition of fat in these areas is commonly referred to as ‘Buffalo-hump’.

Cortisol at higher dose does influence electrolyte and water metabolism. However, aldosterone is the mineralocorticoid hormone secreted from zona glomerulosa of adrenal cortex that regulates electrolyte and water metabolism in the body. Steroidal hormones promote sodium retention and potassium excretion by kidneys. When given in excess, these produce ‘steroidal edema’ as their side effect.

**Antiinflammatory Effects of Steroids**

Steroidal hormones constitute one of the major groups of antiinflammatory drugs used in modern medicine. Antiinflammatory steroids suppress all the phases of inflammation. The most potent steroidal antiinflammatory glucocorticoids currently used are dexamethasone and betamethasone. In fact, synthetic glucocorticoids are commonly prescribed as antiinflammatory drugs, which include inhalation glucocorticoids, employed in the treatment of bronchial asthma.
Glucocorticoids suppress inflammation by several mechanisms as mentioned below:

- Reduce local heat, redness, swelling and tenderness by direct action, regardless of the types of noxious stimuli that produce inflammation.
- Affect gene transcription to synthesise antiinflammatory protein like lipocortin and macrocortin, which in turn inhibit prostaglandins and lymphokine synthesis.
- Lipocortin inhibits phospholipase A₂. Consequently, inflammatory mediators of arachidonic acid are not released.
- Inhibit cell migration.
- Fibroblast activity is blocked.
- Stabilise the lysosomal membrane.
- Reduce the intensity of the action of collagenase.
- Interfere with the synthesis of various interleukins, which have role in inflammation as well as immune reaction.
- Block the action of macrophage migration inhibition factor, which normally causes accumulation of macrophages at the site of inflammation—thus promoting regress of macrophage from inflammation sites.
- Elaboration of chemoattractants by inflammatory cells is suppressed.
- Inhibit platelet-activating factor.

**Antiallergic and Immunosuppressant Effects**

Glucocorticoids are widely used as immunosuppressants as well as antiallergic drugs in many clinical conditions. Immunosuppressant action of corticosteroids is thought to be due to their action on interleukin synthesis. Corticosteroids inhibit the synthesis of interleukins I and II, which are known to activate T-immune cell proliferation. Further, corticosteroids are known to facilitate the actions of γ-interferons. There is a considerable interest among researchers to link the immunosuppressant action of corticosteroids to lymphocyte apoptosis (means programmed cell death or cell suicide). It should be remembered that at usual therapeutic doses corticosteroids do not produce significant immunosuppression.

It is believed that antiallergic actions of corticosteroids are attributable to their effects on immune response and the inhibition of antigen and antibody interaction. In addition to this, corticosteroids reduce antibody formation.

**Antigrowth Effects**

The cell growth of epiphyseal cartilage is inhibited by large doses of glucocorticoids. This action is predominantly observed in children. Fibroblast mitotic activity is also inhibited by glucocorticoids. Hence, corticosteroids delay wound healing.

**Action on Blood**

Glucocorticoids stimulate hemoglobin formation and increase the number of polymorphs, whereas circulating lymphocytes, eosinophils, and basophil number is decreased by steroids. Glucocorticoids stimulate the release of erythropoietin and increase erythrocyte population.
Actions on Bone

Calcium absorption is disrupted and the renal excretion of calcium is augmented by glucocorticoids. There is increased resorption of bone with glucocorticoid therapy. These effects of glucocorticoids result in osteoporosis as these agents have moderate antivitamin D effects. Steroid-induced osteoporosis can be treated with cholecalciferol.

Other actions of glucocorticoids include increased acid and pepsin secretion in the stomach and mucosal resistance to irritants is interrupted by steroids.

PHARMACOKINETICS

Corticosteroids are given by different routes—topical application, inhalation, oral, intravenous, intramuscular and intraarticular. Hydrocortisone (cortisol) remains 95% bound in plasma to transcortin—an α globulin. Steroids are excreted as 17-ketosteroids in the urine besides as glucuronide conjugates.

ADVERSE EFFECTS

A single large dose of glucocorticoid is virtually non-toxic. A few days of therapy with recommended doses may be non-toxic. However, chronic therapy increases the incidence of toxicity and benefits must be measured in terms of potential risks.

