A Short Textbook of MEDICAL PHARMACOLOGY

Md Abdus Salam

Foreword
AFM Saiful Islam

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Dedicated to
my sons
Adan Ibna Salam and Karar Ibna Salam

Foreword

It gives me the heartiest pleasure to put down a few words about this short textbook on medical pharmacology. This book is an honest attempt to provide a clear concept to the MBBS and postgraduate medical students in their preparation for the courses as well as during their research afterwards.

The author has tried his best to keep the language simple and lucid, which even a lay reader will understand. The presentation of drugs is given in a format basis, which can be memorized easily for viva voce and residual knowledge. This book will help the students to prepare for the examinations and strengthen their basic knowledge while making themselves ready for further competitive studies in future life.

I wish every success to the students using this book and would like to congratulate the author and Jaypee Brothers Medical Publishers (P) LTD for bringing out this short textbook, which is enormously useful.

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Preface

It is a difficult job to make a precise preface for any book, but each and every publication demands it. In fact, medical pharmacology is a basic subject, the science of drug, happens to be an apparently small but actually a vast and intricate subject.

As the present curriculum is difficult for the students to be oriented without a proper guidelines well, there is no such books available to guide students through this maze. Norms demand basic question in basic subject should be answered basically. It was with this vision that this endeavor was undertaken to compiling a thorough, yet simple text that would endow a student with ability of answering in the **what, why, when, where, who, and how** (wherever possible), to face the difficulties of memorizing the curriculum.

All the information in this book have been provided by consulting throughly a textbook of pharmacology line by line lest any important fact be eliminated. So, if anybody tries to make his or her study-time mostly effective, this book will motivate the person a lot. Best wishes to all.

"With every breaking of the morn
Fresh opportunities are newly borne"

Md Abdus Salam

Acknowledgments

When I was checking the final proof of this book, my memories suddenly took me back to the time when I had initiated the scheme 18 years ago. I offer my humble submission and express immense gratitude to Almighty Allah for allowing me to live in comfort all these years and helping me finish writing this book.

- I pay tribute to my great teacher Professor SAR Chowdhury, Former Chairman of the Department of Pharmacology at BSMMU, who is currently working with Glaxowelfare Pharmaceuticals. I am largely indebted to him because he basically taught me the studies of pharmacology.
- Professor AFM Saiful Islam, Additional Director General (Admin), Directorate General of Health Services, Bangladesh, has dubbed my book as the greatest work of my life. I am very grateful to him for his kindness and co-operation.
- Professor Shah Abdul Latif, Director, Medical Education, has termed my book a praiseworthy piece of work and said my teaching career has attained its goal with the publication of this book. I am grateful to him for his inspiration and suggestions.
- I have met with so many teachers and colleagues during my service under the Government of Bangladesh. They have encouraged and inspired me throughout my career. I regret that space does not allow me to mention all of them by name. But it would be unfair if I don't mention the following persons for their motivation:
  - Professor Md Nurul Islam of Pharmacology
  - Professor Md Zahurul Haque of Pharmacology
  - Professor Rafiqul Akhter of Pharmacology
  - Professor Feroza Parveen of Pharmacology
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  - Dr Jalal Bangalee, Assistant Professor, Medicine
  - Professor Saiful Bari of Cardiology. He was my Principal during my posting in Dinajpur. He inspired me a lot to continue with writing this book in those apparently uncomfortable days of my professional life.
  - Dr AKM Asaduzzaman, Assistant Professor of Community Medicine, CME.
  - Dr Abdus Satter Fora-a-zi, General Secretary of BMA, Noakhali.
- My students with their thirst for knowledge, profound desire to serve humanity and evergreen youth have given me the motivation to do something for them. Their love and respect have kept me on the right path to completion of this work.
- Finally, my wife Rabeya Akhter Parveen and sons, Adan Ibna Salam and Karar Ibna Salam, with their physical presence have immensely contributed to writing of this book. Without them, I could not come out to be successful. I am grateful to my family members for their continued support to me.

Contents

CHAPTER

1

General Pharmacology

SECTION-I INTRODUCTION TO PHARMACOLOGY

- **Pharmacology** is the **interactions** between the **living system** and various substances **(drugs)**.
- Living system means, either the whole living being or part of the living being (e.g. isolated tissues of animals).
- **According to WHO (World Health Organization) drug is any substance or product that is used or intended to be used to modify or explore the physiological system or pathological states for the benefit of the recipient**. In a simplified language, a drug is a substance which is used for the purpose of —
  a. Prevention, i.e. use of BCG against TB.
  b. Diagnosis, i.e. use of barium sulfate in barium meal X-ray of stomach and duodenum to differentiate lesions in the said organs.
  c. Cure, i.e. INH to cure TB.

INTERACTIONS

Interactions are of two types. These are—

1. What the body does to the drug, i.e. **Pharmacokinetics**, which includes—
   a. Absorption
   b. Distribution
   c. Biotransformation
   d. Excretion.
2. What the drug does to the body, i.e. **Pharmacodynamics**. Major components of pharmacodynamic study are—
   a. Effects of the drug
   b. The mechanism of drug action
   c. Quantitative interrelationship between drug dose and drug effect.

So the two important branches of pharmacology are—

1. **Pharmacokinetics**
2. **Pharmacodynamics**.

Other branches of pharmacology are—

1. **Experimental pharmacology** is the study of drugs in animals other than human being.
2. **Clinical pharmacology** is the scientific study of drugs in cases of human being.
3. **Pharmacy** is the study of preparation and dispensing of drug.
4. **Toxicology** deals with poison and poisoning.
5. **Pharmacognosy** deals with the botanical sources of drugs.
6. **Pharmacogenetics** is the study of genetically mediated variations in drug response.
7. **Therapeutics** is the practical application of drugs in the treatment and prevention of diseases.
8. **Chemotherapy** is the subdivision of pharmacology, dealing with drugs that can destroy invading organisms without destroying the host. It also includes drug treatment of neoplastic diseases.
9. **Pharmacopia** is an official book describing drugs and medicinal preparations published by the authorized body formed by the highest legislative council of the country, i.e. International Pharmacopia (IP) is published by WHO. We follow British Pharmocopia (BP).

SECTION-II PHARMACOLOGICAL TERMS

- Biological barrier
- Diffusion
- Filtration
- Active transport
- Facilitated diffusion
- First-pass effect
- Enterohepatic circulation
- Blood brain barrier
- Ion-channels
- Chemical bonds
- Bioavailability
- Volume of distribution
- Half-life
- Therapeutic range
- Steady state
- Ligand
- Agonist
- Antagonist
- Potency
- Efficacy

DESCRIPTION

Biological Barrier

Drug molecules have to cross various barriers, i.e. —

1. Intestinal epithelial barrier during absorption
2. Blood brain barrier during distribution
3. Cell membrane barrier, to enter within the cell from ECF
4. Renal filtrating membrane—During excretion

5. Capillary barrier to enter in a capillary from tissue, a drug given IM route has to enter.

Diffusion

This is a process where there is transfer of substances across a membrane being directly proportional to concentration gradient on the both sides of membrane. Both lipid-soluble substances and lipid-insoluble substances of small size may cross membrane by simple diffusion. Barbiturates, aspirin, sulfonamides, morphine and pethidine are the drugs, which are absorbed in this way.

Filtration

This is a process where a porous membrane allows the bulk flow of solvent and the substances dissolved in it.

Active Transport

A drug molecule moves from the ECF to the interior of the cell in the apical region of the cell membrane and then again moves to the outside of the cell in its basal region.

Characteristics of active transport

1. Movement against concentration gradient
2. It is carried by special carrier, transport carrier protein
3. For this uphill movement energy expenditure occurs.

Facilitated Diffusion

It is a process where the molecules cross the cell membrane by the help of a carrier protein, but the movement of the drug molecule is along the concentration gradient. Unlike active transport, no energy expenditure occurs.

First-pass Effect

After absorption from the intestine, the drug molecules enter into portal vein → then liver (here they may be metabolized) → hepatic vein → systemic circulation. Therefore, if the drug molecules are metabolized in the liver and metabolized vigorously, then systemic circulation will receive a less amount of drug. Thus, the effect produced by liver is called the hepatic first-pass effect. If the drug molecule is not at all metabolized by the liver or metabolized very slowly, then the hepatic first-pass effect will be negligible, i.e.

a. Where hepatic first-pass effect is remarkable, e.g. Propranolol, Chlorpromazine, Nortriptyline.
b. Where hepatic first-pass effect is negligible, e.g. Chloramphenicol.

Enterohepatic Circulation

Digitoxin is metabolized in the liver and excreted into the gut, via the bile. Cardioactive metabolites (which include digoxin) as well as unchanged digoxin can then be reabsorbed from the intestine, thus establishing an enterohepatic circulation that contribute to the very long half-life of drug.

Blood Brain Barrier

1. The junctional regions in between the endothelial cells of the capillaries of the brain usually belong to the type, what is known as tight junction.
2. Where there is tight junction, nothing can pass through the spaces in between the adjacent cells.
3. If a molecule has to cross the capillary wall, it must cross through the cells.
4. The molecule which is crossing must be highly lipid-soluble so that it can cross the cell membrane (BBB).
5. In addition, there is a vest of processes of astrocytes (a type of neuroglia) which ensheathes these capillaries and thus reinforces the BBB. Anatomically, the BBB is tight junction + vest by the astrocytes.

During inflammation, capillaries engorge. This leads to some weakening of tight junctions (in meningitis, Penicillin can enter the brain but normally cannot).

The BBB is deficient in some places of brain, such areas are collectively known as circumventricular organs. Such as:

1. Area postrema
2. Posterior pituitary
3. Parts of hypothalamus.

Capillaries in these areas (circumventricular) are fenestrated,that is movement in and out of the capillaries are easy even for bigger molecules. Fenestrated capillaries contain many pores in their wall. Obviously, even drugs which are not lipid-soluble, can from the blood enter these areas of brain. Thus, lipid-insoluble antiemetic drugs can from the blood enter the CTZ to stop vomiting.

Propranolol, a β-blocker being highly lipid-soluble can cross the BBB. But its close pharmacological relative atenolol which is not well lipid-soluble, does not cross the BBB.

Ion Channels

Biological membranes contain several specific pores through which Ca^{+2}, Na^{+1}, K^{+1} and Cl^{-} ions can move. These pores are termed as Calcium, Sodium, Potassium and Chloride channels.

Chemical Bonds

The force that attract the drug to its receptor are termed as chemical bonds. The major type of bonds are:

a. Hydrogen bond: Result from attraction between hydrogen atom and pair of free electrons.
b. Ionic bond: Interactions between cationic and anionic groups.
c. Covalent bond: Requires high energy and causes irreversible effect.
d. Van der Waals bond: Weak interaction between dipoles. Bond energy is 0.5 Kcal per mole compared with 100 Kcal per mole for covalent bond.

Bioavailability

It is the amount or fraction of unchanged form of drug that is available (reactive) in the fluids of distribution. Bioavailability may be defined as the fraction of unchanged drug reaching the systemic circulation, following administration by any route. Obviously, the bioavailability can be anything between 0 (zero) and 100%. A 0% bioavailability means no absorption from gut and 100% means total absorption from the gut. The bioavailability depends not only on such factors, which can reduce or accelerate absorption but also on the hepatic first pass effect.

Volume of Distribution

It is the volume of fluid in which the drug appears to distribute with a concentration equal to that in plasma. Or an imaginary volume of fluid expressed in liters, which will accommodate the entire quantity of the drug in the body, if the concentration throughout this imaginary volume were same as that in the plasma. After absorption, question of distribution comes; it becomes complete when the drug has reached all the possible sites, where it can go. But all drugs cannot reach in the every nook and corner of the body, again some drugs concentrated specially heavily in some particular tissue. With this background, the volume of distribution may be expressed as,

$$V_d = \frac{\text{Amount of drug in the body}}{\text{Conc. of drug in the blood}}$$

Obviously, V_d is expressed in liters.

High lights on V_d

1. Some drugs remain mostly or confined within the blood or plasma and cannot go beyond the vascular compartment. Such drugs have a low V_d. (Aspirin, Frusemide, Warfarin).
2. Some drugs can go beyond the vascular compartment and get distributed in the tissue fluid (Ampicillin, Cephalexin). Such drugs have somehow, higher V_d.

3. A 3rd group of drug is not only present in the blood and tissue fluid but are heavily dissolved in adipose tissue. Such drugs, e.g. Thiopental Sodium have a very high V_d.
4. A 4th group of drugs avidly bound and retained by some organs like liver or other tissue proteins so that the concentration of the drug in such organ like liver is tremendously high and the V_d is also very high (e.g. Quinine).

   Some fundamental factors can affect V_d.

Half-life

It is the time in which the total amount of drug becomes half after its peak concentration.

Importance of half-life

a. General guide to doses schedule
b. To predict the duration of drug effect
c. To handle the case of overdose.
d. Gives the knowledge of—
   i. Whether the drug is metabolized or eliminated unchanged
   ii. Whether the drug itself active or is converted to an active metabolite or both
   iii. Whether the drug has irreversible action
   iv. Presence of disease of the organ of metabolism and excretion. For total elimination of a drug from the body at least 4 to 5 half-life is required.

Therapeutic Range

It is the range between the maximal permissible upper limit (beyond which toxic manifestations will appear) and minimal permissible lower limit (below which, the drug will be ineffective).

Steady-state

The term means a state, when the plasma concentration of the drug remains almost constant that is a steady-state where rate of input of the drug (input per unit time) and rate of elimination (elimination per unit of time) of the drug is equal.

Ligand

Any substance which can combind with receptors.

Agonist

Substance which has got both affinity and efficacy.

Antagonist

Substance which has got only affinity but lacks efficacy.

Potency

How much drug concentration is required to obtain a given response.

Efficacy

It is defined as the maximal response given by a drug.

SECTION-III ROUTES OF ADMINISTRATION, SOURCE, FORMS AND DRUG NOMENCLATURE

ROUTES OF ADMINISTRATION

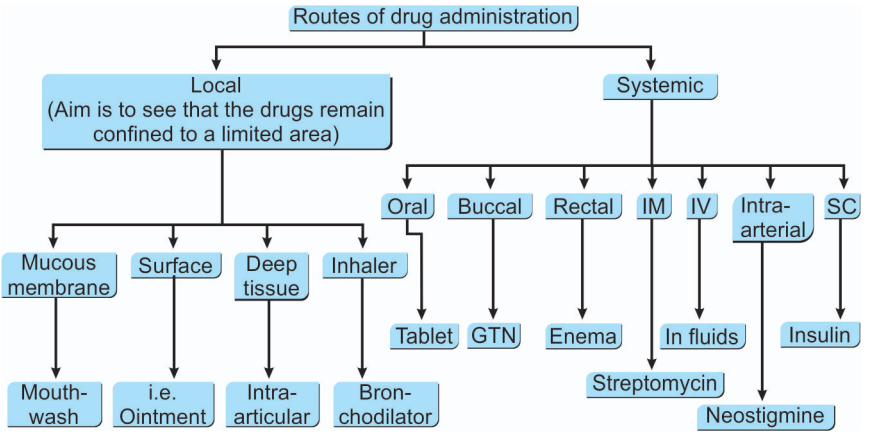
Approaches/ways by which drugs can be introduced or entered into the body are known as routes of administration of drug. It may be—
Local: Drugs remain confined to a limited area.
Systemic: Drug reaches the blood and distributed widely in the body.

Local application may be:

a. Surface only, i.e. ointment, powder and lotions, etc. may be applied on the skin.
b. Mucous membrane, i.e. mouthwash, gargles (buccal), drops, vaginal pellets, etc.
c. Deep tissues, i.e. intra-articular injection of hydrocortisone and intrathecal injection of Xylocaine, Procaine, etc.

Again systemic application may be:

a. Oral ingestion, i.e. Aspirin, Phenoxymethyl penicillin metronidazole tab, etc.
b. Buccal sublingual, i.e. glyceryl trinitrate to relieve anginal pain and Isoprenaline for bronchodilation in bronchial asthma.
c. Rectal, i.e. rectal enema or barium enema for diagnostic purpose.
d. Intramuscular injection, i.e. streptomycin injection in tuberculosis benzathene penicillin in gonococcal infection.
e. Intravenous route, i.e. intravenous fluids, heparin injection, Thiopental Sodium as an IV anesthetic.
f. Intra-arterial, i.e. injection Neostigmine in Myasthenia gravis.
g. Subcutaneous
    i. Pellets- Norplants
    ii. Silastic preparations
    iii. Dermojects.
h. Inhalations, i.e. volatile anesthetics.



SOURCES

Natural Sources

i. **Animals are the main source of hormones and others, e.g.**	
Drug	*Sources*
1. Insulin	1. β-cells of islets of Langerhans of pancreas
2. Oxytocin and vasopressin	2. Supraoptic and paraventricular nucleus of hypothalamus
3. Heparin	3. Liver extract
4. Cyanocobalamin	4. Liver.
ii. **Plants**	
1. Digoxin	1. Digitalis purpura
2. Morphine	2. Papaver somniferum
3. Atropine	3. Atropa belladonna
4. Quinine	4. Cinchona bark.
iii. **Microorganism**	
1. Penicillin	1. Penicillium chrysogenum
2. Streptomycin	2. Streptomyces griseus
3. Chloramphenicol	3. Streptomyces venezuelae.
iv. **Minerals $MgSO_4$, Mg trisilicate and Kaolin may be used as drug**	
1. $MgSO_4$ – Laxative 2. Mg trisilicate – Antacid.	

Synthetic Drugs

1. Aspirin—An analgesic, nonsteroidal anti-inflammatory agent
2. Sulfonamide—A chemotherapeutic agent
3. Pethidine—A opioid analgesic
4. Procaine—A local anesthetic.

Semisynthetic Drug Ampicillin from Penicillins

Active Principles: These are wholly or partially responsible for pharmacological action of the drug. It may be vegetable or animal origin even synthetic, e.g.

i. **From vegetable**: Alkaloids, glycosides, fixed and volatile oils, resins gums
ii. **From animals**: Adrenaline, noradrenaline
iii. **Synthetic**: Apomorphine, homatropine.

FORMS

Drugs can exist in the following 3 forms:

Solids

1. Tablets—Paracetamol
2. Capsules—Ampicillin
3. Powders—Dusting antiseptic powder
4. Pressary—Antifungals
5. Suppository—Analgesics.

Liquids

1. Injections—Benzyl penicillin
2. Mixtures—Potassium chloride
3. Solution—Eyedrop
4. Suspension—Antacid
5. Emulsion—Cod liver oil
6. Lotions—After shave lotions
7. Enema—Barium enema.

Gases

1. Nitrous oxide.

NOMENCLATURE

A drug generally has four categories of names. There are—

i. **Chemical name** is a name, which describes the chemistry of a drug.
ii. **Official name** or nonproprietary name is the name chosen by the official bodies and used by pharmacopias.
iii. **Proprietary name** is a name chosen by the firm manufacturing or marketing the particular drug.
iv. **Generic name** is forms or class or genus in which the drug in question falls.

Chemical name—7 chloro 1,3 dihydro—1 methyl 5 phenyl 2H, 1,4 benzodiazepine—2.
Official name—Diazepam

Proprietary name—Valium
Generic name—Benzodiazepine.

SECTION-IV DRUG ABSORPTION

- Definition
- Processes
- Sites of absorption
- Factors modifying

Definition

Process whereby a drug is made available to the fluids of distribution.

Processes

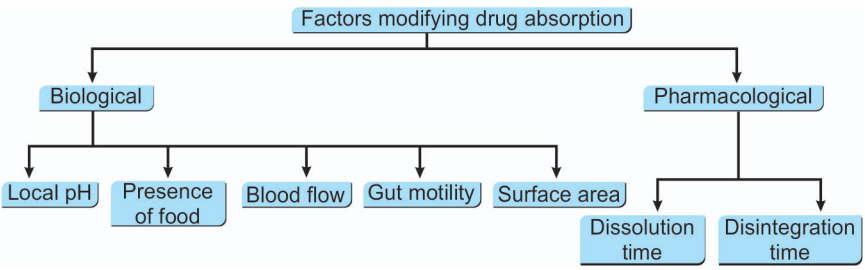
Mentioned in Section-II.