Adverse reactions in terms of glucocorticoids are very well seen even on topical application for a long period. The local adverse effects are: striae, dermal atrophy, rebound pustulations, perioral dermatitis, increased infection due to local tissue level immunosuppression and masking infections caused by fungus and virus.

The systemic adverse reactions of steroids are numerous.

- **Endocrinal toxicity:** “Cushing’s syndrome”: Hyperglycemia, glycosuria, secondary amenorrhoea, suppression of hypothalamo-pituitary-adrenal axis.
- **Metabolic toxicity:** Diabetes mellitus, hyperosmolar coma, hyperlipidemia, centripetal obesity, hirsutism, acne, negative nitrogen balance.
- **Gastrointestinal toxicity:** Peptic ulcer, gastrointestinal hemorrhage, intestinal perforation, pancreatitis.
- **Musculoskeletal toxicity:** Myopathy, osteoporosis, vertebral compression fractures, aseptic necrosis of bone.
- **Cardiovascular toxicity:** Hypertension, edema, congestive cardiac failure, hypokalemia, alkalosis, hypercoagulability of blood.
- **Ocular toxicity:** Glaucoma, posterior subcapsular cataract.
- **Central nervous system toxicities:** Euphoria, acute psychosis, pseudocerebral tumor.
- **Other toxicities:** Superinfection, delayed wound healing and steroidal arthropathy on repeated intraarticular administration.

Sudden withdrawal of corticosteroids from therapy precipitates “steroid withdrawal syndrome”. This may cause acute adrenal insufficiency, hypoglycemia, hypotension, dehydration and death. Therefore, it is important to taper the dose of steroids gradually and withdrawn over a period of a few weeks. Nevertheless, recovery of normal pituitary adrenal function may take 9 months to 2 years.
THERAPEUTIC USES OF CORTICOSTEROIDS

A host of different preparations of steroids are in current use:
• Short acting: Hydrocortisone
• Intermediate acting: Prednisone, Prednisolone, Triamcinolone
• Long acting: Dexamethasone, Betamethasone

Invariably, steroids are given either:
• Short-term high dose
• Long-term low dose
• Alternate day, long-term higher dose to minimize adverse effects.

This also hopefully avoids steroid dependence. To achieve maximum benefit, single total daily morning dose is employed and as early as possible steroids may be gradually withdrawn. However, all clinical conditions may not respond to this kind of administration, for example, systemic lupus erythematosus, nephrotic syndrome and thrombocytopenic purpura.

The doses of steroid must be determined by trial and error method, and to avoid steroid withdrawal effects, it should be withdrawn gradually by tapering the dose on monitoring adrenal function.

The therapeutic uses of glucocorticoids are largely empirical (based on clinical experience). The use of steroids is neither etiological nor curative but remains palliative. However, steroids have been used in a large number of diseases for their antiinflammatory, antiallergic, immunosuppressive effects apart from hormone replacement therapy.

Hormone Replacement Therapy

Both mineralocorticoids and glucocorticoids have to be replaced in primary idiopathic hypofunction of adrenal cortex and adrenalectomised individuals.

In acute addisonian crisis (severe deficiency of corticosteroids), hydrocortisone sodium hemisuccinate is given intravenously along with fluids, electrolyte and glucose supplementation to save the life of patient. For chronic Addison’s disease, hydrocortisone daily morning 20 mg and evening 10 mg is administered with a mineralocorticoid fludrocortisone 0.1 or 0.2 mg/day.

Inflammatory Diseases

Anti-inflammatory glucocorticoids are extensively indicated in a variety of diseases. Rheumatoid arthritis, rheumatic carditis, osteoarthritis and inflammatory gastrointestinal diseases like ulcerative colitis. Also, in ocular diseases like uveitis and other inflammatory diseases of eye, corticosteroids are extensively used. However, the duration of therapy must be as short as possible.

Collagen Diseases

For polymyositis, polyarteritis nodosa, temporal arteritis and polymyalgia, corticosteroids have proven therapeutic value.

Antiallergic Uses

With or without H1 receptor blockers, glucocorticoids are used in various allergic disorders. In fact, glucocorticoid administration is a life-saving measure in anaphylactic shock and status
asthmaticus. Hay fever, serum sickness, contact dermatitis, bee stings, angioneurotic edema are the clinical conditions for which glucocorticoids remain as therapeutically valuable agents.