Differences among the processes of absorption in tabular form is given below:

Point of difference	Simple diffusion	Facilitated diffusion	Active transport
Incidence	Commonest	Less common	Least common
Process	Slow	Quick	Very quick
Relation with gradient	Along the gradient	Along the gradient	Against the gradient
Carrier	No carrier needed	Carrier needed	Carrier needed
Energy	No energy	No energy	Energy required
Selectivity and saturability	No selectivity and saturability	Exhibit selectivity/saturability	Exhibit selectivity/saturability
Direction	Bidirectional	Bidirectional	Unidirectional
Effect on block	Metabolic inhibitor can't block it	Can't block it	Can block it

Sites of Absorption

About 80% of drugs are taken orally, therefore, GIT is the main site of drug absorption, in addition drug can be introduced into the systemic circulation through intramuscular or subcutaneous site skin and respiratory tract.



ROLE OF LOCAL P^H

i. Most drugs are weak electrolytes (acid or bases). When they dissociate or ionized, the ion being insoluble in lipid cannot cross the cell membrane by lipid diffusion. The dissociation or ionization depends upon the pH of the medium.
ii. Polar or ionized molecules cannot cross the cell membrane because they are not lipid-soluble.
iii. Nonpolar or unionized and nonelectrolytes (noncharged) molecules have excellent lipid solubility and can cross the cell membrane by diffusion.

How much an electrolyte will dissociate into ions, depend upon its dissociation constant, pKa and H^+ concentration as pH. When an acidic electrolyte dissociates, then according to the Handerson-Hasselbatch equation, we find

$$P^H = pKa + \frac{\text{Log molecular concentration of nonionized drug}}{\text{Log molecular concentration of ionized drug}}$$

$$3.5 = 3.5 + \log \frac{\text{Molecular concentration of nonionized drug}}{\text{Molecular concentration of ionized drug}}$$

$$= 3.5 + \log \frac{\text{50\% nonionized drug}}{\text{50\% ionized drug}}$$

$$= 3.5 + \log 1 \quad (\text{Log}1 = 0)$$

$$= 3.5 + 0 = 3.5$$

i.e. when the pH=3.5 the nonionization of aspirin is 50%

Again, at one unit fall of pH leads to

$$[3.5 - 1] = 3.5 + \log \frac{\text{Molecular concentration of nonionized drug}}{\text{Molecular concentration of ionized drug}}$$

or $2.5 = 3.5 - \log \frac{91}{9}$ [It is the calculation of H conc. in relation to pH so (–)

or $2.5 = 3.5 - \log 10$ [log 10=1]

or $2.5 = 3.5 - 1 = 2.5$

i.e. when pH=2.5 then the nonionization of the drug is 90%

Further fall of another unit of P^H leads to

$$3.5 = 3.5 + \log \frac{\text{Molecular concentration of nonionized drug}}{\text{Log molecular concentration of ionized drug}}$$

$$= 3.5 + \log \frac{99}{1}$$

$$= 3.5 - \log 100$$

$$= 3.5 - 2 \quad [\log 100 = 2]$$

$$= 1.5$$

i.e. when pH is 1.5 then nonionization is 100%

So, less the pH = More the acidity = More the nonionization = More the absorption.

[When pH 3.5, nonionization 50%; when pH 2.5 nonionization 90%; when pH 1.5 nonionization 100%].

Therefore, an acidic drug like aspirin will be better absorbed in the stomach where the pH is low than the intestine where the pH is higher, by the same logic a basic drug like Quinidine will be better absorbed in the intestine than the stomach. But the story does not end here.

Surface area

Big absorption surface causes greater absorption and vice versa.

Food/Other drugs

In the GIT food can influence the absorption from GIT. Thus, Tetracycline can combine with calcium or iron of food and thus lose its efficacy due to reduced absorption.

Gut motility

Diarrhea drives out the GIT content rapidly, thus may reduce drug absorption.

Blood flow

The absorption of drug from the intramuscular site is usually more rapid and uniform than from subcutaneous site because of the more extensive vascular supply of the muscle compared with the SC fatty tissue.

Disintegration time

It means the time taken for a tablet to disintegrate, i.e. breakdown in the GIT completely. Longer the disintegration time delayed is the absorption.

Dissolution time

This is the time taken for entering the tablet into the solution within the GIT after it has been disintegrated.

SECTION-V DISTRIBUTION OF DRUG

- Definition
- Clarification
- Compartment
- Factors modifying

DEFINITION

It involves the movement of drug molecules from circulatory fluid to the other areas of the body, including the sites of action, sequestration and elimination.

CLARIFICATION

Distribution of drugs begins when it enters blood (i.e. absorbed) and is completed when the drug has reached all the possible sites where it can go. For example, Thiopental sodium after IV administration reaches the RAS system of the brain (**site of action**), exists in a higher concentration than plasma in adipose tissue (**site of sequestration**) and attains in kidneys (**site of elimination**) for removal from the body.

COMPARTMENT

Considering the two fundamental facts, that—

i. All drugs cannot reach every nook and corner of the body equally.
ii. Some drugs are concentrated heavily in some particular tissue—The idea of single vs multicompartmental body model arises.

For some drugs, the body behaves as if it is consisting of multiple compartments. The first compartment is called the central compartment consists of blood and some other organs, i.e. heart and brain which are highly vascular and where the drug can enter very easily. The other compartments are called the peripheral compartments consisting mainly of adipose tissue and muscle where the vascularity is compared to the 1st compartment, rather poor. After IV bolus of drug, the drug is rapidly distributed in the 1st compartment but does not, in the others. Only after, sometime the drug enter the 2nd peripheral compartment.

For some other drugs the body may be visualized to be consisting of only one compartment, the blood and the tissue.

FACTORS MODIFYING

1. Plasma protein binding
2. The rate of blood flow to the various organs
3. Binding with cellular proteins
4. Concentration in fatty tissue
5. Blood brain barrier
6. Peritoneal membrane
7. Breast milk barrier
8. Placental barrier.

Plasma protein binding: Drug exists in two forms in the body—Bound form and free form. Most drugs while in the blood remains bound with plasma proteins and other substances, i.e. acidic drugs with albumin, basic drugs with alpha-1-glycoproteins and glucocorticoids with transcortin, etc. The bound fraction of drug can vary, i.e. 99% of Warfarin, 18% of Ampicillin is bound while lithium remains 100% free.

Only the free drug in the plasma can bind with the receptors and active and available for immediate systemic effect and target for degradation by the liver and filtration for the kidneys. The bound fraction of the drug only acts as a reservoir.

Protein bounding can prolong the half-life of drug because the bound fraction is not filtered through renal glomeruli and is also protected from biotransformation.

It is also restricted from reaching its site of action due to failure of sliping or passing through the capillary pores because of its larger size and will remain confined within the vascular compartment.

The binding capacity of protein is limited, once binding becomes saturated a small increment in dose can cause a large increase in effect and toxicity. In hypoalbuminemia, toxic manifestations of drugs may develop with customary doses due to deficiency of binding protein.

One drug may influence the protein binding of other drugs. Salicylates decrease the binding of thyroxine to proteins.The binding of bilirubin to albumin may be inhibited by a variety of drugs such as Sulfisoxazole and Salicylates. This can particularly be hazardous in neonates when this mechanism increase the accessibility of bilirubin to the brain, fatal kernicterus has occurred in premature infants who were given Sulfisoxazole.

Binding with cellular proteins: Some cellular proteins of some tissues can bind some particular drugs avidly and tenaciously. Thus, chloroquine remains in eye and hepatic cells in very heavy amounts, a phenomenon called sequestration.

The rate of blood flow to the various organs: The rate of blood flow affects drug delivery to various organs. After IV administration, concentration of lipid-soluble drugs reaches equilibrium in brain with free drug conc. very rapidly which is less well-perfused, takes up the drug more slowly. Fat because of its limited blood flow, receive the drug most slowly.

The almost immediate anesthetic effect (unconsciousness) of Thiopental sodium is due to its rapid uptake by the brain. Recovery of consciousness then occurs within minutes, because adipose tissue and muscle continue to absorb the drug, the concentration of drug in brain decreases.

Concentration in fatty tissue: It also affects distribution. Highly lipid-soluble drugs like glutathemide distribute into fat which then serves as a depot.

Extraction of such drugs from plasma by metabolism or excretion, results release from fat into blood with restoration of the circulatory concentration.

The blood brain barrier: (Discussed in Section—II).

The peritoneal membrane: Shows a barrier where transport from peritonium into blood is much greater than the reverse. For example, patients treated by peritoneal dialysis frequently develop peritonitis. Instillation of many antibiotics into peritonium results in substantial

absorption into the systemic circulation. The converse is not true, the very little of these antibiotics enters the peritoneal space after systemic injection.

Breast milk barrier: Passage of drug from blood into breast milk of lactating mothers demand special attention to protect her child from potential danger of toxicity.

Placental barrier: Placenta is not a good barrier. Most drugs can cross placenta at ease with variable extent like oral anticoagulants and hypoglycemic agents. Some of these drugs can produce effects on fetus and they may be teratogenic.

SECTION-VI BIOTRANSFORMATION OF DRUGS

- Definition
- Difference between biotransformation and metabolism
- Organs involved
- The chemical reactions
- Purposes of biotransformation
- Enzyme induction and inhibition—Clinical importance.

DEFINITION

Chemical alteration of drugs within the living body.

DIFFERENCE BETWEEN BIOTRANSFORMATION AND METABOLISM

Drugs, which are the chemical substances, must be removed from the body after its effect on living organism. Otherwise, there would be a persistent effects on the body which may not be desired. Our body gets ride of this persistent effect by changing the drug molecules. This kind of chemical change of drugs that occur in living body is known as biotransformation or drug metabolism. Though, drug biotransformation and metabolism are used interchangebly there is some difference between these two terms. Metabolism is also a chemical change, which is associated with involvement of energy and products of new materials required for growth and maintenance of body. But in biotransformation involvement of energy or new material productions are rare. So, biotransformation is used preferably.

ORGANS INVOLVED

1. Major: Liver
2. Intermediate: Lungs, kidney and intestinal mucosa
3. Minor: Leukocyte, spleen, eye, brain and gonads.

THE CHEMICAL REACTIONS

Involved in the biotransformation can be classified as:

1. Oxidation
   a. Microsomal
   b. Nonmicrosomal.
2. Reductions
3. Hydrolysis
4. Conjugations.

Since, the microsomal enzymes play a pivotal role in biotransformation, their functions are mentioned first. The microsomal enzymes of the liver, which are part of the smooth endoplasmic reticulum, convert many lipid-soluble drugs and foreign compounds into more water-soluble metabolites. These enzymes are located in the lipophilic membranes of endoplasmic reticulum of the liver and other tissues. When these lamellar membranes are isolated by homogenization and fractionation of the cells, they reform into vesicles called microsomes. Microsomal drug oxidation require (1) cytochrome P-450 (2) cytochrome P-450 reductase (3) NADPH (4) molecular oxygen.

Oxidized (Fe^{+3}) cytochrome P-450 combines with a drug substrate to form a binary complex. NADPH donates an electron to the flavoprotein reductase, which in turn reduces the oxidized cytochrome P–450 drug complex. A second electron is introduced from NADPH, via the same flavoprotein reductase, which serves to reduce molecular oxygen and to form an activated oxygen-cytochrome P–450 substrate complex. This complex in turn transfers activated oxygen to the drug substrate to form the oxidized product.

Oxidation Reactions are

A. *Microsomal*

a. Hydroxylation of aromatic ring, i.e. **Phenytoin is changed to para-hydroxyphenytoin**
b. Aliphatic (side chain) hydroxylation, i.e. **Tolbutamide is metabolized to hydroxytolbutamide**
c. N-dealkylation, i.e. **Imipramine is converted to Desimipramine**
d. Q-dealkylation, i.e. **Encainide to 0- demethyl encainide**
e. S-dealkylation, i.e. **6-methyl thiopurine to 6-marcaptopurine**
f. Deamination, i.e. **Amphetamine is changed to Phenylacetone**
g. Desulfuration, i.e. **Parathion is changed to paroxon**
h. Sulfoxidation, i.e. **Chlorpromazine to Chlorpromazine sulfoxide**
i. N-oxidation, i.e. **Meperidine is converted to Meperidine N-oxide.**

B. *Nonmicrosomal*

Ethyl alcohol to acetaldehyde.

Reductions

a. Nitroreductions, i.e. Chloramphenicol is reduced to arylamine
b. Azoreduction, i.e. Prontocil to Sulfanilamide
c. Chloralhydrate to Trichloroethanol(alcohol hydrogenation).

Hydrolysis

Enalapril to active Enalaprilat.

Conjugation

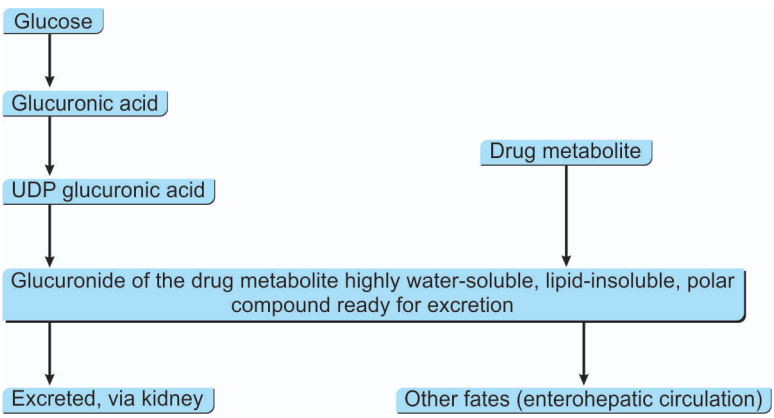
By these processes, there occurs—

i. Inactivation of parent compound
ii. Addition of endogenous substance with the help of energy and synthesis of larger molecular new substances.
Hence, the reactions are also known as synthetic reactions.

The reactions are—

a. Glucuronidation
b. Acetylation
c. Methylation
d. Sulfate conjugation
e. Glycine conjugation.

The metabolite of the drug like Digoxin, Morphin, Diazepam, Aspirin, etc. combines with glucuronic acid, which is obtained from glucose. Subsequently, activated by uridine diphosphate (UDP). The active complex, viz. UDP, glucuronic acid, conjugates with the drug metabolite. The whole process is shown here.



Other conjugation reactions are shown here in tabular form:

Name of reactions	Conjugating agent	Active compound	Enzyme required	Examples of drugs
Acetylation	Acetyl CoA	Acetyl CoA	Acetyl CoA transferase	INH, procaine, sulfonamide
Methylation	CH_3 group	Adenosyl methionine	Transmethylase	AD, histamine
Glycine conjugation	Glycine	Acetyl CoA	Glycine transferase	Benzoic acid
Sulfation conjugation	Sulfuric acid	Adenosyl phosphosulfate	sulfotransferase	Estrogen, methyldopa

PURPOSE OF BIOTRANSFORMATION

All these reactions are to make the drug from lipid-soluble to more water-soluble or nonpolar to polar compound or unionized to ionized by:

i. Converting active drug to inactive substance
ii. Active drug to active metabolite
iii. Inactive drug to active substance
iv. More toxic drug to less toxic drug, so that they can be easily excreted out from the body.

ENZYME INDUCTION AND INHIBITION—CLINICAL IMPORTANCE

Enzyme induction is a phenomenon by which the endoplasmic drug metabolizing enzymatic activity is increased, as a result, there will be increased metabolism of the drug along with its reduced therapeutic effect. Barbiturates can induce the hepatic microsomal enzyme which will reduce the theraputic effects of coumarin anticoagulants, similarly Rifampicin can reduce the effect of oral contraceptives similarly enzyme inhibition is a phenomenon by which the activity of drug metabolizing enzymes in the endoplasmic reticulum is decreased. So that the drug degradation rate is slowed and drug effect is increased.

1. Coadministration of Cimetidine with Diazepam cause increased effects of Diazepam, similarly INH can increase the effect of Tolbutamide.

SECTION-VII ELIMINATION OF DRUGS

- Definition
- Orders of kinetics
- Brief description
- Differences between the 1st and '0' order kinetics
- Process of elimination.

DEFINITION

It is the last component of pharmacokinetics, which may be defined as the process whereby a drug is removed from the body after producing its effects with or without the process of metabolism. Most of the drugs are eliminated from the body after metabolism but some drugs do not follow the process, e.g. Digoxin, Ephedrine, Proctalol and Inhalation anesthetics.

ORDERS OF KINETICS

During the movement of drug molecules from one site to another or its metabolic change, it may follow:

i. First order kinetics
ii. Zero order kinetics.

First order kinetics (Exponential clearing)—A constant fraction of drug is eliminated per unit time.

Zero order (Linear clearing)—A constant quantity of drug is eliminated per unit time.

BRIEF DESCRIPTION

If we consider that at 0 hour the drug was 1000 mg in the body and it followed 1st order kinetics and a constant fraction of 10% is filtered(and hence excreted) out by the kidneys per hour. Then at the end of first hour, the amount of the drug in the body would be

1000 – (1000 × 1/10) = 1000 – 100 = 900 mg. At the end of 2nd, 3rd and 4th hour the amount of drug still remaining in the body would be

900 – (900 × 10/100) = 900 – 90 = 810 mg

810 – (810 × 10/100) = 810 – 81 = 729 mg

729 – (729 × 10/100) = 729 – 72.9 = 656.1 mg and so forth.

If we followed of zero order kinetics, the quantity moving was a fixed amount. To continue with the previous example, let the quantity of the drug in the body was 1000 mg and its excretion followed zero order kinetics and a fixed quantity, i.e. 10 mg is passed out every hour then at the end of 1st, 2nd, 3rd, and 4th hour the body would contain.

1000 – 10 = 990 mg
990 – 10 = 980 mg
980 – 10 = 970 mg
970 – 10 = 960 mg and so on.

Unlike the first order kinetics, the amount excreted remains a fixed 10 mg/hr.

PROCESS OF ELIMINATION

Drugs are eliminated by two ways—

a. Metabolism
b. Excretion.

Table 1.1 Differences between the 1st and '0' order kinetics

Points of difference	1st order kinetics	'0' order kinetics
Definition	Already mentioned	Do
Rate of elimination	Proportional to the amount of drug in the body	Does not have such relation
Drug metabolizing enzymes	Remains unsaturated	Becomes saturated so that constant amount is removed per unit time
Graph	Exponential curve	Linear curve
Examples	Most of the drugs follow it	Alcohol follow the order of kinetics
Other name	Flow limited excretion	Capacity limited excretion

Metabolism and **excretion** taken together constitute **elimination**. Three processes are involved in renal excretion of drugs as:

a. Passive glomerular filtration—Directly proportional to the excretion
b. Active tubular secretion—Inversely proportional to excretion
c. Passive tubular reabsorption—Directly proportional to excretion.

Alkaline drugs are excreted to a greater extent, if the urine is acidic; whereas acidic compounds are excreted more readily, if the urine is alkaline. A practical application of this principle is in the treatment of poisoning by weak acids like phenobarbital and salicylic acid; where alkalization of urine increases the proportion of ionized drug, thereby decreasing reabsorption and enhancing excretion.

Administration of sodium bicarbonate is a therapeutically useful strategy for management of either type of poisoning.

Since, urine is normally acidic, the elimination of weakly acidic drugs by excretion alone would require a long time. Fortunately, metabolism tends to transform these drugs into stronger electrolytes, thereby increasing the percentage in the ionic form and limiting tubular reabsorption.

SECTION-VIII PHARMACODYNAMICS

MECHANISM OF DRUG ACTION

Body functions are mediated through control systems that involved receptors, enzymes, carrier molecules, specialized macromolecules, such as DNA. Most drugs act by altering the body's control systems. An overview of the mechanism of drug action shows that drug acts on—

A. **Cell membrane by** the following approaches:
   1. Action on receptors
   2. Interference with selective passes of ions across membranes

3. Inhibition of membrane bound enzymes and pumps
4. Physicochemical interactions.

B. **Metabolic processes** within the cell by:
1. Enzyme inhibition
2. Inhibition of the transport processes
3. Incorporation into large molecules
4. Inhibition of cell wall synthesis.

C. **Outside the cell**:
1. Surface adsorption
2. Chemical neutralization
3. Chelation process
4. Osmosis.

DETAILS

Highlights on Receptors

- Definition
- Chemistry
- Activation
- Formation
- Difference in affinity
- Structure activity relationship
- Ligand-receptor complex formation
- Site
- Number of receptors
- Specificity of receptors
- Agonist-antagonist on receptor site.

Definition

Receptors are part of the cells that can interact with a drug or endogenous material so that a series of chemical events occurs leading to the biological effect of the drug.

Chemistry

All receptors are macromolecules (proteins), following cellular structures behave as receptors.

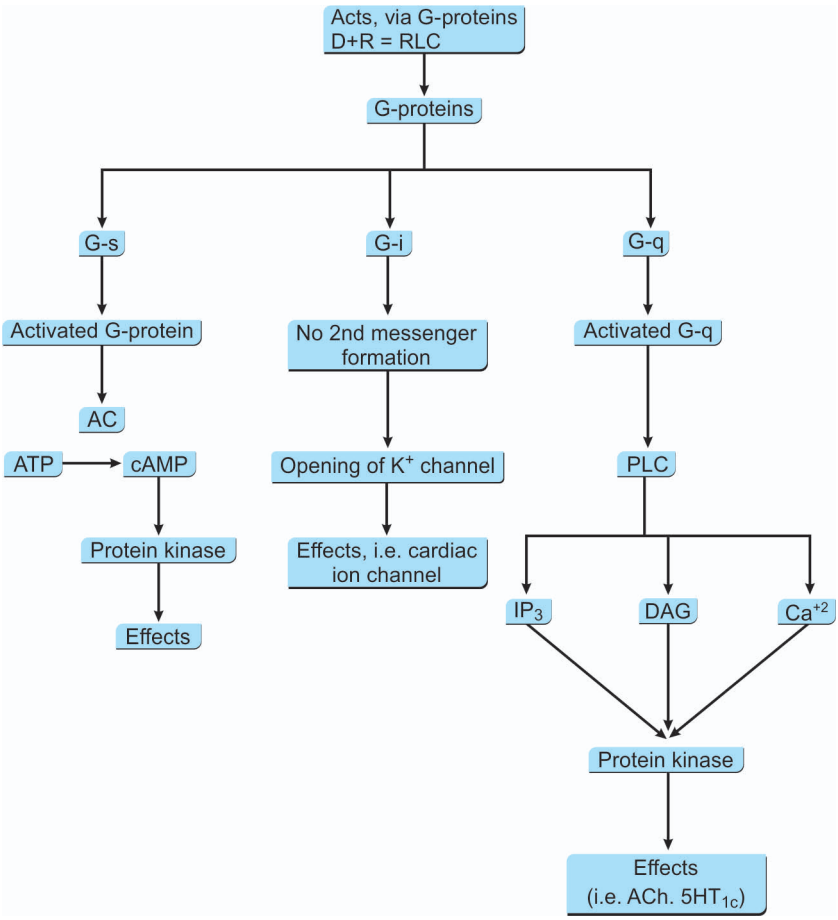
1. Regulatory proteins — Act as receptors, e.g. albumin for acidic drug. α_1-glycoprotein for basic drug; transcortin for glucocorticoids.
2. Some enzymes — Dihydrofolate reductase for methotrexate.
3. Transport proteins — $Na^+ - K^+$ – ATPase for digitalis.
4. Structural proteins — Tubulin for colchicines.

Activation

Types on the basis of site, they are of three types, but according to MOA they are:

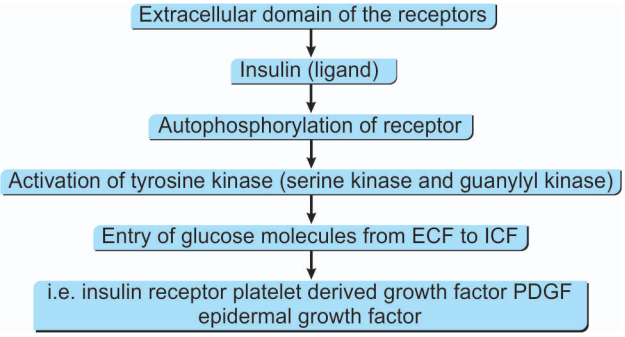
1. Receptors present in the cell membrane—
   (a) They act, via G-proteins and (b) Act, via ligand gated channels.
2. Present as transmembrane receptors have tyrosine kinase and realeted kinase activities.
3. Present in the cytosol or on the nucleus.
4. Cytokine receptors.

- **Membrance Receptors**

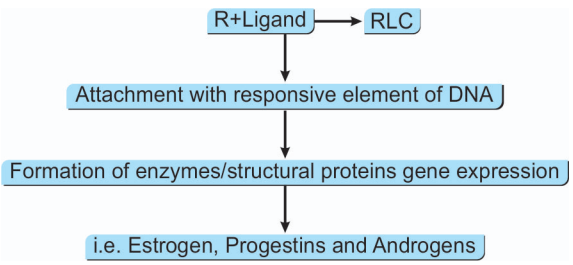


Ligand Gated Channels: Acetylcholine, gaba, glutamic acid, butyric acid receptors have a central canal or channel within the cylinder. Normally they remain closed but when the ligand gets attached with the acetylcholine receptors (AChR) the channel opens up. Now, Na^+ ions from extracellular fluid (ECF) enter the muscle cells through the channel, this ultimately results in development of action potential (AP).

- **Transmembrane Receptors**



- **Intracellular Receptors**



- **Cytokine Receptors**

Role of the receptors in the production of therapeutic and toxic effects

Graded Dose Response Curve

1. Depends upon the concentration of drug, reaching the receptors, upto a point, greater the number of drug molecules reaching the receptors, greater will be the effect.
2. It also depends upon the quality of receptors. After formation of the drug receptors complex that is, RLC, if the receptors are not sufficiently activated, response will be weaker.
3. It also depends upon the presence of antagonists competitive or irreversible.

On the basis of above facts, two important clinical issues, viz. *potency* and *efficacy* to be considered.

Efficacy is defind as the maximal response given by a drug.

Potency means how much drug concentration is required to obtain a given response, usually the fifty percent of the maximal response.

This means, EC_{50} (of ED_{50}) is a measure of potency, a drug whose ED_{50} is low, is a highly potent drug whereas a drug whose ED_{50} is high, has a low potency.

Formation

Receptor molecules are synthesized by the cells.They have a fixed lifespan, i.e. insulin receptor has a half-life of about 7 hours. After expiry of the life-span, they become degraded by the cell and is replaced by a new one.

Difference in affinity

When a receptor can combine with more than one drug, the receptor's affinity (love or attraction) can vary. NA can bind with α_1-receptor and β_1-receptor, but NA has greater affinity for alpha and lesser affinity for beta- receptors.

Structure activity relationship

Same receptor can combine with different drug molecules; provided they are closely similar in chemical structure. α_1- receptor can combine with NA or AD but they cannot combine with ACh, because NA and AD are structurally very similar and chemically dissimilar with ACh.

Ligand-receptor complex formation

After the ligand has combined with a receptor, a ligand-receptor complex (LRC) is formed. This LRC can stimulate the postreceptor signals causing biological effects. Thus, a ligand may be agonist or an antagonist.

Site

They may be present in the—
1. Cell membrane—Type I
2. In the cytosol— Type II
3. In the nucleus— Type III.

Number of receptors

Recently, with the help of radioligand binding technique, the receptors in a cell can be counted. The count can increase, a phenomenon called **up regulation**, the reverse is called **down regulation**.

Specificity of receptor

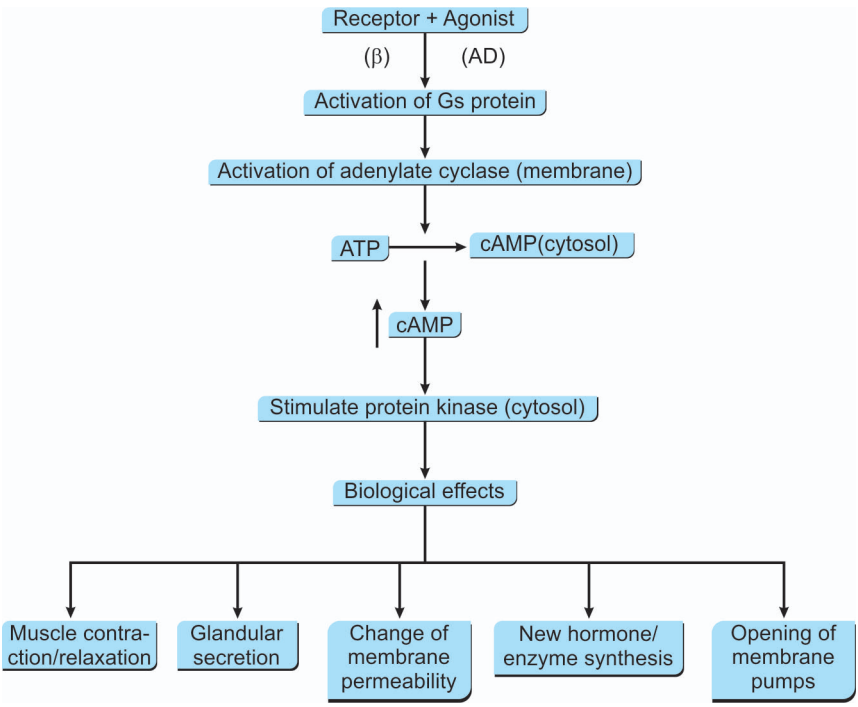
Receptors are specific, that is, a receptor supposed to bind with a particular drug will not bind with any other drug. This explains the phenomenon of specificity of drug action. As for example, AD causes **vasoconstriction** and bronchodilatation and NA causes **vasoconstriction** but not **bronchodilatation**. The reason is that the ligand (drug) must combine with β_2-receptors of bronchial muscle to produce bronchodilatation, as well as, it must combine with α_1-receptors of vascular smooth muscle to produce vasoconstriction. Bronchial muscle contain β_2-receptors but not α_1-receptors. Vascular smooth muscle contain α-receptors but not β_2-receptor. Again, AD can combine with α_1 and β_2- receptors but NA can combine with α_1-receptor but not with β_2 -receptors. That is why, the target cells of NA is smooth muscle of blood vessels but not the smooth

muscle of bronchus, whereas the target cells of AD include the smooth muscle of bronchus and blood vessels both.

Agonist-antagonist on receptor site

After LRC formation, if the complex stimulates the postreceptor signals to cause biological effect in such cases the ligand is called agonist, if no effect is produced then called antagonist.

LRC Formation and its Consequences



Interference with the selective passage of ions across membrane: Calcium channel blockers are the drugs used for the treatment of hypertension to reduce BP, because calcium enters into the smooth muscle cell of blood vessels. After entry into the cells, they combine with calmodulin. Subsequently, the 'cal-cam complex' causes the stimulation of excitation-contration coupling(actin-myosin). So that there is vasoconstriction and rise of BP. Calcium channel blocker (Nifedipine) blocks the entry of calcium through the channels. So that, there is interference of exitation contraction coupling and vasodilatation and finally fall of BP.

Inhibition of membrane bound enzymes and pumps: Membrane bound ATPase is inhibited by cardiac glycosides which is used in the treatment of congestive cardiac failure, where there is fall of cardiac output.

Physiologically, Na^+ – K^+ ATPase helps in the entry of K^+ and exit of Na^+ from the cardiac muscle cell. After inhibition of Na^+– K^+ ATPase, the active transport of Na^+ out of the cell is reduced. So, the intracellular Na^+ content is increased, which inturn causes the entry of large number of Ca^+ within the cell, via Na^+–Ca^{++} exchange mechanism. Permeability of calcium to membrane and release from sarcoplasmic reticulum is also increased. All these three factors as a whole increase the intracellular calcium concentration. This increased intracellular calcium concentration with the involvement of troponin, finally stimulates the excitation–contraction coupling of actin and myosin. So that, there is increased force of contraction and cardiac output. This is the rationality of using cardiac glycosides in the treatment of congestive cardiac failure(CCF).

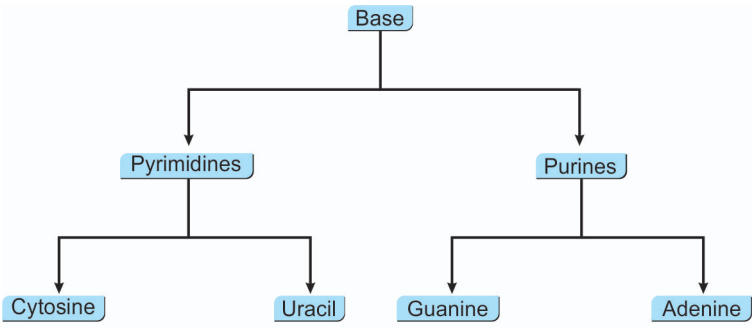
Physicochemical interactions: The effects of some G/As and barbiturates and alcohol do not depend on drug receptor interaction but on the relative saturation at some cellular phase. They do not act on specific receptors but they prevent some metabolic functions probably by reaching a certain level of saturation at some cellular sites. The mechanism or mechanisms by which G/As exert their effects is not known. But there are some hypothesis, i.e.— (a) Hydrate hypothesis, (b) Ionic pore hypothesis, and (c) Membrane fluidity hypothesis.

Metabolic Processes within the Cell

1. **Enzyme inhibition**: It is believed that bronchodilatation by xanthines produced is due to suppression of cAMP degradation, resulting from inhibition of degrading enzyme phosphodiesterase, i.e. Theophylline administration leads to rise of intracellular cAMP and bronchodilatation.

   In gouty arthritis there is increased concentration of uric acid due to excessive activity of xanthine oxidase. Allopurinol inhibits, xanthine oxidase, as a result uric acid formation is reduced.
2. **Inhibition of the transport process**: Inhibition of transport process that carry substances across cells—Probenecid competes with Penicillin for the same excretory process in the kidney. So Penicillin is retained in blood for a longer period. Which is required in the treatment of resistant cases of venereal disease to get the maximum effect of Penicillin. By competing with the same reabsorption process in the kidney aspirin reduces uric acid concentration in blood of gouty arthritic patients.
3. **Incorporation into large molecules**: 5-fluorouracil, an anticancer drug; is incorporated into mRNA in place of uracil so that defective mRNA is formed within the cancer cell which cannot carry information

properly from DNA to ribosome for protein synthesis. Constituents of mRNA is as follows.



4. **Inhibition of cell wall synthesis**: The basic structure of bacterial cell wall is composed of a complex polymer, called mucopeptide (murein).The murein is a liner polymer, consisting of alternating units of two amino sugars N-acetyl glucosamine and N-acetyl muramic acid. To each molecule of N-acetyl muramic acid, a tetrapeptide is attached. Tetrapeptide consists of L-alanine, D-alanine, Lysine and D-glutamic acid. Finally, these polymer strands are cross-linked by amino acid bridges formed by glycine which connect the L-lysine of one tetrapeptide to D-alanine of another. This cross linking (transpeptidation)is carried out by an enzyme called transpeptidase, gives rigidity of the cell wall.

   Penicillin binds to D-alanine site of the enzyme transpeptidase in the bacterial cell wall and inhibits the enzyme transpeptidase and suppress transpeptidation reaction(cross linking). So that, there is defective formation of cell wall and lysis of bacterial cell wall due to higher internal osmotic pressure and there is extrusion of protoplasmic contents and death of the bacteria.

Outside the Cell

Biological activity of some drug depends on

1. **Surface adsorption**—Some chemically inert substances adsorbed, dissolved or suspended substances such as gases, toxins and bacteria, i.e. ultracarbon is given before radiological examination of abdomen to absorb gas in GIT.
2. **Chemical neutralization**—Protamine sulfate (positively charged) acts as an antidote of heparin (negatively charged) by neutralizing it.
3. **Chelation**—A chemical process of formation of complexes with metabolic ions and the compounds which form such complexes

are called chelating agents. The chelating agent form a ring sructure with the metal which is nontoxic, highly water-soluble and excreted in the urine, e.g. dimercaprol chelates arsenic and is used in arsenic poisoning.

4. **Osmosis**—Osmotic diuretics like mannitol, osmotic purgatives like magnesium sulfate act by osmosis.

SECTION-IX FACTORS MODIFYING DRUG ACTION

An understanding of the reasons for individual variation in response to drugs is relevant to all who prescribe. But pharmacokinetic and pharmacodynamic effects are involved and the issues fall in two general categories. Factors related to patient and drugs—

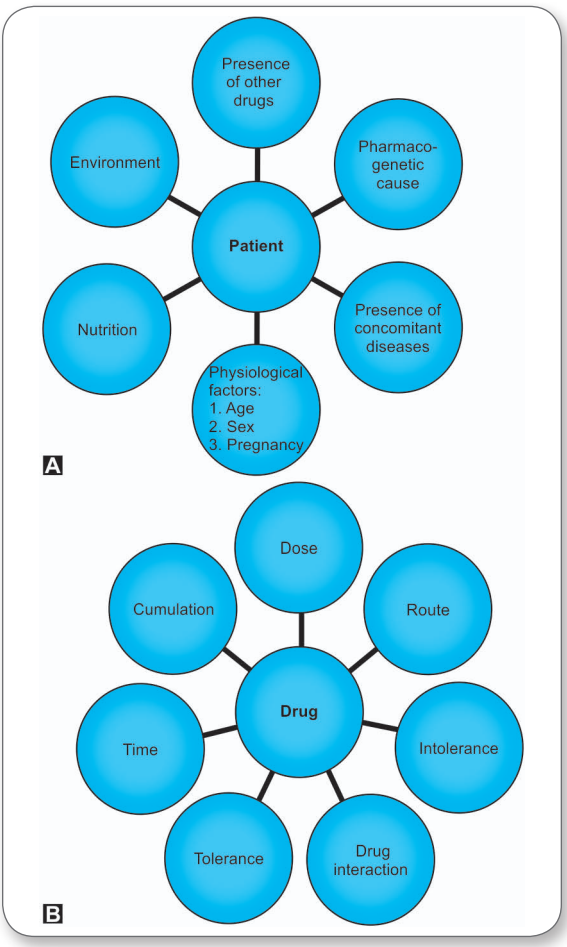


Fig. 1.1: Factors modifying drug action

I. Patients are	II. Drugs are
Age	Dose
Sex	Routes
Body weight	Time
Nutrition	Drug combination
Alcoholic	Drug interaction
Cigaret smoking	Cumulation
Pregnancy	Tolerance
Genetic factor	Intolerance
Environmental condition	
Pathological condition	

FACTORS RELATED TO PATIENT

Age

Young human beings differ greatly from adults, not merely in size but also in the proportions and constituents of their bodies and the functioning of their physiological systems. Special examples exists, e.g. enzyme systems that inactivate drugs are present at birth, they are functionally immature, in the preterm baby and specially for oxidation and for conjugation with glucuronic acid. lnability to conjugation and thus inactivation of chloramphenicol causes the fatal gray baby syndrome in neonates. After the first week of life, the drug metabolic capacity increases rapidly. Glomerular filtration, tubular secretion and reabsorption are also low in neonates.

The incidence of adverse drug reactions rises with age, in the adult, specially after 65 years of age because of—

1. The increasing number of drugs that they need to take because they tend to have multiple diseases.
2. Poor compliance with dosing regime.
3. Bodily changes of the aging that requires modification of dosage regimens.

Absorption of drugs may be slightly slower because GI blood flow and motility are reduced but the effect is rarely important.