**Antiimmune Uses**

Prednisolone was the first drug to be used as antirejection agent to prevent graft-versus-host disease. In acute lymphocytic leukemia, lymphomas and myasthenia gravis, antiimmune effects of corticosteroids are of substantial therapeutic benefit.

**Skin Diseases**

Pemphigus vulgaris is one of the definite indications for glucocorticoids. Hypersensitivity skin rashes do respond well for glucocorticoid administration. In eczema and fulminating systemic lupus erythematosus in particular, steroids are useful.

**Other Uses**

- Shock
- Cerebral edema
- Sarcoidosis
- Nephrotic syndrome
- Hepatic necrosis
- Idiopathic thrombocytopenic purpura
- Some forms of hemolytic anemia
- As a component of antiemetic treatment to prevent anticancer drug-induced emesis
- As diagnostic agents in hypercorticism, adrenal neoplasia and ACTH producing tumors.

**DRUG INTERACTIONS**

1. Corticosteroids counteract the actions of drugs that reduce intraocular pressure in glaucoma.
2. With NSAIDs, steroids act synergistically to render more therapeutic benefit.
3. Vitamin A reduces antiwound healing effects of steroids.
4. Metyrapone inhibits the synthesis of glucocorticoids by arresting 11-β-hydroxylase.
5. Aminoglutethimide inhibits steroidogenesis.
INTRODUCTION
Sex steroids influence development, maintenance of structures directly and indirectly associated with reproduction. Sex hormones are secreted from gonads, placenta adrenal cortex and adipocyte. Conventionally, sex steroids are grouped as:
1. Estrogen and progesterone (female sex hormones)
2. Androgens (male sex hormones).

Besides natural sex hormones, various steroids and non-steroidal synthetic analogues of sex hormones have been in use. Mainly, sex steroids have been indicated in conditions of hormonal deficiency-related clinical conditions. Hence, this is popularly referred to as hormonal replacement therapy. In addition, female sex hormonal preparations have been extensively used as contraceptives to avoid unwanted pregnancy. Some success have been achieved in infertile men and women with antiestrogens. Abuse of androgens for their anabolic action among sportsmen has been a menace in the world of sports. Sex steroids should not be used indiscriminately.

ESTROGENS
Estrogens based on their source and structure are classified into following groups:

<table>
<thead>
<tr>
<th>Natural</th>
<th>Synthetic steroids</th>
<th>Synthetic non-steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>Ethinylestradiol</td>
<td>Diethylstilbestrol</td>
</tr>
<tr>
<td>Estrone</td>
<td>Mestranol</td>
<td>Chlortrianisene</td>
</tr>
<tr>
<td>Estriol</td>
<td>Quinestrol</td>
<td>Equlilin</td>
</tr>
</tbody>
</table>

Mechanism of Action
Estrogen combines with estrogen receptors present in various tissues namely female reproductive tract, hypothalamus, pituitary, breast, bone and liver and causes transcriptional activation by enhanced gene expression. As a result, new proteins are synthesized which produce action on an organ system.

Pharmacological Actions
Estrogens produce numerous physiological functions and are responsible for the development of female habitus features—secondary sexual characteristics. Estrogen controls ovulation,
cyclic preparations of the female reproductive tract for fertilization and implantation. Further, estrogen has major action on mineral and other metabolic pathways. The female sex hormone estrogen increases mass of bone by inhibiting bone resorption. The hydroxylase enzymatic activity that converts vitamin D into vitamin D₃ is augmented by estrogen. On lipid metabolism estrogen increases HDL level and LDL is reduced. The synthesis of clotting factors is also enhanced by estrogen.

Estrogens are administered by various routes. The commonly used routes are oral, transdermal, subcutaneous implantation in the form of pellets, intramuscular and topical vaginal applications. Estrogens are excreted in urine as sulphate and glucuronic acid conjugates. The rate of metabolism of estrogen is known to vary with menstrual cycle stages and pre- and post-menopausal phases.

Adverse Effects
Administration of estrogen produces a wide variety of toxicities some of which may abate with time and some definitely cause concern.

Gastrointestinal System
Nausea and vomiting appear as characteristic adverse effects of estrogen therapy. To minimize this, estrogen may be taken before retiring at night. Jaundice and gallstones have also been reported.

Cardiovascular System
Thromboembolic diseases, hypertension, edema

Reproductive Tract
Menstrual disorders, tenderness in the breast, breast enlargement, gynecomastia and feminization in males.