Distribution is influenced by the following changes:

1. There is a significant decrease in lean body mass so that standard adult slower.
2. Drugs that are normally extensively eliminated in 1st pass through the liver appear in higher concentrate in the systemic circulation and persists here for longer periods, e.g. Major tranquillisers, TCAs cardiac antidysrhythmic agents.
3. Capacity to hepatic enzyme induction appears to be lessened. Elimination renal blood flow, glomerular filtration and tubular

secretion decreases with age above 55 years. Particular risks of adverse effects arises with drugs that are eliminated mainly by the kidney and that have a small therapeutic ratio, i.e. aminoglycosides chloramphenicol, digoxin, lithium.

Sex

Women may show increased sensitivity to certain drugs due to hormonal effects. Sex difference in drug metabolism is due to males having higher MFO activity than females as testosterone can induce microsomal enzymes whereas estradiol decreases their activity.

Body Weight

Usually big bodied persons (bigger surface area) require bigger dose. A special problem arises with the children, they have smaller body weight and the physiology differs from that of the adults. Then how to adjust the dose? There are several formula—(GlowGills Clarke's) available for calculating drug dose in a child. Clarke's formula is—Wt. of the child in pound × adult dose/150.

Alternatively with the help of charts, one can calculate the drug dose of a child.

Nutrition

i. Because of the diseases patient may remain in a state of starvation or semistarvation.
ii. The patient may be on a severe diet restriction for reduction of obesity.
iii. Some persons specially the poor may be in a stage of malnutrition with edema or malnutrition without edema.
iv. In some chronically ill patients (anorexia nervosa/coma/severe coma) there may be water and electrolyte imbalance in addition. While prescribing drugs, the pertinent question is whether the conditions alter the pharmacology of the drugs.

Major features of starvation are loss of—

i. Total body wt.
ii. Loss of body wt.
iii. Ketosis.
iv. Fall of plasma albumin.
v. In some cases, e.g. in a semicomatose patient on heavy antibiotic—an antibiotic which destroys the bacterial flora of the GUT (hence stops availability of vitamin K from intestinal bacteria) and receiving no vitamin supplements, lack of vitamin K can develop and thus introduce additional hazards.

Alcoholic

Acute alcohol intake inhibits and chronic intake can increase the biotransformation of drug. As for example, the plasma half-life of Tolbutamide (an oral hypoglycemic agent) of a nonalcoholic person is 5 to 9 hours. And it can reduce upto 2 to 7 hours in a case of chronic alcoholics. Increased rate of biotransformation of drug in chronic alcoholic is due to increased hepatic microsomal cytochrome P-450 activity and proliferation of the smooth endoplasmic reticulum.

Cigaret Smoking

The biotransformation of some drugs such as Theophylline, Caffeine and Imipramine are several times higher in cigaret smokers than in nonsmokers. Cigaret smoke is a rich source of Benzopyrine which is a potent enzyme inducer. There is a 12 fold increase in pulmonary mono-oxygenase activity after continuous exposure of rates to a mixture of cigaret smoke and air for five hours daily for 3 days.

The elimination half-life of Theophylline is about 8 hours in adult nonsmokers and about 4 hours in adult smokers.

Pregnancy

While prescribing drugs to the pregnants, the clinician has to consider two special points, viz.

i. Special problem due to altered physiology in the mother
ii. Special problems regarding whether the proposed drug is going to harm the fetus—This requires considerations of placental barrier as well as teratogenicity of the drug.

Relevant physiological changes in pregnancy:

1. Total body water increases in pregnancy
2. Body fat increases to some extent
3. Plasma albumin fall remarkably
4. Renal clearance increases.

Expected effects therefore might be:

1. V_d of water-soluble drug will increase and the total concentration of drug in plasma should fall.
2. Free form of the drug in plasma should rise and in cases of drugs which are mostly bound with the plasma protein risks increase.
3. V_d of fat-soluble drugs increased.
4. Drugs like Penicillin will be excreted even more quickly.

Genetic Factor

Genetic factors may affect the individuals capacity to metabolize a drug and thus causes increase, decrease, or bizarre drug response—

1. Glucose-6-phosphate dehydrogenase deficiency:
   Strandard dose of Primaquine may cause acute hemolysis and hematuria of a patient having deficiency of the above enzyme.
2. Pseudocholinesterase deficiency: During surgery the decrease metabolism of Suxamethonium by pseudocholinesterase can cause apnea after surgery.
   In this case fresh blood transfusion is the management.

Environmental Condition

Among urban people → increased hydrocarbon production → induction of microsomal enzyme → increased drug metabolism → decreased drug action.

Pathological Condition

In liver damage, drugs that are inactivated by liver can accumulate and may produce toxic effect.
Antipyretics—It acts only when there is pyrexia.
Antiemetics—It acts only when there is vomiting.
Antibiotics—It acts only when there is infection.
Antihypertensives—It acts only when there is hypertension.

FACTORS RELATED TO DRUGS

Dose

Dose can modify drug action, e.g.

1. Chlorpromazine in low dose acts as an antiemetic but in high dose acts as antipsychotics.
2. Aspirin in low dose shows its antiplatelet effect, but in high dose it is anti-inflammatory.

Routes

Magnesium sulfate given orally acts as a purgatives but when given intramuscularly acts as sedatives.

Benzodiazepines given orally acts as an anxiolytics but when given IV, it acts as an anesthetics.

Time

Sedative effect of Benzodiazepines is more marked at night than the day time.

Drug Combination and Drug interaction (See later)

Tolerance: Gradual diminish of tissue response to a drug due to repeated administration is termed tolerance.

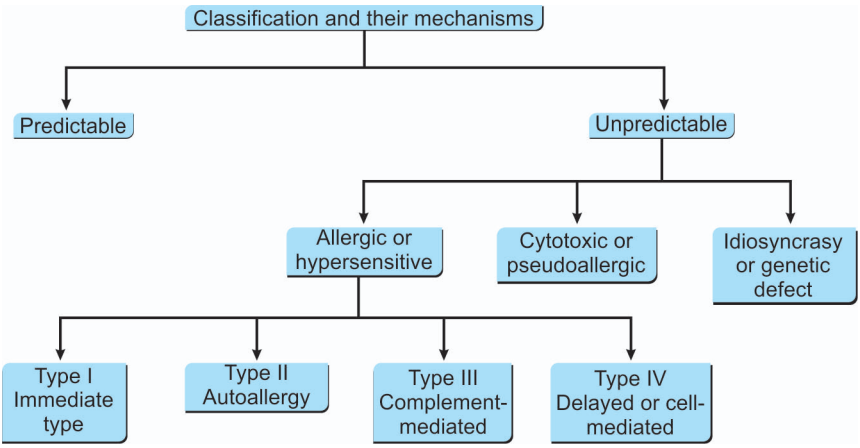
Stages: Habituation → addiction → dependence → tolerance.
Example: Morphine, pethidine, heroin.

SECTION-X ADVERSE DRUG REACTIONS (ADRs)

- Definition
- Classification and their mechanisms
- Terms related to ADRs
- Understanding/Abbreviation
- Comparison among predictable unpredictable and cytotoxic drug reaction.

DEFINITION

According to Karch and Lasagna, 'Reactions which are unintended and harmful and which occur when an usual or standard dose is given for therapeutic, diagnostic, prophylactic purposes, are referred as ADRs.



Predictable

ADRs are due to extension of pharmacological response. They account for 80% of total ADRs. Causes of predictable ADRs are–

i. Excess dose intake
ii. Slow metabolism
iii. Hyperreactivity
iv. Drug interaction
v. Extremes of age
vi. Fault of kidney, liver, heart
vii. Hypoalbuminemia
viii. Dehydration.

Unpredictable

A different family of ADRs, which are not merely due to an extension of pharmacological effects, such reactions are called unpredictable ADRs. Their subfamilies are —

1. Allergic or hypersensitivity reactions
2. ldiosyncrasy or genetic defects
3. Cytotoxic or pseudoallergic reactions.

Hypersensitivity or Allergic Reactions

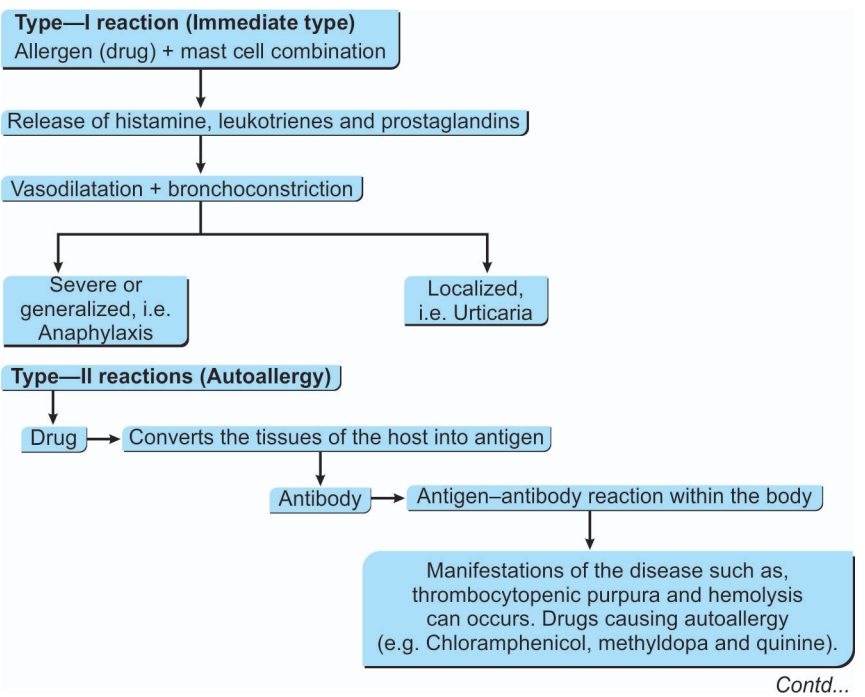
Most drugs are relatively low molecular weight and only become antigenic when they are combined covalently and irreversibly with other substances of high molecular weight, usually proteins. Allergic reactions to drugs are the results of interactions of drug or metabolite or a nondrug element in the formulation with the patient, and subsequent reexposure.

The chief target organs of hypersensitivity reactions are skin, respiratory tract, GIT and blood vessels. Hypersensitivity reactions may be of four types. Any of which can be produced by drugs.

Step–I Drug (Hepten) combines with—Body protein—Forming (Antigen).

Step–II Antigen (Stimulates-Reticuloendothelial systems)—Producing (Antibody).

Step–III Subsequent reexposure to drug (Antigen) (Combines with antibody) (Allergic reactions).



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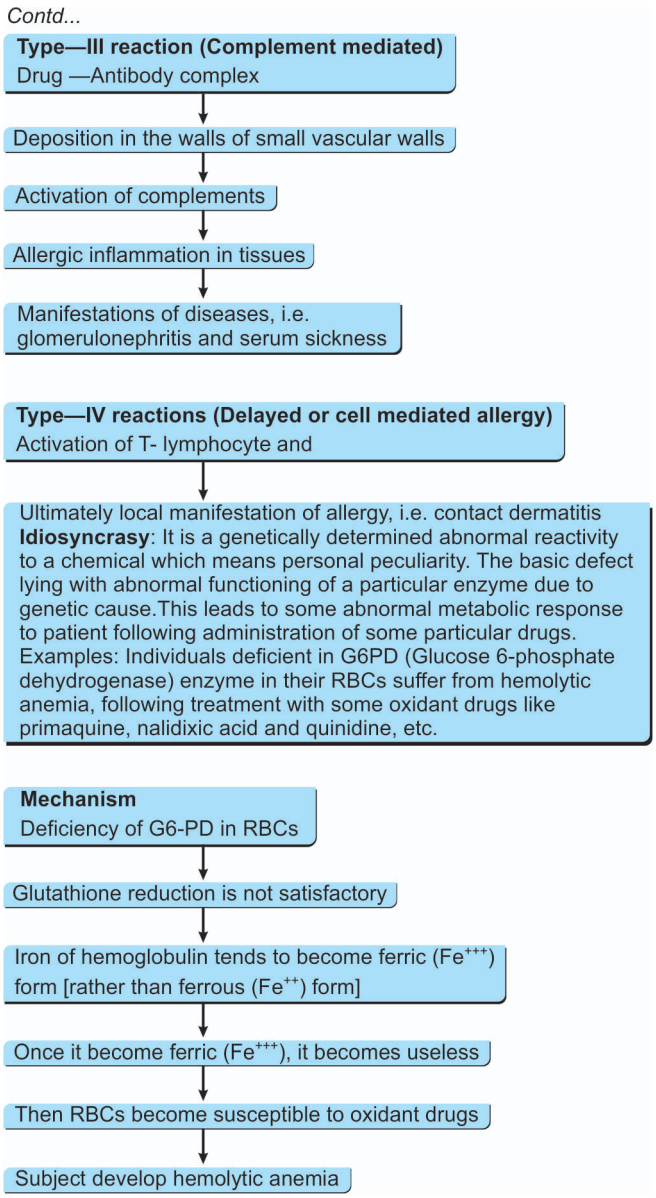


Other examples of idiosyncrasy are–

1. Warfarin resistance
2. Glaucoma after corticosteroid eyedrops
3. Malignant hyperpyrexia after general anesthesia.

Cytotoxic or pseudoallergic reaction: Dose independent type of allergic reactions without immunological basis are the cytotoxic or pseudoallergic reaction. They occur on first contact with a drug rather

than after previous sensitizing exposure. These reactions are produced by compounds that are able to release histamine and other mediators directly from mast cells without involving an antigen–antibody reaction.

The basic mechanism of cytotoxicity is as follows:
Metabolized drug → Binding of drug metabolite covalently with tissue macromolecule (protein) → Damage of the tissue.

Example, INH an antitubercular drug which is first converted in the liver to acetyl Isoniazide and then undergoes further metabolism and the metabolites bind irreversibly with the hepatic cells and hepatotoxicity occur in susceptible individuals, so that drugs that induce hepatic enzyme for drug metabolism (Phenobarbitone/Rifampicin) intensify the hepatotoxicity in susceptible persons.

TERMS RELATED TO ADR$_S$

Side Effects

Effects which are produced with therapeutic doses of the drug during the course of treatment, e.g. dryness of mouth with atropine, Drowsiness with histamine.

Unwanted Effects

Undesirable effects, produced by therapeutic dose, severe form of which necessitate the cessation of treatment, e.g. vomiting and diarrhea with para-aminobenzoic acid.

Toxic Effect

The potential harmful effects of a drug in the living human body. Toxic effects may be acute or chronic, e.g. chlorpromazine induced cholestatic jaundice.

Supersensitivity or Intolerance

It is a phenomenon, where some persons began to show responses, when the dose of the drug is very small in contrast to subjects requiring heavier doses for the response. This people are said to have intolerance or are supersensitive to the particular drug.

There are certain adverse reactions which are encountered on clinical practice but they do not fall under the types mentioned above. These are—

1. Teratogenic
2. Mutagenic

3. Carcinogenic
4. Drug intolerance
5. Photosensitivity.

Teratogenic

Reaction—Some drugs given in the first three months of pregnancy may cause congenital abnormalities and are said to be teratogenic.

Effects of teratogen

Effects are due to direct action on the fetus. This drug affect cell division, e.g. Thalidomide, anticancer drugs and many antibiotics.

Primary effects of the drugs are on the uterus placenta and so on. Effects on the fetus are secondary here, e.g. Uterine vasoconstrictors (fetal anoxia, isotretinoin(used in acne) (placenta) fetal damage.

The most important period for teratogenesis is 'three to ten weeks of age of fetus', when the organogenesis (development of organs) occurs. Teratogenicity may be—

1. Anatomic when there is phokomelia
2. Growth retarding
3. Behavioral
4. Sex related
5. Even carcinogenic.

Following drugs are highly teratogenic thalidomide, androgenic steroids, anticonvulsants, antineoplastic, diethylstilbesterone, lithium, penicillamine, warfarin, and tricyclic antidepressants.

Mutagenic and carcinogenic: Some drugs produce adverse effects only after prolonged treatment. The precise mechanism is unknown. For example, cataract due to chloroquine and corticosteroid, nephropathy with phenacetin, gold salts and penicillamine. Carcinogenesis and mutagenesis are caused by alkylating agents, Niridazole and estrogens.

Photosensitivity: A minority group begin to respond (show the effect) when the dose of the drug is very small.This minority group of persons are said to be supersensitive or drug intolerant. Some drugs play important role in the pathogenesis of photoallergy and phototoxicity which together constitute photosensitivity.

UNDERSTANDING/ABBREVIATION

A – Augmented – Oral hypoglycemics in DM causes hypoglycemia
B – Bizarre – Chloramphenicol → aplastic anemia
C – Chronic – Analgesic nephropathy
D – Delayed – Omeprazole → carcinoma of stomach
E – Ending of dose – Rebound adrenocortical insufficiency.

Table 1.2 Comparison among predictable, unpredictable and cytotoxic drug reactions

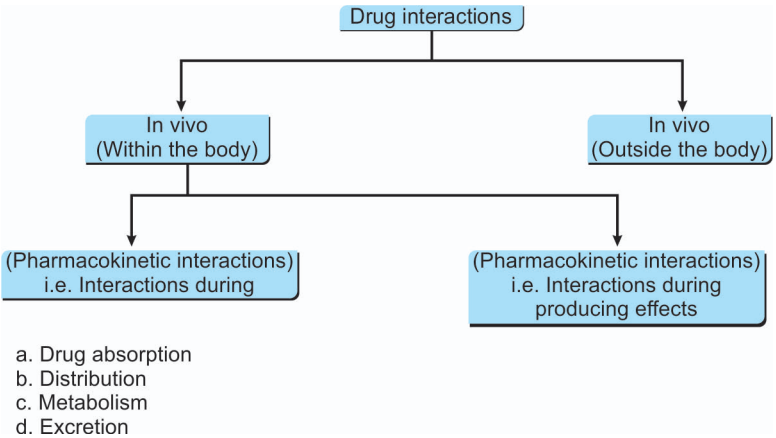
Drug reaction	All individuals	All drugs	Relation with dose	Previous sensitivity	Management
Predictable	Affected	Does	Dependent	No	Dose reduction
Unpredictable	Not	Does not	Independent	Yes/no	Stoppage of drug
Cytotoxic variety of unpredictable type	Not	Does not	May/may not	No sensitization	Avoidance of drug

SECTION-XI DRUG INTERACTIONS

DESCRIPTION

Drug interactions may be defined as the effects those are produced due to administration of one or more drugs simultaneously or subsequently.

They may be beneficial or harmful to the patient. Interactions may increase the effect (i.e. additive effect and synergism) or may decrease (i.e. drug antagonism). They may occur both in vitro and in vivo. Again in vivo reactions may be Pharmacokinetic or Pharmacodynamic.



IN VITRO DRUG INTERACTION

A serious loss of potency can occur from incompatibility between an infusion fluid and a drug that is added to it. Similarly, addition of more than one drug to the same infusion fluid may result in interactions causing loss of activity. The immediate effect of soluble insulin is reduced if it is drawn up with potassium zinc insulin in the same syringe and drip.

Examples of in vitro interactions

1. Thiopentone+Suxamethonium → Precipitation
2. Diazepaum+lnfusion fluids → Precipitation
3. Phenytoin + Infusion fluids → Precipitation
4. Heparin + Hydrocortisone → Inactivation of heparin
5. Kanamycin + Hydrocortisone → Inactivation of Kanamycins
6. Carbenicillin + Gentamicin → Inactivation of Gentamicin.

IN VIVO INTERACTIONS

a. **Interactions during drug absorptions**

Drugs may interact in the GIT resulting in either decreased or increased absorption. Altered absorption may be due to any of the following mechanism.

Direct chemical interactions; aluminium and magnesium containing drugs can interact and calcium and calcium form chelation with tetracycline causing reduced bioavailability of tetracyclines. Similar interactions occur between iron and tetracycline. Furthermore, cholestyramine interferes with absorption of thyroxin, digoxine and warfarin by the process of absorption.