Carcinogenicity
Endometrial carcinoma and breast cancer may be produced. The risk of endometrial carcinoma can be minimized by cyclic treatment of estrogens and concomitant use of progesterone where possible.

Skin
Hyperpigmentation, chloasma, melasma

Others
Migraine, depression and weight gain.

Therapeutic Uses
1. Hypogonadism—hormone replacement therapy
2. Osteoporosis
3. Postmenopausal syndrome
4. Atrophic vaginitis
5. As hormonal contraceptive with progesterone
6. Prostatic cancer

**Drug Interactions**
1. With rifampicin decreased efficacy because rifampicin increases the rate of estrogen metabolism.
2. Warfarin efficacy is reduced by estrogen since it enhances the clotting factor synthesis.

**Contraindications**
1. Estrogen-dependent neoplastic conditions
2. Thromboembolic diseases
3. Severe cardiovascular diseases
4. Endometriosis
5. Liver diseases

**ANTIESTROGENS**
Progesterone and androgens produce antiestrogen actions. However, clomiphene and tamoxifen by blocking estrogen receptors produce their therapeutic actions. Clomiphene is used as ovulation-inducing agent in infertility and tamoxifen in breast carcinoma.

**PROGESTERONES (PROGESTINS)**
Progesterone is the natural hormone secreted from ovary and placenta. Synthetic progestins are grouped into two subtypes:
1. 21 carbon derivatives: Hydroxyprogesterone, medroxyprogesterone
2. 19 carbon derivatives: Norethisterone, norgestrel.

**Mechanism of Action**
Progesterone combines with its receptor and activates gene transcription.

**Pharmacological Actions**
*On reproductive tract:*
- Progesterone controls estrogen-stimulated endometrial proliferation, an antiestrogen action.
- The development of secretory endometrium is regulated by progesterone and abrupt decline in progesterone release is the main cause of onset of menstruation.
- Modulates endocervical gland secretion to scant viscid material to water secretion instead.
- Known to play a role in affecting the penetration of sperm in the cervix.
- In pregnancy, progesterone inhibits menstruation and reduces uterine contractility.
- Proliferation of milk secreting acini is also influenced by progesterone.
Pharmacology for Physiotherapist

On central nervous system:
- Progesterone is a thermogenic hormone
- It increases the CO₂ stimulant action on respiratory system
- Under normal physiological circumstances progesterone acts as a hypnotic

Therapeutic Uses
1. Major use of progesterone is in combination with estrogen to control fertility as hormonal contraceptive
2. Dysmenorrhoea
3. Endometriosis
4. Dysfunctional uterine bleeding
5. Metastatic endometrial carcinoma.

Adverse Effects
Nausea, vomiting, edema, weight gain, hypertension and galactorrhoea are the adverse reactions commonly seen with progesterone therapy.

ANTIPROGESTERONES
Mifepristone
Mifepristone competitively blocks the progesterone receptor. This drug is used in endometriosis and as postcoital contraceptive.

ANDROGENS
Hormone testosterone is a natural androgen secreted from testis and adrenal cortex as well as adipocyte. Therapeutically used androgens are classified into the following groups:
1. Natural: Testosterone
2. Synthetic: Methyltestosterone, testosterone enanthate, fluoxymesterone
3. Anabolic steroids: Nandrolone decanoate, stanozolol, oxandrolone
4. Impeded androgen: Danazol.

Mechanism of Action
Testosterone combines with intracellular receptors to enhance gene transcription and protein synthesis. Testosterone increases RNA polymerase enzyme action.

Pharmacological Actions
Testosterone transforms boy to a man. It promotes the development of male type skin, prostate, seminal vesicle, epididymus, long bones, vocal cord and sebaceous glands.

In pharmacological doses, androgen produces anabolic effect. An androgen with anabolic actions is known to produce growth of muscles above the normal level, increases bone mass, and stimulates erythropoiesis with lack of fatigue, euphoria, salt and water retention. Further, anabolic steroids reduce HDL levels, testicular size and weight decrease.

All over the world, anabolic steroids are misused by sportsmen. In view of increasing athletic performance anabolic steroids have been abused. This is universally deplored because this cannot be substantiated with any scientific or medical evidences so far. On the other
hand, abuse to anabolic steroids invites risk of hepatic malignancies, suppression of spermatogenesis, edema, decreased HDL and side effects are more in men. Therefore, abuse to anabolic steroids needs to be discouraged.