Examples are:

Interacting drugs	Mechanism	Results
Tetracycline + sodium bicarbonate	Altered pH	Decreased absorption of TC
Tetracycline + calcium	Chelation	Decreased absorption of TC
Tetracycline +magnesium	Chelation	Decreased absorption of TC
Tetracycline + aluminium	Chelation	Decreases absorption of TC
Tetracycline + iron	Chelation	Decreases absorption of TC
Digitalis + cholestyramine	Complex formation	Decreased absorption of digitalis
Warfarin+ cholestyramine	Complex formation	Decreased absorption of warfarin (increased coagulation)
Thiazide+ cholestyramine	Complex formation	Decreased absorption of thiazide (less diuresis)
Metoclopramide + digoxin	Change of motility	Increased absorption of digoxin (arrhythmia)
Metoclopramide+aspirin	Unknown	Increased absorption of aspirin

b. **Interactions during distribution**

Immediately after absorption, drug may exist in two forms, free or active and binding or inactive form. A drug, which is extensively bound to protein, can be displaced from its binding site by another drug having more binding capacity, thereby raising the free concentration of displaced drug. Aspirin displaces Warfarin from binding site resulting in increased adverse effects of Warfarin. Other examples are given below:

Interacting drugs/ligands	Displacing drug	Result	Explanation
Bilirubin	Sulfonamide	Kernicterus	Increased bilirubin causes icterus
Bilirubin	Vitamin K	Kernicterus	Increased bilirubin causes icterus
Tolbutamide	Salicylate	Hypoglycemia	Due to increased action of tolbutamide
Methotrexate	Salicylate	Agranulocytosis	Due to inhibition on bone marrow
Methotrexate	Sulfonamide	Agranulocytosis	Due to inhibition on bone marrow
Warfarin	Salicylate	Bleeding	Due to more anti-coagulant action
Digoxin	Quinidine	Severe bradycardia	Due to toxic effect of digoxin

c. **Interactions during metabolism**

Most drugs are metabolized by hepatic enzymes. Many drugs can induce, i.e. they can enhance the synthesis of these enzymes. Such inducers will quicken the degradation of other drugs and $t_{1/2}$ of the drug will be reduced and dose have to be increased to obtain the desirable result. On the contrary, some other drugs inhibit the hepatic enzymes for drug metabolism therefore, these drugs (inhibition) cause delay in degradation of the other drug, increase the $t_{1/2}$ of the drug and usual dose may produce toxicity in these cases. Examples are—

a. Enzyme inducer	Induced drug	Result	Explanation
Barbiturates	Coumarin anti-coagulants	Failure of coum-arine effect	Increased coagulation
Phenytoin	Digoxin	Failure of digo-xin to produce desirable action	Due to low concentration of digoxin
Rifampicin	Oral contrace-ptive	Failure of contraception	Chance of conception

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b. **Enzyme inhibitor**	**Drugs producing accelerated effect**	**Result**	**Explanation**
Cimetidine	Diazepam	Increased sedation	Due to increased effect of diazepam
INH	Tolbutamide	Hypoglycemic shock	Due to increased effect of tolbutamide

d. **Interactions during excretion**

Drugs, which are excreted, via kidneys, may be interfered in two ways:

i. Interference with active transport
ii. Interference with passive diffusion.

Probenecid competes with Penicillins for active transport process and prolongs the action of Penicillin, which is beneficial. Other examples are given in the Table 1.3.

Table 1.3 Competitive interaction for renal tubular transport

Primary drug	**Competitive drug**	**Mechanism**	**Results**
Penicillin	Probenecid	Competition on renal tubular transport	Prolonged action of penicillin
Methotrexate	Salicylate	Competition on renal tubular transport	Agranulocytosis
Methotrexate	Sulfonamide	Competition on renal tubular transport	Agranulocytosis
lndomethacin	Probenecid	Competition on renal tubular transport	GI bleeding
Salicylate	Probenecid	Competition on renal tubular transport	GI bleeding
Digoxin	Spironolactone	Competition on renal tubular transport	Severe bradycardia

Alteration of urinary pH influences ionization of drugs and their excretion. Thus, basic drugs are better excreted in acidic urine and acidic drugs are better excreted in alkaline urine. Enhanced excretion of barbiturate occurs if sodium bicarbonate is given, similarly Benzodiazepine is rapidly excreted if ammonium chloride is added.

Pharmacodynamic interactions: Drugs may react chemically and neutralize each other's action, forming an inert compound, i.e. use of

British Anti Lewisite (BAL) in the treatment of heavy metals like arsenic, cobalt and mercury poisoning. Other examples are used of antacid in the treatment of peptic ulcer (antacid + gastric HCl) cause relief of pain by neutralization. Heparin + Protamine sulfate (neutralization). All these are the examples of chemical antagonism.

Physiological antagonism: When two drugs produce opposite effect on the same physiological system, one drug canceling the effect of other, i.e. histamine and adrenaline constrictor and dilator effect on bronchus.

Pharmacological antagonism: When two drugs competes for the same receptor and the inactive drug prevent the access of active drug. It is of two types:

i. Competitive
ii. Noncompetitive.

a. Thus propranolol (β-blocker) nullifies the effects of adrenaline by blocking the receptors on the β_1 and β_2-receptor. Atropine nullifies the effects of acetylcholine on the muscarinic receptors and so on.
b. In this type of antagonism the antagonist may combine irreversively with the receptor or portion of the receptor in which cases increasing the concentration of the agonist will never fully overcome the **inhibition, e.g. Acetylcholine and decamethonium at the neuromuscular junction**.

Table 1.4 Some clinically important drug interactions

Drugs	Mechanism	Result	Explanation
Allopurinol+ anticoagulants	Inhibits hepatic drug metabolizing enzymes	Increased bleeding	Due to increased effect of anticoagulants
Antacids+ quinolones	Antacids may adsorb drugs in GIT, thus reducing absorption	Failure of antimicrobial activity	Due to decreased GI absorption of quinolones
Anticoagulants + metronidazole	Inhibition of metabolism of anticoagulants	Bleeding	Due to increased anticoagulants action
Propranolol+ cimetidine	Decreased metabolism of propranolol	Bradycardia	Increased beta-blocking effect
Propranolol+ furosemide	Decreased metabolism of propranolol	Bradycardia	Increased effect propranolol
Propranolol+ rifampicin (in hypertensives)	Increased metabolism of propranolol	Sudden attack of hypertension	Decreased beta-blocking effect

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Drugs	Mechanism	Result	Explanation
Propranolol+ indomethacin (in hypertensive)	Increased metabolism of propranolol	Sudden attack of hypertension	Reduced antihypertensive effect
Propranolol + insulin	Can block sympathetic activity	a. Inhibition of glucose recovery from hypoglycemia b. Inhibition of symptoms of hypoglycemia c. Increased BP during hypoglycemia	——
NSAIDS+ACE inhibitors	Reduced renal sodium excretion	Decreased antihypertensive effect	Due to expansion of plasma volume
Probenecid + penicillin	Decreased renal excretion penicillin	Better antimicrobial effect	Due to prolong action of penicillin

SECTION-XII PHARMACOKINETIC PRINCIPLES (CALCULATIONS)

Calculate the followings:

1. Clearence (CL)
2. Maintenance dose (MD)
3. Dose interval (DI)
4. Fraction oral ('F'oral)
5. Steady-state concentration (Css)
6. Volume of distribution (V_d)
7. Loading dose (LD)
8. Half-life ($t_{1/2}$).

1. Clearance (CL) We know $Css = \frac{'F'\,oral \times MD}{Cl \times DI}$

$$\therefore CL = \frac{'F'\,oral \times MD \times 1}{DI \times 1mg\ /1ml}$$

$$= \frac{96 \times 350}{12 \times 1}\ \text{ml/h/70 kg}$$

$$= 2800\ \text{ml} = 2.8\ \text{L/h/70 kg}$$

2. Maintenance dose (MD)

$$= \frac{Css \times CL \times DI}{'F'\ oral \times 1}$$

$$= \frac{1 \times 2.8\ Lt/h \times 12}{96}\ \text{mg}$$

$$= \frac{28 \times 100 \times 12}{96}\ \text{mg} = 250\ \text{mg}$$

3. Dose interval (DI) $= \frac{'F'\ oral \times MD}{Css \times CL}$ hour

$$= \frac{96 \times 350}{1 \times 2.8\ Lt}\ \text{hour}$$

$$= \frac{96 \times 350}{1 \times 28 \times 100\ (ml)}\ \text{hour}$$

$$= \frac{96 \times 350}{28 \times 100}\ \text{hour} = 12\ \text{hour}$$

4. Fraction oral ('F'oral) = 'F'-oral $= \frac{DI \times CL \times Css}{MD}$

$$= \frac{12 \times 28 \times 100}{350}\ \% = 96\%$$

5. Steady-state concentration (Css) = Css $= \frac{'F'\ oral \times MD}{CI \times DI}$

$$= \frac{96 \times 350\ \text{mg}}{12 \times 2.8\ Lt}$$

$$= \frac{96 \times 350\ \ \text{mg}}{12 \times 28\ \ 100\ \text{mg}}$$

$$= \frac{96 \times 350\ \ \text{mg/ml}}{12 \times 28 \times 100} = 1\ \text{mg/ml}$$

6. Volume of distribution (V_d) = $V_d = \frac{D}{C}$

7. Loading dose (LD) = $LD = Css \times V_d$

8. Half-life ($t_{1/2}$) = $\frac{V_d \times K_c}{CL}$

V_d = Volume of distribution
K_c = Constant (0.693)
CL = (total) Clearance

V_d = 1.6 liter / kg
CL = 10 ml/min/kg
$t_{1/2}$ = ?

$$= \frac{0.693 \times 1/6\ \text{liter/kg}}{10\ \text{ml/ min/kg}}$$

$$= \frac{1.1088\ \text{liter}}{10\ \text{ml/min}}$$

$$= \frac{1108.8\ \text{ml}}{10\ \text{ml/min}}$$

$$= \frac{110.8}{60} = 1.8\ \text{hour}$$

CHAPTER

2

Autacoids

SECTION-I AUTACOIDS

- Definition
- Classifications
- Chemistry
- Biosynthesis
- Mechanism of action
- Functions
- Roles
- Eicosanoids (Prostaglandins)
- Inhibitors of eicosanoids
- Other inhibitors for common autacoids
- Examples of H_1 receptor blockers
- Bronchial asthma and its management.

DEFINITION

Substances which are—

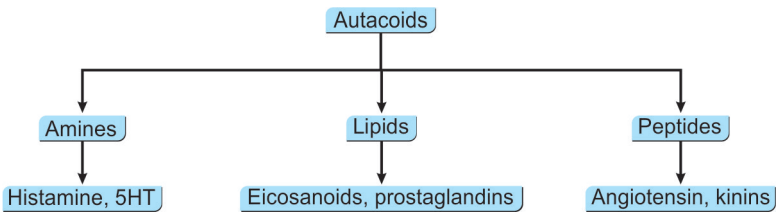
i. Secreted by specialized cells
ii. Acts locally
iii. Protects the body from some adverse situations
iv. Degraded quickly are termed as autacoids. (From Greek, autos (self) coid (remedy), i.e. full meaning is 'self-remedy'.

However, in spite of such distinct features the status of a substance as autacoids may remain uncertain, i.e.

1. Mast cells situated at the base of gastric parietal cells exert a paracrine effect by histamine on the parietal cells.
   Here, histamine acts as a neuromodulators.
2. Histamine is secreted by some CNS neurons, where histamine acts as a neurotransmitter.
3. Histamine secreted in the bronchial tree/skin (producing

bronchospasm or triple response) acts as a neuromediators [Here histamine is considered as autacoids].

CLASSIFICATIONS



CHEMISTRY

The structures of A. A and PGs (prostaglandins) may be considered to be the derivatives of prostanoic acid, which however is a hypothetical acid not occurring in the nature.

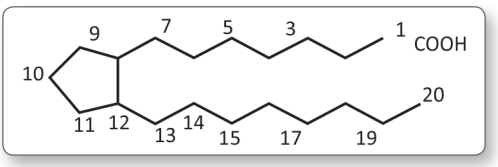


Fig. 2.1: Structure of prostanoic acid (hypothetical)

BIOSYNTHESIS

See the anti-inflammatory effects of aspirin.

MECHANISM OF ACTION

Eicosanoids
↓ + Specific receptors
Activation of membrane bound
↓ G proteins
Generation of 2nd messengers
↓ IP_3 /DAG/cAMP
Biological actions

FUNCTIONS

a. Platelet aggregation—A particular type of cells can produce one or two but not all the varieties of eicosanoids. Different eicosanoids can

have opposing actions. TXA_2 produced by platelets help in platelet aggregation, while PGI_2 secreted by the vascular endothelium opposes it.

b. Blood vessels—PGE_2 and PGI_2 (Prostacycline) are powerful vasodilators.
c. Kidneys—PGE_2+PGI_2 cause renal vasodilatation, increased renal blood flow and diuresis.
d. Reproductive system
   1. Regression of size of pregnancy occurs by PGE_2.
   2. PGE_2 +PGF_2 cause contraction of uterine muscles, it is more in pregnancy.
   3. High conc. of PGs in seminal fluid → cause uterine contraction during coitus → suction of sperm → conception.
e. Gastric mucosa—There is ↑ vascularity of mucosa ↓ HCl secretion and ↑ cytoprotection.

ROLES

Followings are the conditions where PGs have some roles—

i. Inflammation
ii. Bronchial asthma
iii. Patent ductus arteriosus (PDA)
iv. Dysmenorrhea
v. Bartter syndrome
vi. Rheumatoid arthritis
vii. Hypercalcemic states.

EICOSANOIDS (PROSTAGLANDINS)

- Eicosa means twenty (indicating a 20C structure)
- Enoic means double bonds are derivatives of A. A which has 20 carbon atoms and contain 4 double bonds.

INHIBITORS OF EICOSANOIDS

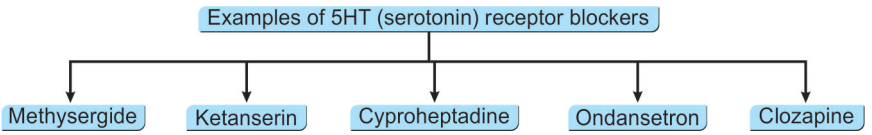
Inhibitors	Enzymes for eicosanoids
Glucocorticoids	Phospholipase A_2 enzyme
NSAIDs	Cyclooxygenase enzyme
Benoxaprofen	Lipooxygenase enzyme
Tranylcypromine	PGI_2
Imidazole	Thromboxane

OTHER INHIBITORS FOR COMMON AUTACOIDS

1. Antihistamines
   a. Physiological antagonist—Adrenaline
   b. Mast-cell stabilizer—Cromoglycate
   c. Receptor blockers
      i. H_1
      ii. H_2.

EXAMPLES OF H_1 RECEPTOR BLOCKERS

1. Ethanolamines —Diphenhydramine
2. Ethylaminediamines — Pyrilamine
3. Piperazine derivatives — Meclizine
4. Alkalamines — Chlorpheniramine
5. Phenothiazine — Promethazine
6. Others —
   a. Piperidines— Loratadine
   b. Others — Astemizole.



BRONCHIAL ASTHMA AND ITS MANAGEMENT

- Definition
- Types
- Precipitating factors
- Basic pathology of bronchial asthma
- Pathogenesis
- Drugs used in asthma
- Mechanism of action of drugs.

Definition

Asthma is a chronic inflammatory disorder of airway which is characterized by episodic, reversible bronchospasm resulting from an exaggerated bronchoconstrictor response to various stimuli.

Types

1. Extrinsic
   a. Allergic
   b. Occasional
   c. Atopic
2. Intrinsic.

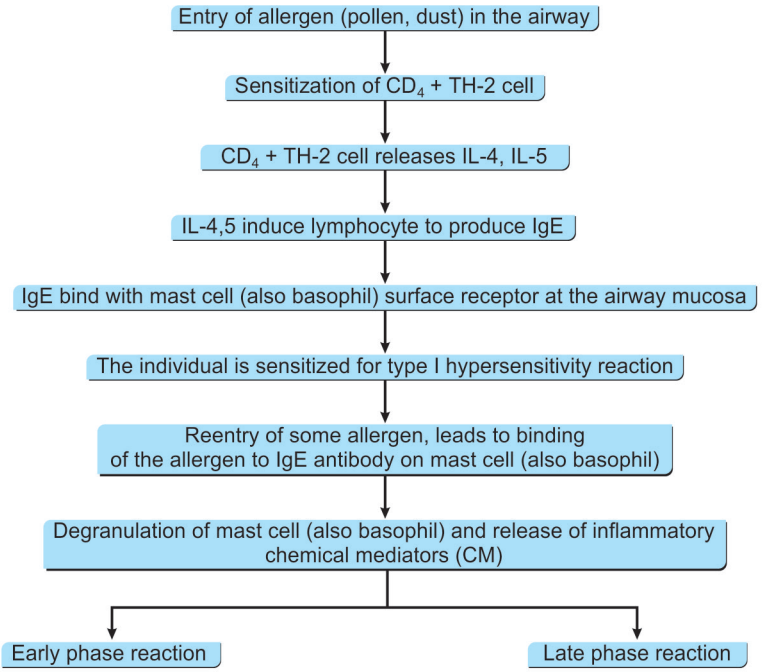
Precipitating Factors

1. Allergens—Pollen, mite, dust, feather of pillow, specific foods
2. Exercise—Emotion, environment
3. Infection—Respiratory tract infection
4. Occupation—Industrial chemicals
5. Drugs—Aspirin, Propranolol.

Basic Pathology of Bronchial Asthma

1. Bronchial smooth muscle contraction.
2. Persistent inflammation of bronchial tree and damage to epithelium of bronchus.
3. Increased mucus production by goblet cells.
4. Exaggerated bronchoconstrictor response.
   Or, bronchial hyperresponsiveness or increased airway reactivity to various stimuli (i.e. allergens and chemicals).