Anabolic steroids are used in the state of chronic debility to promote tissue growth. Aplastic anaemia and HIV wasting along with cytotoxic drug therapy are other few occasions where anabolic steroids are indicated.

CONTRAINDICATIONS FOR ANABOLIC STEROIDS
1. Jaundice
2. Pregnancy
3. Breast carcinoma
4. Prostate carcinoma
5. Congestive cardiac failure
6. Hypertension.

DANAZOL
Danazol is an impeded androgen, in the sense it has mild androgen action with no estrogen or progesterone activity. Danazol reduces gonadal and adrenal steroidogenesis. Being an orphan drug, danazol is used in hereditary angioneurotic edema. It is also used in gynaecomastia in men, idiopathic thrombocytopenic purpura, menorrhagia, endometriosis and precocious puberty.

HORMONAL CONTRACEPTIVES
Contraceptive is an agent that inhibits conception and used to control unwanted pregnancies. The contraceptive preparations must be simple, safe, effective, affordable, acceptable and completely reliable. More importantly, a contraceptive preparation must produce reversible loss of fertility. As and when couple desire to have a child, they may do so by discontinuing the contraceptive. Currently, this is possible with pharmacologic methods of contraception, as against surgical methods, by which reversibility of fertility control is not always successful.

The pharmacological methods of contraception include the following types:
1. **Oral contraceptives:**
   a. Steroidal preparation:
      i. Combined pill
      ii. Sequential pill
      iii. Mini pill
      iv. Postcoital pill
   b. Non-steroidal:
      i. Centchroman (SAHELI)
2. **Parenteral contraceptives:**
   Medroxyprogesterone injection—IM
3. **Implantable contraceptive:**
   Norgestrel: May work for 5 years.

Among the hormonal contraceptives, combined pill is very popular since it is reliable and highly efficacious. This preparation contains both estrogen and progesterone administered from 5th day of menstruation cycle up to 25th day. There are various types of combined
pill preparations—monophasic, biphasic and triphasic where estrogen content is more rationalized to minimize its side effects.

**Mechanism of Action**
The combination of estrogen and progesterone for contraceptive purposes acts by several mechanisms to control fertility:
1. Inhibition of ovulation
2. Inhibition of mid-menstruation cycle surge of FSH and LH
3. Inhibition of graafian follicle maturation
4. Reduction of GnRH pulse secretion
5. Act as antiimpregnation and antiimplantation agent
6. Impeding tubal transport of fertilized ovum
7. Reduction of cervical mucus secretion.

**Method of Administration**
Combined and sequential oral contraceptive pills are given for 21 days from 5th day of menstruation cycle, a pill for the day. Regularity in medication is of great importance; if the pill is missed, it should be taken within 12 hours. If this is not possible, other methods for contraception needs to be adopted to avoid pregnancy.

**Minipill** contains only progesterone. This pill should be taken daily non-stop in all the menstruation days and throughout the cycle.

**Postcoital pill** regimens are of different types. These are known as emergency contraceptive pills usually employed in rape and incest. Mifepristone 600 mg single dose or ethinyl estradiol 2.5 mg twice daily for 5 days or 25 mg of diethylstilbestrol twice daily for 5 days are given. To be on safer side, postcoital pill should be taken within 72 hours of sexual intercourse.

**Adverse Effects**
Modern hormonal contraceptive pill is relatively non-toxic with minimal health risks. However, these can cause nausea, vomiting, headache, edema, uterine bleeding, weight gain, migraine, thromboembolic diseases, depression, hypertension, hyperpigmentation, chloasma, melasma, jaundice, carcinoma of cervix, breast and liver, acne, teratogenicity, hirsutism and gallbladder diseases.

**Contraindications**
Contraceptive pill is contraindicated in thromboembolic diseases, cerebrovascular diseases, myocardial infarction, breast carcinoma, carcinoma of reproductive tract, undiagnosed vaginal bleeding and pregnancy. These preparations have to be used with extreme caution in migraine, diabetes mellitus, hypertension, obstructive jaundice, epilepsy and eczema.

**Drug Interactions**
1. Enzyme inducers like rifampicin decrease the efficacy of hormonal contraceptive pill resulting in pregnancy.
2. Vitamin C increases the pill efficacy.
The clinical management of wound involves prompt, effective and specific modalities of treatment. If these are attended judiciously and meticulously, both patient’s agony and cost of medical care can be substantially reduced. Any wound—traumatic or surgical would eventually heal. But the rate and quality of healing and consequential scar may be different under different circumstances. This is a source of concern in clinical practice. A few decades ago, almost no one knew that normal wound healing could be therapeutically manipulated. Now, this approach is making a significant trend leading to the advent of a new field—pharmacology of wound.

WOUND HEALING
A clear understanding of the biology of wound healing is essential to design treatment modalities for wound complications and problems. The process of wound healing involves the following phases:

- Hemostasis and fibrin deposition
- Inflammation
- Wound debridement
- Collagenation
- Wound contraction
- Epithelialization
- Scar modulation

In short, wound healing is the result of cell movement, cell division and cellular synthesis of various proteins culminating in the formation of scar. Wound healing never restores the original architecture of disrupted tissue.

Coagulation of blood is a prelude for wound repair. Unless the bleeding is stopped at the site of injury, healing cannot occur. Chemotaxis, cell migration, cell adhesion and inflammation pave the way for tissue repair. A plethora of cytokines, chemoattractants, proteolytic enzymes, fibrin degradation products, growth factors, matrix proteins, prostaglandins, kinins, histamine, serotonin, oxygen and trace elements take part in the
process of wound healing. Further, immune response is also inextricably linked to wound healing. Many endogenous and exogenous factors affect wound repair (Table 15.1).

**Table 15.1: Endogenous and exogenous factors that affect wound repair**

<table>
<thead>
<tr>
<th>Local factors</th>
<th>Infection, radiation, surgical trauma, hypovolemia, hypoxia, oxygen tension, wound dressing, temperature, histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic factors</td>
<td>Age, nutritional state, anemia, mineral deficiency, vitamin deficiency, malignant disease, diabetes mellitus, uremia, jaundice</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Platelet-derived growth factor (PDGF), transforming growth factor (TGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), macrophage-derived growth factor (MDGF), tumor necrosis factor (TNF), growth inhibitory factor, insulin growth factor I and II, nerve growth factor (NGF), interleukins</td>
</tr>
<tr>
<td>Drugs</td>
<td>Cytotoxic drugs, immunosuppressants, NSAIDs, corticosteroids, antiseptics, local anesthetics and others</td>
</tr>
</tbody>
</table>

Therapeutics of wound repair is emerging as a specialty by itself. Methods of suturing, types of dressing, suture materials and drug therapy are all vital for clinical management of wound. It is well perceived that all the events that occur during healing are amenable to drug action. Hemostatics, antiplatelet drugs, procoagulants, anticoagulants, anti-inflammatory agents and immunosuppressants are known to affect tissue repair process. Similarly, antigrowth factors, antiangiogenesis agents, antibiotics and antiproliferative cytotoxic drugs may well affect the process of wound healing. Therefore, there is every reason to have wound healing profile of all the drugs that are employed before, during and after surgery. Indeed, this will avoid any variation in the quality of tissue repair.

Currently, clinicians are left with a few choices of drugs with wound management. Frequently, hemostyptics, antiseptics, astringents, local anesthetics, antiinflammatory and antimicrobials have been used for wound care. Nobody knows that such use of drugs disrupt or promote wound healing. Of late, there is tendency to understand these implications of drug therapy on wound healing in clinical practice. Obviously, drug therapy can be designed for co-morbidities should not impair wound healing. Unfortunately it is not always so. It is necessary to declare that any drug that is administered for different purposes is free from adverse effects on wound repair, for example, withdrawal of adriamycin and steroidal antiinflammatory drugs in presence of extensive injury are now being considered to avoid wound complications. These observations span the development of wound therapeutics.

Evidently, drugs do not affect all the wound parameters in the same way. Grossly, the agents that affect healing process can be classified into two broad groups—prohealers and antihealers (Table 15.2).