Pathogenesis



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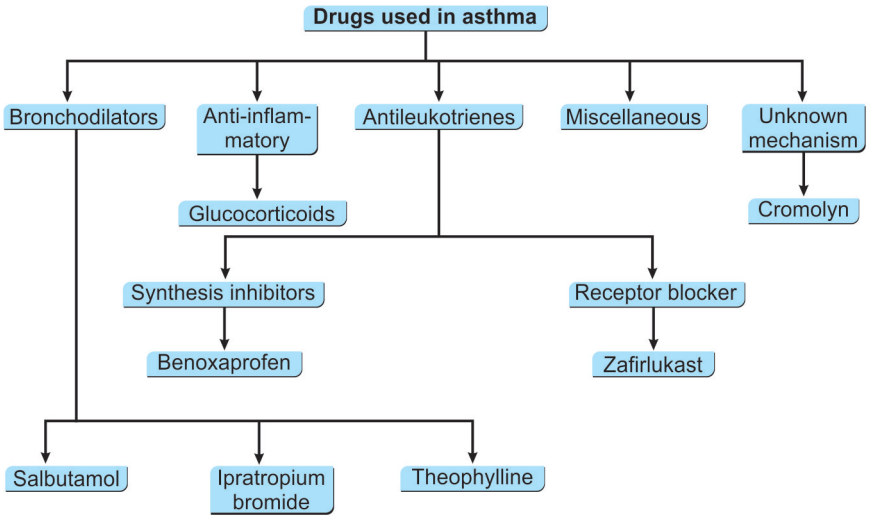
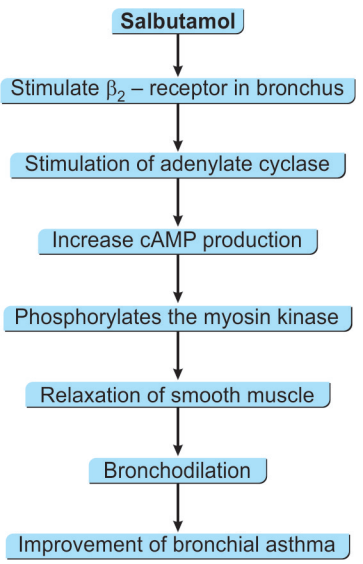
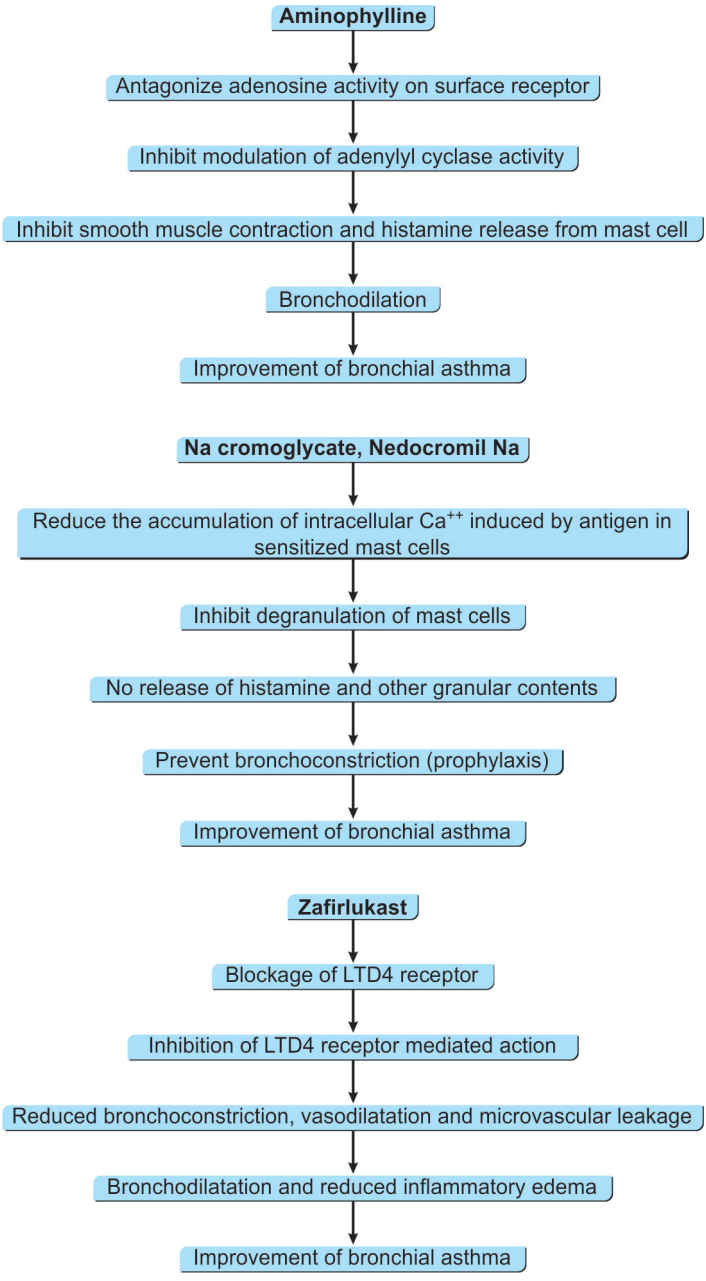
via neuronal reflex induce bronchoconstriction
3. CM from mast cell cause vasodilation and increased vascular permeability, leading to edema
4. Increased mucine/mucus secretion
5. Recruitment of leukocytes

3. Overwhelming inflammatory reaction by recruited leukocytes



Mechanism of Action of Drugs





Glucocorticoids

Corticosteroids induce formation of Lipocortin (a protein), which inhibits membrane phospholipase A_2, so no formation of arachidonic acid and it's metabolites (PGs, LTs, PAF).

Based on this mechanism, corticosteroids help in bronchial asthma, in following ways:

1. Reduction in bronchial hyperreactivity, by—
   - Inhibition of influx of inflammatory cells into the lung, that follows exposure to an allergen.
   - Inhibition of release of chemical mediators (CM) from macrophage and eosinophils.
2. Reduction of bronchial inflammation, by—
   - Decreasing microvascular leakage
   - Reversing mucosal edema.
3. Increase efficacy of circulating catecholamines
   - This is known as permissive action of steroid.

CHAPTER

3

Drugs Opposing Homeostasis

SECTION-I DRUGS OPPOSING HOMEOSTASIS

- Definition
- Components
- Drugs
  - Antithrombotics
  - Anticoagulants
  - Thrombolytics.

DEFINITION

The normal physiological process, to arrest a hemorrhage is called homeostasis.

COMPONENTS

It has three major components.
1. Vasoconstriction, 2. Platelet plugging, 3.Coagulation in the local region.

DRUGS

Antithrombotic or Antiplatelet

They effect by opposing platelets activation, i.e. Aspirin (in low dose), Sulfinpyrazone and Dipyridamole.

Anticoagulants

They effect by opposing procoagulant, i.e. Heparin, Warfarin and the other coumarin anticoagulants.

Thrombolytics

They effect by promoting fibrinolysis, i.e. Streptokinase, Urokinase, tissue plasminogen activator (tPA).

Antithrombotics or antiplatelets

Platelets are the smallest of the formed elements of blood, are enclosed by a membrane containing receptors (thromboxanes) concerned mainly with homeostasis, the cessation of bleeding. Normally, they can a negative surface charge and are therefore separated by mutual repulsion and remain in inactive state. But following an injury platelets are activated.

ADP induces platelet aggregation and is thought to act by converting AA into thromboxanes, via cyclooxygenase pathway, after proper stimulation. This thromboxane combines with the membrane receptors of neighboring platelets causing reversible platelet aggregation.

Platelet aggregation is also produced by collagen, thromboxanes, serotonin, catecholamines, and POE_2. The aggregate induced by these substances undergo a viscious metamorphosis in which platelets become fused, i.e. irreversible platelet aggregation and their contents are liberated. Thus, the clotting process is facilitated by the release of platelet factor-III and the vascular endothelium released PGI_2 combines with platelet membrane, this binding causes production of cAMP within the platelet. cAMP inhibits the liberation/release of platelet contents, so that no ADP is secreted. cAMP is normally degraded by phosphodiesterase. Prevention of degradation of cAMP leads to cAMP accumulation, and more vigorous inhibition of release of platelet contents.

Since aggregation of platelets serves as a focus for initiation of blood clotting, it is thought that inhibitors of platelet aggregation may be value in the Rx of thrombotic diseases with antithrombotics.

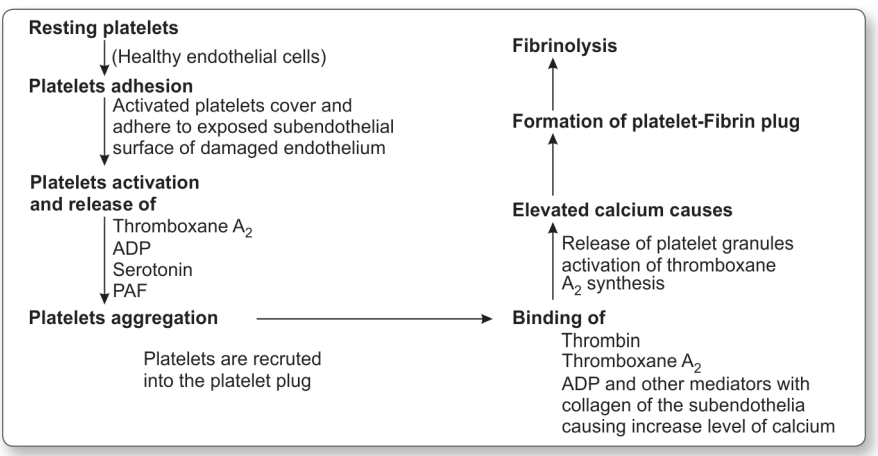


Fig. 3.1: Mechanism of platelet aggregation

Individual drugs

Aspirin: There are two sets of chemicals acting on the platelets—

i. TxA_2 cause platelet activation, i.e. leading to platelet adherence, aggregation, secretion and vasospasm.
ii. The other set, i.e. prostacycline, (PGI_2) leading to platelet inactivation and vasodilatation.

TxA_2 is produced by the platelet through cyclooxygenase pathway but PGI_2 from vascular endothelium although through cyclooxygenase pathway. Aspirin in low doses inhibits the platelet cyclooxygenase pathway but not the endothelium cyclooxygenase pathway (in other words TxA_2 synthetase but not the PGI_2 synthetase) so that Aspirin in low doses opposes homeostasis by suppressing TxA_2 but, PGI_2 is not suppressed.

The great use of aspirin as antihomeostatic agent is as prophylaxis where there is increased risk of blood clotting, i.e.

i. Angina pectoris
ii. Early in MI
iii. Coronary artery bypass graft
iv. Atrial fibrillation particularly in the elderly where use of warfarin can be risky.

Further details of aspirin see in CNS.

Dipyridamole

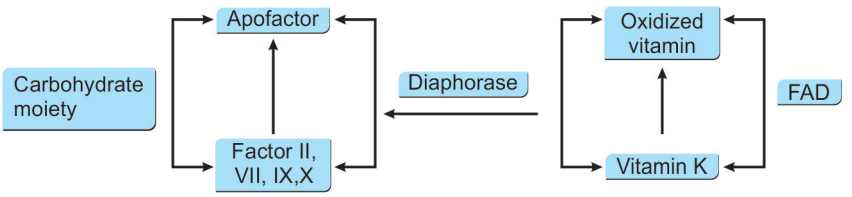
It inhibits the phosphodiesterase enzyme. Inhibition of phosphodiesterase causes accumulation of cAMP. Accumulation of cAMP within the platelet causes inhibition of release of ADP, so no platelet aggregation occurs. However, as an antiplatelet agent, it is weak and usually given with aspirin.

SECTION-II ANTICOAGULANTS

Role of vitamin K in coagulation: The role played by vitamin K in the synthesis of prothrombin and factors II, VII, IX and X has not been fully elucidated. There are three main hypothesis.

First one is that the genes controlling the synthesis of protein clotting factors operate in conjunction with a gene that produces a repressor substance. The inhibitory effect of the repressor substance is prevented by vitamin K. Therefore, synthesis proceeds. In the absence of vitamin K, synthesis is suppressed.

The second hypothesis depends on the fact that the vitamin K, dependent clotting factors are glycoproteins and invokes the following scheme in the attachment of the carbohydrate moiety to the peptide chain.



In the absence of vitamin K, the functional glycoprotein is not formed

The third hypothesis proposes that vitamin K is a necessary cofactor in the final stage of the synthesis of prothrombin and factors II, VII, IX, with X. This final stage is the Y-carboxylation of some of the glutamic acid residues in the protein. The Y-carboxyl glutamic acid residues formed, bind with Ca^{+2} and are necessary for the action of the group of factors in the clotting process.

In the first hypothesis, vitamin K antagonists are thought to prevent the inhibitory effect of vitamin K on the suppressor. In the second hypothesis, it is thought that antagonists prevent the reinstitution of vitamin K by inhibiting the FAD-dependent enzyme diaphorase. In the third hypothesis, the antagonist prevent the role of vitamin K in the Y-carboxylation of glutamic acid residues.

ANTICOAGULANTS

Anticoagulants may be used in the Rx and prophylaxis of disorders resulting from the blockade of blood vessels by intravascular clotting, i.e. formation of thrombi or emboli.

In Vivo Anticoagulants

a. Parenteral — Heparin
b. Oral.
   i. Coumarin derivatives—Dicumarol, Warfarin sodium, Warfarin potassium
   ii. Indandione derivatives—Phenindione, Anisindione.

Table 3.1 Differences between heparin and dicumarol

Points	Heparin	Dicumarol	Explanation
Source	Animal → Mast cells	Plant → Sweet cloves	Natural source
Route	Parenteral IV	Oral	Heparin is degraded by branching enzyme
Molecular weight	More (10000–20000)	Less (exactly not known)	Due to large molecular size of heparin
Site of action	Both vivo and vitro	Vivo only	Formation of clotting factors in vitro is impossible
Onset of action	Immediate—Within 10–15 mints. So used in emergency	Delayed —After 12–24 hours. So routinely used	Preformed clotting factor requires time to be exhausted

Contd...

Contd...

Points	Heparin	Dicumarol	Explanation
Duration of action	4–6 hours	3–7 days	OAC have high plasma protein binding
Mechanism of action	Direct → antithrombic action	Indirect by → preventing synthesis of factors II, VII, IX, X	
Allergy	Due to histamine release	Absent	Biological drug, so may have high antigenicity
Antidote	Protamine sulfate	Vitamin-K_1 or whole blood	• Protamine sulfate cause chemical antagonism • Vitamin-K_1 or whole blood helps finally the role of clotting factors in coagulation
Use in pregnancy	Used	Not used	As it crosses placental barrier and causes uterine death of fetus

MECHANISM OF ACTION OF BOTH GROUPS

Heparin

It is believed to cause anticoagulation, by accelerating with the formation of complexes between antithrombin-III and several proteases, involved with the coagulation cascade. This includes factors II, VII, IX, X, as well as thrombin. Antithrombin-III is an α-globulin, normally present in the blood, is an important controlling protein. It forms a complex with active serine proteases which interact with its arginine containing site. In absence of exogenous heparin, the complex forms very slowly. After combining with exogenous heparin, it potentiates the action upto 1000 folds.

Pharmacological actions of heparin

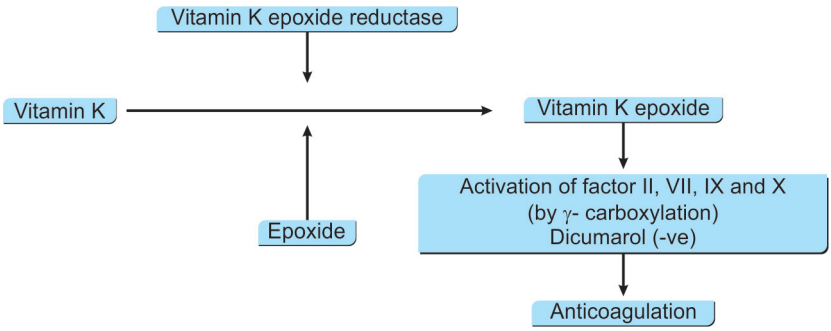
1. Apart from its effects on coagulation, heparin can cause.
2. Plasma clearing effect—After a fatty meal. Normally, after heavy fat ingestion, plasma becomes milky. This milkiness can be cleared up by heparin. Milkiness is caused by presence of excess triglycerides

obtained from food fat. These triglycerides are hydrolyzed by lipoprotein lipase causing clearance of milkiness.

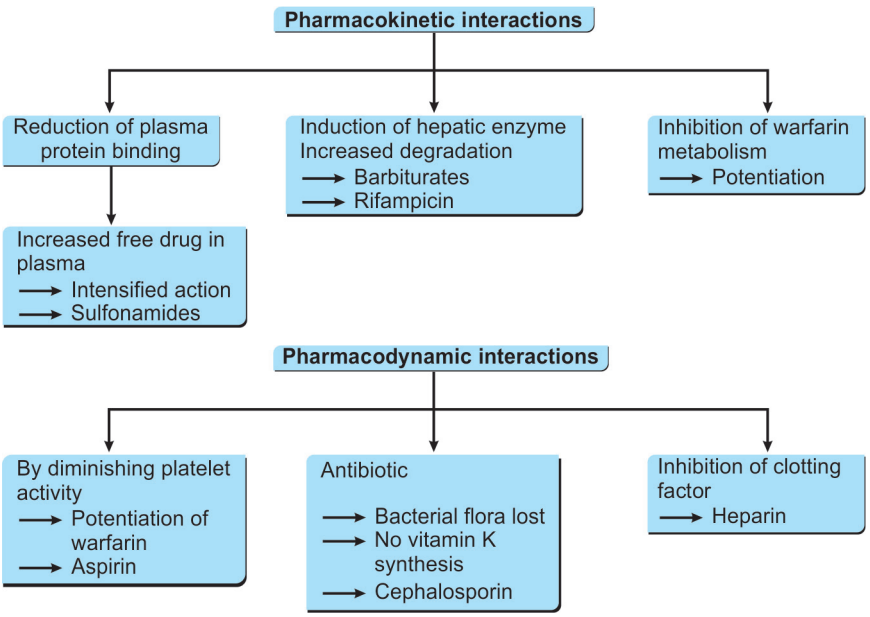
3. Reduction of aldosterone secretion.
4. Delay in wound healing.

Vitamin K Antagonist

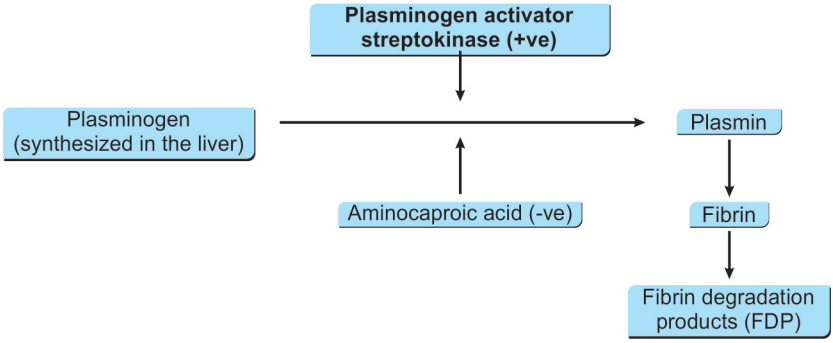
The action of vitamin K in promoting the synthesis of prothrombin and factors II, VII, IX and X is completely antagonized by a number of Coumarin and Indanedione derivatives. Vitamin K antagonists are known collectively as systemically acting or indirect acting anticoagulant. They cause a decrease in plasma levels of vitamin K dependent clotting factors and thereby reduce the coagulability of the blood.



DRUG INTERACTIONS WITH WARFARIN



SECTION-III THROMBOLYTICS



Many substances can dissolve an established clot in our body, like plasminogen activators. Two of them, tPA and urokinase are endogenous whereas streptokinase is exogenous.

Tissue plasminogen activator (tPA) also called tPA. (Recombinant tPA). It is a naturally occurring substance, synthesized from vascular endothelium. Commercially, tPA is now prepared by DNA recombinant technology which can be used for therapeutic purposes.

Normally, plasminogen as well as tPA are present in circulating blood, but as tPA has originally very weak action so that no plasmin is formed. Alter a clot is formed, both plasminogen and tPA bind with the clot, now the efficacy of tPA increases greatly → acts on the bound plasminogen much intensely and faster → formation of plasmin.

tPA is a fibrin selective agent—(1) Heparin is usually given concomitantly to prevent reocclusion, (2) It is given in AMI, (3) Serious allergic reactions are virtually unknown, and (4) On the whole, it appears to produce more bleeding disorders (hence more risky).

Streptokinase is obtained from group C-β-hemolytic streptococci.

It combines with plasminogen molecule and streptokinase plasminogen complex is formed. Streptokinase alone has no enzyme activity. In the form of a complex, it can act on both (1) Circulating plasminogen as well as. (2) Plasminogen in a clot. Therefore, tPA acts only on the plasminogen in clot. Therefore, tPA is "fibrin selective", i.e. dissolves the clot but its action remains confined on the clot and clot alone, no systemic effects occurs. Whereas streptokinase also acts on circulating plasminogen, so it should produce more bleeding disorders.

As Streptokinase is obtained from streptococcus, so it is a foreign protein. Most persons in their lifetime have had streptococcal infections causing antistreptococcal antibodies to appear. These antibodies can and does neutralize with the Streptokinase.

There will be Two Fall Outs

1. Dose of Streptokinase should be high to overcome neutralization by the antibodies.

2. There can be allergic reaction when IV Streptokinase is given, urticaria anaphylaxis can develop with IV Streptokinase.

Urokinase is an enzyme obtained from fetal kidney. In many respect, it has similarity with Streptokinase. However, allergic reactions are less frequent and is usually mild.

SECTION-IV HEMATINICS (ANTIANEMICS DRUGS)

- Definition
- Clarification
- Erythropoietin
  a. Source
  b. Chemistry
  c. Indication
  d. Hematopoietic growth factor.
- Vitamin and cancer
- Iron
  a. Oral and parenteral forms of iron
  b. Total requirements
  c. Turnover.

DEFINITION

Agents which are used in the treatment of anemia. They increase the number of RBC or Hb content of RBC or both to normal level.

CLARIFICATION

By the term hematinics—Iron, Vitamin B_{12} and folic acid are usually meant. Though erythropoietin should also be called hematinic because hematinic means blood forming agents.

ERYTHROPOIETIN

a. Source

It is normally produced by the kidneys. Hypoxia stimulates its secretion. It acts on the most primitive precursors of erythrocytes. On the cell membrane of the such progenitor cells, erythropoietin receptors are present. It stimulates erythrocyte proliferation and erythroid cell maturation and differentiation. It follows, where kidneys are grossly damaged, anemia would develop.

b. Chemistry

It is a 165 amino acid containing peptide and is given parenterally, but surprisingly despite the chemistry it is not antigenic.

c. Indication

Major therapeutic indications of erythropoietin are—

i. Patients of chronic renal failure on chronic dialysis with anemia
ii. AIDS cases receiving AZT.

d. Hematopoietic Growth Factor

In recent times, a new term, hematopoietic growth factors has been introduced, erythropoietin is one of them. *The well known hematopoietic growth factors include*:

i. Erythropoietin
ii. Granulocyte colony stimulating factor (G-CSF)
iii. Granulocyte macrophage colony stimulating factor (GM-CSF)
iv. Interleukin -m (LL-3, CSF)
v. Stem cell factor (SCF). Many others are on the pipeline.

VITAMIN AND CANCER

Particularly, vitamin A, E and C are developing honor. They are suspected to have protective action against cancer, though hard proof is lacking. A probable mechanism can be as follows.

In our body several free radicals are always developing such as—(1) Nitric oxide, (2) Free radicals, (3) Super oxides, and (4) Hydrogen peroxide and so on. These free radicals are extremely unstable, very active and are injurious to cell membrane as well as DNA materials of the nucleus.

They cause—(1) Per oxidation of polysaturated fatty acids → so cell membrane is damaged. (2) Cross linking of proteins so proteins (enzyme) become useless, and (3) Damage of DNA → so maturation of DNA/apoptosis (i.e. cell suicide) can develop. This mutation of DNA strands can give rise to cancer.

However within our body, there is also a mechanism which terminates the free radicals. Well known mechanism to terminate free radicals include—

1. Antioxidant (vitamin E, C)
2. Super oxide dismutase (SOD)
3. Glutathione and so on.

Vitamin B_{12} is a group name. The term cyanocobalamin and vitamin B_{12} are usually regarded as synonymous. There are several forms: (i) 5 deoxy-adenosylcobalamin, (ii) Hydroxycobalamin, (iii) Methylcobalamin, and (iv) Cyanocobalamin and so forth. Of them methylcobalamin and deoxyadenosylcobalamin alone are active forms of vitamin B_{12}. Dietary ones are active forms and circulate in the blood.

Vitamin B_{12} has two parts—(i) A corrin part, resembling porphyrin of haem, and (ii) A nucleotide. In the corrin part, a cobalt atom instead of iron is present hence the name cobalamin.

All animal products like, liver, milk, egg, meat, etc. are the richest source of vitamin B_{12}.

The strict vegetarians (not even taking the milk products usually) have no significant low level of vitamin B_{12} in their body—why?

i. Vegetables in their skin contain lot of bacteria which synthesize vitamin B_{12}
ii. Human colonic bacteria also synthesize vitamin B_{12}.

IRON

Oral and Parenteral Forms of Iron

Iron preparations are

a. **Oral iron preparations are:**
- Ferrous sulfate
- Ferrous gluconate
- Ferrous fumarate
- Ferrous succinate
- Ferrous acetate
- Ferrous carbonate.

b. **Parenteral iron preparations are:**
i. IM iron dextran complex iron—Sorbitol citric acid complex
ii. IV iron dextran, saccharated iron dextran.

Iron Dextran is the preparation of choice for parenteral iron therapy. Each ml of iron dextran contains 50 mg of elemental iron.

Total Requirements

Elemental iron required by the patient in gm = 0.25 × D. Where D = normal hemoglobin concentration which is regarded as 14.5 gm, patients hemoglobin concentration. The entire dose can be given either in single sitting or in a very slow drip or in daily or twice weekly IM regime.

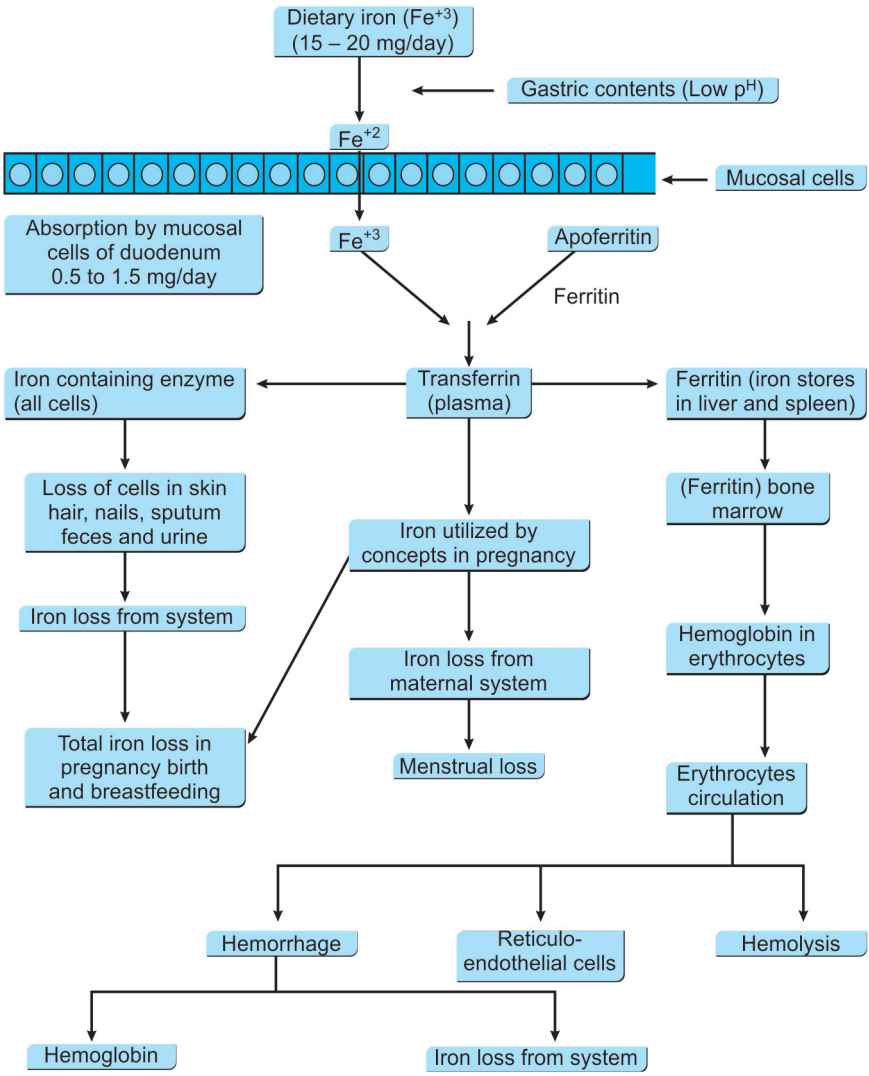
Total amount of iron in the body ranges from 2gm to 6gm. The mean amounts being about 50 mg/kg in men and 40 mg/kg in women. Its distribution is approximately as follows:

1. Erythrocyte hemoglobin 70%
2. Iron stores (ferritin) 24%
3. Myoglobin 4%
4. Iron containing enzyme 0.34%. Therefore, the iron content about 500 mg/l. Mean values are 530 mg/l in men 466 mg/l in women. The normal turnover of erythrocytes results in 1/20th of this iron passing from erythrocytes to iron stores and vice versa/day.

Turnover

Iron metabolism—Intake, losses and turnover.

There is no excretory mechanism for iron but iron is lost from the body at a rate of about 0.5 mg/day as a constituent of cells that are normally being replaced continually. These include epidermal cells of skin, hair, nails, mucosal cells of the alimentary with respiratory tracts, epithelial cells of the urinary and genital tracts. The loss and intake of iron and the turnover of iron in the body are summarized below:



Transferrin is a β-globulin with a molecular weight of about 88000 which occurs in plasma in a conc. of 3 to 4 gm/l.

Ferritin is the complex formed by iron with apoferritin (MW 450000) contains 20% to 24% of iron by weight giving a molar ratio of about 1800.

"After disintegration of hemoglobin, its iron is not thrown out of the body but stored and recycled into hemoglobin synthesis again. But despite this, small amount of iron (1mg/day in adult male and 2.5 mg/day in adult nonpregnant women) is required"—why?

Intestinal epithelium contain some iron (in Fe^{+3} state) as ferritin and these epithelium is regularly desquamated. Thus, some iron (about 1mg) is daily lost, via feces. In addition, loss due to menstruation drainage by fetus, etc. must be made good. This is why we require iron at all.

- **Iron Absorption Occurs in Two Ways**

a. Active process or mucosal block theory
b. Passive process directly goes to circulation, by diffusion.

Mucosal block theory—Exact mechanism is unknown. Rate of absorption is directly proportional to iron present in food in ferric state. In gastric acid medium iron compounds are broken into ferrous form. Ferrous iron easily enter into mucosal cells of upper part of small intestine and oxidized to ferric form. This ferric iron combines with apoferritin of mucosa and form a iron phosphorus complex called ferritin. At the vascular surface of the mucosal cells, ferritin releases ferric iron. Ferric iron is reduced by vitamin C into ferrous iron and enter the circulation and oxidize to ferric form. Then ferric iron again combine with β-globulin and forms transferrin.

Transferrin carries iron to different tissues of the body. Major part of absorption goes to bone marrow for the synthesis of Hb. Remaining part goes to the storage sites, and stored there as hemosiderin.

- **Determination of Iron Deficiency**

1. Easiest way to screen iron deficiency is to examine the peripheral blood—Microcytic and hypochromic films are strongly suggestive of iron deficiency.
2. Degree of saturation of iron of plasma—Nearly 30% of TIBC is normally saturated with iron. But in iron deficiency, less than 15% is saturated with iron, i.e. Serum iron level = less than15% TIBC.
3. A sophisticated method is to determine bone marrow iron reserve—In iron deficiency bone marrow store of iron is very low.

CHAPTER

4

Pharmacology of GIT

SECTION-I PHARMACOLOGY OF GIT

- Vomiting and its management
- Diarrhea and its management
- Constipation and its drugs
- Peptic ulcer and its management
- Amebiasis and its management
- Drugs used against helminths

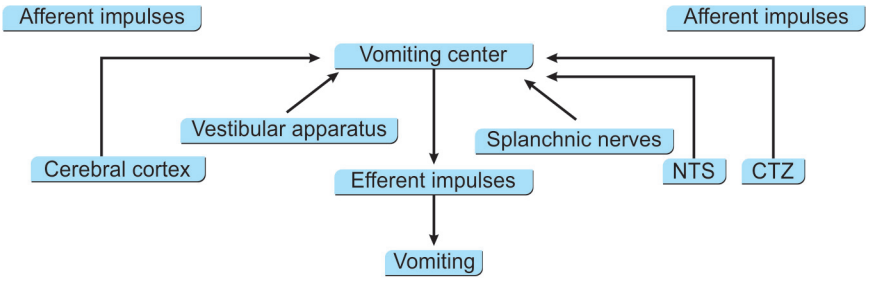
VOMITING AND ITS MANAGEMENT

- Definition
- Background physiology
- Mechanism of vomiting
- Definition of antiemetics
- Classification
- Indication of antiemetics
- Domperidone.

Definition

Vomiting is a forceful expulsion of gastric content to the exterior, via oral cavity while nausea is an urge to vomit.

Background Physiology



- NTS — Nucleus tractus solitarius
- CTZ—Chemoreceptor trigger zone

Mechanism of Vomiting

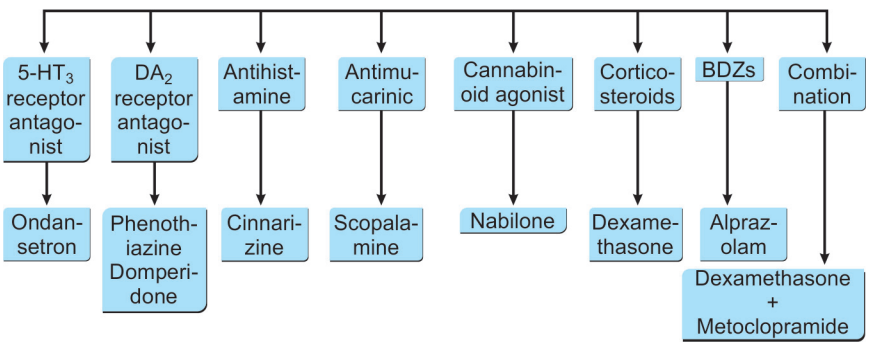
Pyloric region of the stomach contracts while lower esophageal sphincter relaxes, intra-abdominal pressure rises because—

1. Diaphragm descends
2. Anterior abdominal muscles contract so that stomach is subjected to high pressure contents escapes, via esophagus. A reverse peristalsis in the stomach and esophagus probably develops to help vomiting. All these motor effects occur due to neural discharges, i.e.
    1. Diaphragm is supplied by phrenic nerve. Phrenic nerve rises from the anterior horn cell of the T_3 and T_4 segments of the spinal cord, which are, in turn, subjected to a neural discharge from the vomiting center.
    2. Similarly, contraction of abdominal muscles is also due to motor discharge from vomiting center and so.

Definition of Antiemetics

These are drugs, used to prevent or suppress vomiting.

Classification



Indication of Antiemetics

1. During therapy by anticancer and other drugs and radiotherapy — **Ondansetron**
2. Prevention and treatment of postoperative vomiting — **Metoclopramide**
3. To combat with vomiting due to uremia
4. Disturbance of vestibular apparatus (Ménière's syndrome) — **Promethazine**
5. Motion sickness — **Cinnarizine**
6. Prophylaxis for morphine induced vomiting in AMI — **Cyclizine**
7. Treatment of gastrointestinal disease induced vomiting and so forth— **Metoclopramide**.

Domperidone

Chemically it is a benzimidazole, and DA_2 antagonist both at CNS and periphery. However, it does not cross the BBB appreciably, therefore, it produces no more than little signs of CNS dopamine suppression (motor dystonia, hyperprolactinemia) but as the CTZ is not protected by the BBB, domperidone acts on CTZ→ inhibits vomiting.

It also like Metoclopramide acts peripherally → blocks DA → prokinetic action (produces kinesia or movement in the stomach).

In short, Domperidone has the advantages (antiemetic action) of Metoclopramide but is largely free of the disadvantages (proparkinsonism) of Metoclopramide. Here lies the cause of popularity of Domperidone.

SECTION-II DIARRHEA AND ITS MANAGEMENT

- Definition of a. Diarrhea and b. Dysentery
- Causes of diarrhea
- Difference between
  - Bacillary and amebic dysentery
  - Between Crohn's disease and ulcerative colitis
- Drug therapy
- Fluids used in diarrhea.

Definition

a. **Diarrhea**: It is the passage of stool more than 3 times a day or when the stool is liquid or semiformed irrespective of frequency.
b. **Dysentery**: It is the passage of stool mixed with blood and mucus.

Causes

Specific treatment depends upon the cause. Probably the commonest form of diarrhea is due to infections. The spread of infection is usually due to fecal-oral transmission from person to person by direct/via utensil/water/food and so on.

a. The infective agents can be—

1. Bacteria —
   a. *Shigella dysenteriae* → Bacillary dysentery
   b. *Vibrio cholerae* → Cholera
   c. *Salmonella typhi* → Enteric fever.
2. Virus — Rotavirus or enteric virus.
3. Protozoa —
   a. E. histolytica → Amebic dysentery
   b. Giardia lamblia → Giardiasis
4. Helminths —
   a. Lumbricoids → Ascariasis
   b. Ancylostoma duodenale → Ancylostomiasis.

b. Noninfective causes of diarrhea are—

1. Celiac disease
2. Ulcerative colitis
3. Pancreatic insufficency

4. Malnutrition or PCM
5. Antibiotic induced pseudomembranous colitis
6. Insecticide ingestion.

Differences between Bacillary and Amebic Dysentery

During clinical practice, one should know the difference—(i) Between bacillary and amebic dysentery and (ii) Ulcerative colitis and Crohn's disease for proper management of diarrhea.

Differences between bacillary and amebic dysentery

Points	Bacillary dysentery	Amebic dysentery
Onset Bowel motions Stool contains	Usually very acute More than 10/day Blood and mucus very little feces	Less acute Less than 10/day Blood and mucus mixed with fecal matter
Flushing down the pan Odor Color Fever Blood examination	Very difficult Not very offensive Bright red Usually present Leukocytosis	Not difficult Very foul smelling Dark red Usually no fever Normal TC, DC

Differences between Crohn's disease and ulcerative colitis

Points	Crohn's disease	Ulcerative colitis
Depth of involvement	Transmural	Mucosa and submucosa
Granuloma	Common (noncaseating)	Very rare
Occurrence of malignancy	Rare	Occasional
Rectal bleeding	Infrequent	Common
Fistula formation	Common	Rare
Right colon involvement	Cobble-stone appearance	Hose pipe appearance
Lesions	Discontinuous	Continuous
Friability	Uncommon	Common
Complication	Stricture formation	Toxic dilatation

Drug Therapy

It consists of—
a. Specific antimicrobial drugs
b. Nonspecific antidiarrheal drugs.

a. Specific antimicrobial drugs

One or more antimicrobial agent has been routinely prescribed to every patient of diarrhea. In fact, such drugs have a limited role in the overall treatment of diarrhea patients; the reasons are—

1. Bacterial pathogen is responsible for only a fraction of cases.
2. Even in bacterial diarrhea, antimicrobials alter the course of illness only in selected cases.
3. Antimicrobials may prolong the carrier state.

Diarrhea

Patients can generally be placed in one of the two categories—

a. **Abundant watery diarrhea**: Lacking mucus or blood, usually dehydrating, with frequent vomiting but little or no fever → are generally caused by enterotoxigenic bacteria such as cholera, ETEC or by rota and other viruses: ORS and riot the antimicrobials are the main therapy.
b. **Slightly loose**: Smaller volume stools, frequently with mucus and or blood, mild dehydration,usually attended with fever and abdominal pain but not vomiting → are generally caused by enteroinvasive organisms like shigella, enteropathogenic *E. coli* (EPEC), campylobacter, salmonella, *Yersinia enterocolitica*, *E. histolytica, clostridium difficile*; antimicrobials are needed in many of these.

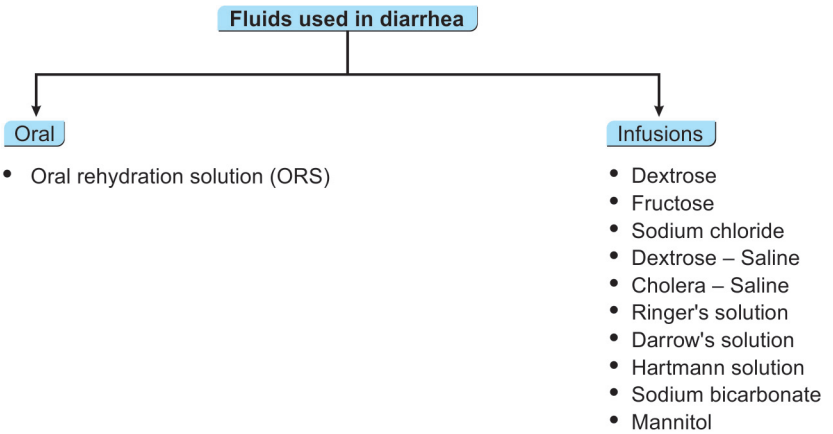
1. **Antimicrobials are of no value** in diarrhea due to noninfective causes such as—
   a. Irritable bowel syndrome
   b. Celiac disease
   c. Pancreatic enzyme deficiency
   d. Tropical spuro (except with secondary infection)
   e. Thyrotoxicosis.
2. **Antimicrobials do not benefit** when the disease is mild **but are useful in severe disease**—
   a. Traveler's diarrhea—Cotrimoxazole, Doxycycline and Erythromycin shorten the duration and total fluid needed in severe cases.
   b. EPEC is less common but causes shigella like invasive illness — Cotrimoxazole, Neomycin, Colistin, Nelidixic acid, Norfloxacin may be used in acute cases and in infants.
   c. Shigella enteritis — Nelidixic acid can be used.
3. **Antimicrobials are regularly useful in**
   a. *Cholera*—P. tetracyclines reduce the stool volume to nearly half, cotrimoxazole and chloramphenicol are alternatives.
   b. *Campylobacter jejuni*—P. norfloxacin and other fluoroquinolones eradicate the organism from the stool erythromycin and firazolidone are fairly effective.
   c. *Clostridium difficile*— It produces antibiotic associated pseudomembranous enterocolitis → Vancomycin, Metronidazole is an alternative. Offending antibiotic must be stopped.
   d. *Diarrhea*— It is associated with bacterial growth in blind loops. Diverticulitis may be treated with → Tetracycline or Metronidazole.

e. Amebiasis
f. Giardiasis

→ Metronidazole, diloxanide furoate, Furazolidone are effective drugs

b. Nonspecific antidiarrheal drugs

i. Absorbants — Ispaghula
ii. Adsorbants — Kaolin
iii. Antisecretory — Mesalazine
iv. Antimotility — Codeine.



a. Oral rehydration solution (ORS)

The composition of oral dehydration salt/solution has been debated. The general principles are—

1. It should be isotonic (diarrhea fluids are approximately isotonic with plasma).
2. The molar ratio of glucose should be some what higher than Na^+ (excess glucose will be utilized in absorbing Na^+ present in the intestinal secretions in addition to that present in ORS itself).
3. Enough K^+ and HCO_3^- should be provided to make up the losses in stool. The WHO has recommended a universal formula.