**Table 15.2: Different group of drugs that modulate tissue repair process**

<table>
<thead>
<tr>
<th>Prohealers</th>
<th>Platelet-derived growth factor, epidermal growth factor, fibroblast growth factor, thrombin, Botropase, vitamin A, vitamin C, insulin growth factor, zinc, placental extract and others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihealers</td>
<td>Anticancer agents, immunosuppressants, NSAIDs, glucocorticoids, vitamin E, semicarbazide, transforming growth factor-β (TGF-β), progesterone, potassium permanganate, penicillamine, lathyrogens</td>
</tr>
</tbody>
</table>
Wound healing can be stimulated by PDGF, FGF and EGF. A few formulations of these have already been introduced. Certainly, this would bring new trends in the management of wound. Modern wound healing research has recognized the wound healing stimulant actions of macrophage-derived growth factor, tumor necrosis factor, insulin-like growth factor, nerve growth factor and some of the interleukins. However, much remains to be done to introduce these growth factors as prohealers. Many vitamins and trace elements produce pronounced effects on wound healing. Vitamins play a critical role in wound healing. Vitamin A maintains the epithelial integrity and counteracts the wound healing suppressant actions of cytotoxic drugs like cyclophosphamide. Pyridoxine and thiamine deficiency affect collagen organization and the wound strength. Ascorbic acid is essential for hydroxylation of proline and lysine in collagen synthesis. Vitamin D as a potent regulator of cell growth and differentiation interacts with hemopoietic, immune and skin cells. This will affect wound healing by multiple ways. Vitamin E is known to affect collagen synthesis.

Steroidal and non-steroidal antiinflammatory drugs suppress wound healing. However, the copper or zinc complexing of NSAIDs has knocked out the antihealing effects of NSAIDs. Days are not far wherein copper and zinc salts of NSAIDs may be preferred for wound pain management over conventional preparations.

One of the major problems of wound healing studies is to understand how the process of wound healing is called off. What regulates wound repair? The answers for these are yet to come. However, it is believed that transforming growth factor-β (TGF-β) functions as ‘pan regulin’ of tissue repair. Nevertheless, overproduction of TGF-β has been implicated as causative factor in lung fibrosis, hepatic cirrhosis, bleomycin-induced lung fibrosis and cardiac fibrosis after infarction. Further, TGF-β antigen is used to curb fibrosis. Yet, time is not ripe to define therapeutic approaches to mitigate the mechanism of overfibrosis, stenosis and stricture.

In modern clinical practice, sterile bulky gauze wound dressing is commonly employed. Often, antibiotic impregnated dressings, wet dressings and dry dressings have also been used. It has been well observed that petroleum-impregnated fine mesh gauze dressing is superior to wet dressing. Wet dressing promotes re-epithelialization. Antibiotics used along with wound dressings do interfere with the process of wound healing. However, the available data are sparse. Pertinently, various ointment bases used for wound application interfere with wound repair. The significance of this intervention is often neglected in the profession.

Recently, it has been revealed that exercise increases the expression of mechanogrowth factor, which induces local protein synthesis and prevents apoptosis. Mechanogrowth factor has an important role in local tissue repair and remodeling. There is a link between physical activity and mechanogrowth factor with muscle insulin growth factor I and gene expression. This underlines the need for remaining active which regulates muscle mass.

EXERCISE AND WOUND HEALING

A well-designed therapeutic exercise should not be a hurdle for wound healing. When the wound is large, the type of dressing employed may offer obstacle to exercise. Simple exercise may not alter the quality of wound healing. However, vigorous exercise is likely to cause undue stretching of wound tissue and may alter collagen fiber orientation and fibrilogenesis.
Care is essential to avoid this. Exercise may increase blood supply to peripheral wound. The impact of increased blood flow to wound and wound dressing pressure during exercise are likely to disturb texture of wound tissue. As a result, the strength of wound scar may be reduced and the healed tissue resilience may be poor. This is a source of concern because wound dehiscence may occur eventually leading to incisional hernia.

In diabetic patients, wound complications are common. Surgical wound debridement, antibiotics, proper hormonal glycemic control and topical formulations have been used for diabetic ulcer wounds. The physiotherapist must be aware of this fact and take appropriate steps not to aggravate wound complications in diabetic patients. It is essential to design a beneficial and sustainable exercise program for injury stricken patients. It is better to indulge in active exercise after the healing of wound.
Drugs for Parkinsonism

WHAT IS PARKINSONISM?

Parkinsonism is a neurodegenerative disease, which generally afflicts elderly male after 50 to 65 years of age. This was first described by James Parkinson in the year 1817 and hence the name. The etiology of parkinsonism is yet a mystery to science. It is believed that both internally generated and extent toxic substances-induced mechanisms are responsible for Parkinson’s disease. Neuropathologically, parkinsonism is due to progressive destruction of dopaminergic neurons in substantia nigra in the brain.

TYPES AND CLINICAL FEATURES

Clinically, parkinsonism is classified into:
1. Idiopathic parkinsonism (reasons unknown)
2. Postencephalitic parkinsonism (viral infection)
3. Parkinsonism plus syndrome
4. Drug-induced parkinsonism (Reserpine and neuroleptic drugs)

Parkinsonism is characterized by three cardinal clinical features as well as secondary signs. Tremor, muscle rigidity and bradykinesia are the major features. Tremor is most frequent at rest and disappears with movement and sleep. Muscle rigidity offers persistent resistance to passive movement. Parkinsonism presents an excessive array of secondary signs; patient’s handwriting becomes smaller, facial expression and eye blink rate are reduced. Soft voice, excessive salivation, constipation, mental depression, impairment of cognitive functions and orthostatic hypotension can also be seen.
CLASSIFICATION OF DRUGS USED IN PARKINSONISM

Antiparkinsonism drugs are classified on their mechanism of action into the following groups.
1. Neuroprotective: MAO-B inhibitor—Selegiline
2. Dopaminergic agonists: Bromocriptine, Pergolide
3. Dopamine precursor + peripheral decarboxylase inhibitors: Levodopa + Carbidopa
4. Anticholinergics-antimuscarinics: Trihexyphenidyl (Benzhexol), Benztropine
5. Miscellaneous: Amantidine, Memantidine, Pramipexole, Entacapone, Naxagolide, Ropinirole

SELEGILINE
Selegiline is a selective monoaminooxidase-B (MAO-B) enzyme inhibitor. Selegiline acts by increasing dopamine turnover in substantia nigra. This drug has received more attention for its possible neuroprotective effect. It is given by mouth with breakfast and lunch. Selegiline when administered with levodopa increases the adverse effects of latter. Hypertension, chest pain, nausea, vomiting, psychosis and difficulty in micturition have been disturbing effects of selegiline. Selegiline is being tried in dementia and depression in vain. Selegiline is given in the early stage of parkinsonism to postpone levodopa therapy.

LEVODOPA + CARBIDOPA
Parkinsonism is due to deficiency of dopamine in substantia nigra. Dopamine as such cannot be given because it does not cross blood-brain barrier. Hence, dopamine precursor levodopa (L-di-hydroxy phenylalanine, L-dopa) which reaches brain readily is used in parkinsonism. On reaching brain it gets converted into dopamine by catalytic action of central dopamine decarboxylase enzyme. Levodopa is given by oral route. It is important to inhibit peripheral conversion of L-dopa into dopamine, to promote its central effects and to minimize peripheral adverse effects of L-dopa. Therefore, a peripheral decarboxylase inhibitor carbidopa is given with L-dopa. Carbidopa does not cross blood-brain barrier and cannot inhibit central conversion of L-dopa into dopamine. The combination of L-dopa with carbidopa enables the dosage of L-dopa to be reduced, which may diminish peripheral side effects of L-dopa.

Levodopa is the single most effective agent for idiopathic and postencephalitic parkinsonism. L-dopa is not effective in drug-induced parkinsonism. Drugs that produce parkinsonism block dopamine receptors and L-dopa administration do not deblock the receptors effectively.

L-dopa therapy may not be beneficial after continued administration for 5-8 years. Disability in mobility increases as a result of decrease in the efficacy of L-dopa.

Adverse Effects
In the early part of treatment, nausea, vomiting and anorexia are common with L-dopa. Orthostatic hypotension and cardiac arrhythmias, anxiety, agitation, dizziness, depression, malignant neuroleptic syndrome, abnormal involuntary movements and severe choreoathetoid movements may occur with L-dopa therapy. End-dose-dyskinesia is one of the long-term complications of L-dopa perennial treatment. It is recognized that this may be due to
progression of disease rather than to L-dopa. L-dopa is contraindicated in patients with narrow angle glaucoma.

**Drugs Interactions**

1. L-dopa + Selegiline: High incidence of L-dopa adverse effects
2. L-dopa + Antidepressants: Hypertensive crisis with amitriptyline
3. L-dopa + Diazepam: Reversible deterioration of L-dopa effects.
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