NCl–3.5 gm	to be dissolved
KCl–1.5 gm	in one liter of
Sod. citrate–2.9 gm	water
Glucose–20 gm	

b. **Infusion fluids**

Different infusion fluids are used to manage severe form of dehydration arising from diarrhea are—

1. **Dextrose infusions**: They are sterile, pyrogen–free solutions of anhydrous dextrose in water for infusions may be 5%, 10% or 25% dextrose infusions.
2. **Fructose (fruit sugar) infusion**: Fructose is considered as an alternative to glucose in diabetic patients and patients with clinical obesity.

3. **Sodium chloride infusions**: They are sterile, colorless preparation of normal saline containing 9 gm sodium chloride per liter.
4. **Dextrose-saline infusion**: They are containing 5% dextrose in 0.9% sodium chloride solution.
5. **Cholera-saline infusion**: It is a balanced fluid for infusion in cases of cholera or severe gastroenteritis, containing
   Na^+ – 133 mEq/liter
   K^+13 mEq/liter Cl–88 mEq/liter
   Acetate 48 mEq/lliter → available in 1000 ml.
6. **Ringer's solution**: It contains in each liter sodium chloride 8.6 gm, potassium chloride 0.3 gm and calcium chloride 0.48 gm.
7. **Darrow's solution**: It is a sterile colorless solution for intravenous use each liter contains sodium chloride 4 gm. Potassium chloride 2.7 gm. molar solution of sodium lactate 53.3 ml.
8. **Hartmann solution**: It is also known as Ringer lactate solution. Each liter of Hartmann solution contains sodium chloride 60 gm, potassium chloride 0.4 gm, calcium chloride 0.27 gm, sodium lactate equivalent to 2.4 ml lactic acid.
9. **Sodium bicarbonate injection**: 15% sodium bicarbonate solution is available in 10, 20, 25 and 50 in of ampoule.
10. **Mannitol**: It is a 10% to 20% W/v mannitol in water for injection, is a hyperosmolar solution used as dehydrating agent to promote polyurea.

SECTION-III CONSTIPATION AND ITS DRUGS

- Definition
- Causes
- Drugs used
- Mechanism of drug action
- Choice and use of purgatives.

Definition

It is difficult to define, because different persons have different bowel habits, if the bowel frequency is 3 times a week then, it is considered as constipation.

Causes

Constipation may be due to (1) an obvious pathology or (2) found in cases where there is no obvious pathology.

Drugs Used

These are drugs that promote evacuation of bowels.

A distinction is sometimes made according to the intensity of action.

a. Laxative → Milder action, eliminations of soft but formed stools
b. Purgative → Stronger action resulting in more fluid evacuation.

Many drugs in low doses act as laxative and in larger doses as purgatives.

1. Bulk forming → Dietary fiber—Bran, lspaghula, Methylcellulose
2. Stool softener → Decussates (DOSS)
3. Lubricant → Liquid paraffin.
4. Stimulant (contact) purgatives → Phenolphthalein, Bisacodyl, Castor oil.
5. Osmotic purgatives → Magnesium salts, Lactulose.

Mechanism of Drug Action

All purgatives increase the water content of feces by

a. A hydrophilic or osmotic action → retaining water and electrolytes in the intestinal lumen → increase volume of colonic content and make it easily propelled.
b. Acting on intestinal mucosa to decrease net absorption of water and electrolyte; intestinal transit is enhanced indirectly by the fluid bulk.
c. Increasing propulsive activity as primary action-allowing less time for absorption of salt and water as a secondary effect.

For some of the drugs, controversy continues as to whether they increase water content of stools as the primary action or it is a consequence of increased motility. The term contact purgative used as an alternative to stimulant purgative avoids this controversy and signifies action by coming in contact with intestinal mucosal cell rather than an action in the lumen. However, certain purgatives do increase motility through an action on the myenteric plexuses.

Choice and Use of Purgatives

Laxatives act by

1. a. Inhibiting Na^+ K^+ ATPase of villous — Impairing water and electrolyte absorption.
   b. Stimulating adenylyl cyclase in crypt cells — Increasing water and electrolyte secretion.
   c. Enhancing PG synthesis in mucosa which increases secretion.
   d. Structural injury to the absorbing intestinal mucosal cells. Choice and use of purgatives—I) Spastic constipation (irritable bowel). The stools are hard, rounded, stone (marble) like and difficult to pass. The first choice of laxative is dietary fiber or any of the bulk forming agents; stimulant purgatives are contraindicated.
2. Atonic constipation — (sluggish bowel) — Mostly due to advanced age, debility or laxative abuse. Nondrug measures like plenty of fluids, exercise, regular habits and reassurance should be tried.
3. Bedridden patients — (myocardial infarction, stroke, and fracture, postoperative) bowel movement may be sluggish and constipation can be anticipated.

To prevent — Give bulk forming agents on regular schedule.
To treat—Enema, liquid paraffin, Bisacodyl or Senna may be used.

4. To avoid straining at stools—(hernia, cardiovascular disease, eye surgery) and in perianal affictions (piles, tissue, anal surgery), it is essential to keep the feces soft. One should not hesitate to use adequate dose of a bulk forming agent.
5. Preparation of bowel for surgery, colonoscopy, abdominal X-ray—The bowel needs to be emptied of contents including gas. Saline purgative, Bisacodyl or Senna may be used.
6. After certain anthelmintics — (specially for tape worm) Saline purgative or senna may be used to flush out the worm and the drug.
7. Food/drug poisoning — The idea is to drive out the unabsorbed irritant/poisonous material from the intestines.
   Only saline purgatives are satisfactory.

SECTION-IV PEPTIC ULCER AND ITS MANAGEMENT

- Definition
- Sites of a peptic ulcer
- Physiology
- Mechanism of gastric HCl secretion by parietal cells
- Pathogenesis
- Drugs used in the Rx of peptic ulcer.

Definition

An ulcer is a local defect or excavation of the surface of an organ or tissue which is produced by the sloughing of inflammatory necrotic tissue. Ulcers which arise at any site of the GIT exposed to acid pepsin digestion are called peptic ulcers.

Sites of Peptic Ulcer

Common sites

1. Ulcer at duodenum principally the first part — *Duodenal ulcer*
2. Stomach mainly at the antrum — *Gastric ulcer*
3. At the lower end of the esophagus — *Esophageal ulcer*
4. At the jejunum — After gastrojejunal anastomosis ulcer is called *anastomotic ulcer*
5. Meckel's diverticulum — When it contains ulcers in its mucosa then it is called *diverticular ulcer*.

Immune site

Second part of duodenum is almost immune to ulcer, because of arrival of pancreatic and biliary secretion, the HCl of gastric chyme is neutralized, pH is raised, and pepsin becomes inactive.

Physiology

Parietal and peptic cells are normally present in the gastric mucosa, HCl is secreted by the parietal cells whereas pepsin (in the form of pepsinogen) is secreted by the peptic cells. Pepsin can digest protein only when the pH is sufficiently low, between 2 to 3. At higher pH (>5) pepsin becomes inactive and cannot digest protein. Therefore, presence of a strong acid (like HCl) is necessary to convert pepsinogen to pepsin. Now a question is, if acid pepsin mixture can digest the food protein, then why it does not digest the gastric mucosa itself ?

The answer is, in the gastric mucosa, as well as in the first part of the duodenum there is a defense mechanism. In normal persons the defense mechanism is adequate and no ulcer develop. Where the defense mechanism is weakened or the aggressive mechanism is strengthened, the peptic ulcer should be developed.

Components of the gastric defense mechanism

1. Gastric mucus
2. HCO_3^- secreted by the gastric mucosal cells
3. Vasculature
4. Presence of tight junctions between the epithelial cells.

- **Gastric mucus** forms a layer over the epithelium of the mucosa. Some mucosal cells secrete HCO_3^- which remain in between epithelial cells and the mucus and the pH at this spot is higher (6 or 7). Therefore, in the luminal surface of the mucus the pH is low, about 1.5 to 3. The peptic activity is high, digestion is possible.

Mechanical barrier offered by the mucus, present on the surface of gastric epithelium is very important component of the defense. If this mucus is thick and sticky, the **acid-pepsin-mixture** fails to penetrate it. Acid-pepsin-mixture cannot reach close to the epithelial cells, so no digestion of the epithelial cells.

Sequences

1. Big pepsin molecules require good deal of spaces through which they can traverse.
2. Normally mucopolysaccharide molecules are polymerized in the mucosa.
3. Depolymerization of mucopolysaccharide cause loss of stickiness and increases the permeability of pepsin.

- **Tight junction**: Nothing passes through them normally, but Aspirin like drugs can damages tight junction and inhibits the PGs synthesis within the gastric epithelial cells. These are two effects which weaken the defense mechanism.

Mechanism of Gastric HCl Secretion by Parietal Cells

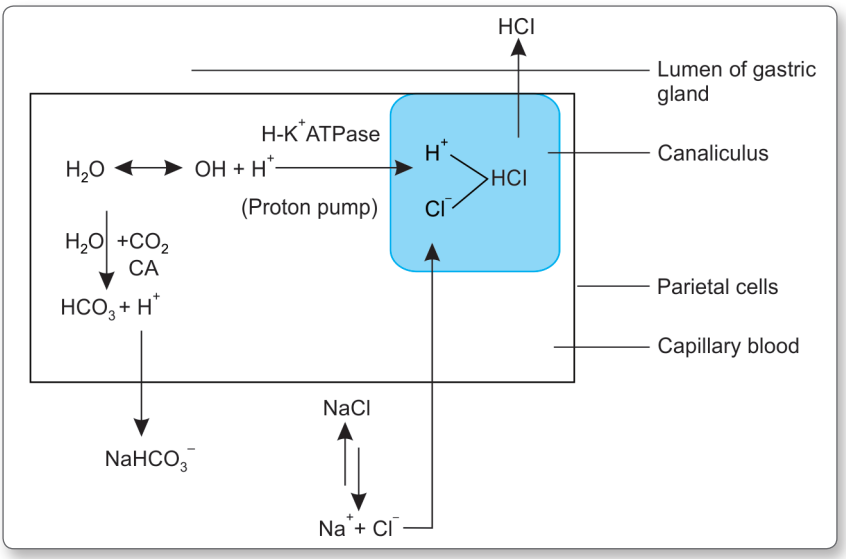


Fig. 4.1: Mechanism of gastric HCl secretion by parietal cells

H^+ ion is generated from HOH within the parietal cell and Cl^- ion is obtained from NaCl of the adjacent capillary blood. The two ions unite within the canaliculus of parietal cell to form HCl and then HCl flows into the gastric lumen. H^+ ion generated from the H_2O molecule within the parietal cells is pumped into the canaliculus by a proton pump (here H^+ is the proton). Proton pump is $H^+ – K^+$–ATPase, i.e. because of the action of $H^+ – K^+$– ATPase, enzyme, the H^+ is pumped from the cell to the canali-culus.

Parietal cell

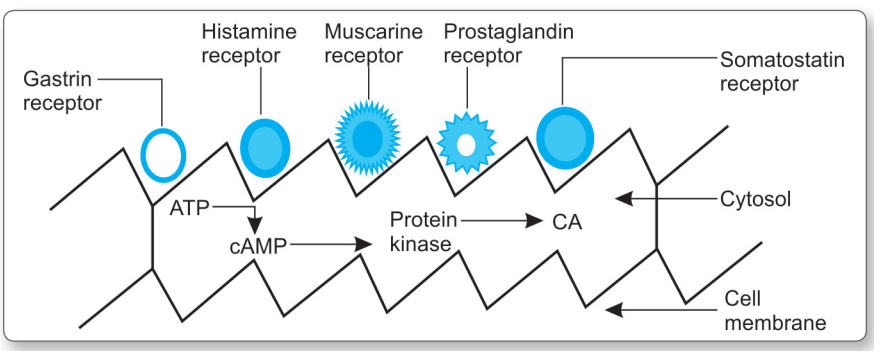


Fig. 4.2: Receptors present on parietal cells

Parietal cells contain five types of receptors, namely—

a. **Muscarinic receptor**: Which can be stimulated by release of ACh by vagal stimulation. This causes secretion of HCl by parietal cells.
b. **Gastrin receptor**: Combination of gastrin with these receptor cause parietal cell stimulation and thereby production of HCl.
c. **Histaminic receptor**: After combination with histamine they stimulates gastric HCl secretion.
d. **Somatostatin receptor**: After combination with somatostatin they inhibit HCl secretion.
e. **Prostaglandin receptors**: These are also inhibitory to gastric HCl secretion. Role of histamine in HCl secretion requires special attention.

Histamine is secreted by mast cells also called enterochromaffin like cells, situated very close to the parietal cells. Gastrin can stimulate the parietal cells directly no doubt, but gastrin also stimulates the cells to produce histamine and histamine in turn stimulates the parietal cell to produce HCl. ACh also behaves like gastrin. The situation can be explained by a flow chart.

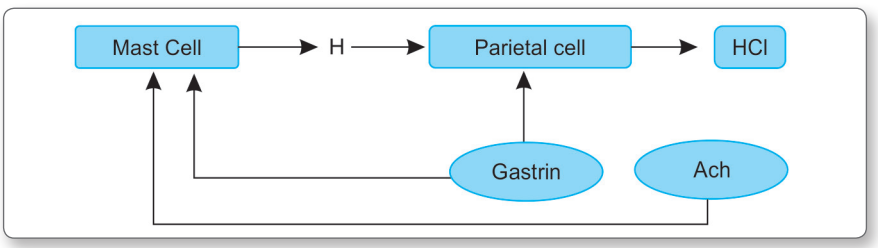


Fig. 4.3: Control of HCl secretion by ACh

Viewed in this way, histamine is sometimes called the, final common path, because both gastrin and ACh act largely, via histamine. However regarding this role, there is some controversy. Nevertheless, if H_2 blockers are used, effects of gastrin and ACh on HCl secretion are very much but probably not totally blunted. For all these reasons, H_2 blockers have assumed a supreme role in peptic ulcer treatment.

Pepsin is produced from pepsinogen, provided the environment (medium) is strongly acidic. Also pepsin activity can occur only in strongly acidic medium. Pepsin is the ultimate digesting (proteolytic) enzyme. Hence, elevation of gastric pH blunts peptic activity.

Pathogenesis

1. **Helicobacter Pylori**—In recent years, H. pylori has captured attention. It is a gram-negative bacteria found in gastric and duodenal mucosa of most elderly persons. But how they cause peptic ulceration?

   They, while in the mucosa, split urea into ammonia and thus clevates the local pH, with high alkalinity, almost achlorhydria. Prolonged achlorhydria can lead to excess gastrin secretion and thereby excess

gastric HCl, by stimulating the gastrin receptors on parietal cells. In this way, they strongly help in the causation of peptic ulcer.

2. **Gastric HCl**— If the HCl secretion is stopped or neutralized, then the activity of pepsin is inhibited, the digestive ability of APM is remarkably reduced.

Drugs Used for the Rx of Peptic Ulcers

1. **Drugs opposing the development of gastric acidity**
   a. Antacids — Neutralize acid that is already secreted.
   b. Antisecretory agents.
      1. H_2 blockers, i.e. Cimetidine, Ranitidine, Famotidine, Nizatidine
      2. Proton pump inhibitors, i.e. Omeprazole and Lansoprazole
      3. Anticholinergics, i.e. Pirenzepine
      4. Somatostatin, i.e. Octreotide.
2. **Drugs enhancing defense mechanism**
   1. Prostaglandins, i.e. Misoprostol
   2. Mucus secretion stimulants, i.e. Carbenoxolone
   3. Anti H. pylori agents, i.e. Amoxicillin 500 mg 3 times in a day with Metronidazole 400 mg 3 times in a day for 2 weeks + Colloidal bismuth subcitrate 120 mg 4 times in a day for 2 weeks.
   4. Coating agents, i.e. Sucralfate.

Antacids

- Properties
- Examples
- Mechanism of action
- Dosing
- Combination.

Properties: An ideal antacid should be:

1. Nonabsorbable from GIT
2. Should contain low amount of sodium
3. Should be palatable
4. Should be chief.

Examples: Major antacids are:

1. Aluminum compounds $Al(OH)_3$ $ALPO_4$
2. Magnesium compound $Mg(OH)_2$, $MgCO_3$, Mg – trisilicate
3. Calcium compounds $Ca(OH)_2$, $CaCO_3$, $Ca_3(PO_4)_2$
4. Sodium bicarbonate ($NaHCO_3$), Na^+-citrate, Na^+-acetate.

Mechanism of action: Antacids are weak bases, react with HCl of stomach to produce salt and water, thus removing HCl and raising the

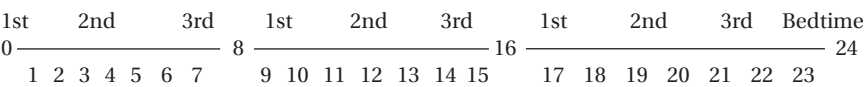
pH of gastric content and causing loss of peptic activity. Finally, there is blunting of aggressive factor.

$Al(OH)_3 + HCl — AlCl_3 + H_2O$

Other mechanisms may be:

1. Antacids may cause synthesis and release of PGs which can bolster the mucosal defense.
2. Antacids may bind with some unknown substances, which damages the gastric or duodenal mucosa (i.e. cytoprotective effect). This explains why lower doses of antacids may be enough.

Dosing: After a standard meal, gastric HCl secretion rises, rate of gastric secretion after such a meal is about 40 mEq per hour, and at this rate or newly so, the secretion continues for several hours. This means, after a standard meal, about 120 mEq (more in hypersecretors) of HCl is usually secreted in about 3 hours. The quantity of antacid should be, officially speaking, enough to neutralize this amount of HCl. So, the technic should be to administer a dose of antacid, which contains 120 mEq of antacid. For example, $Al(OH)_3$ liquid contains about 2mEq/gm; the total amount of the individual dose can be calculated from this:



In short, the standard protocol is one hour after each meal, administer the first dose and after 3 hours repeat the dose. Therefore, a person receiving 3 meals a day, a total of 9 doses are necessary. Plus, add another dose at bedtime to guard against noctural secretion. This means, an inconveniently heavy dose and that too inconveniently frequent intervals need to be taken, however, it is strongly felt, that the dosage of antacid need not be as heavy as mentioned above, for lower doses may be equally effective. The reason is probably that, antacids produce their effects not only by acid neutralization but by other means also; (mentioned in mechanism of action) that is why lower doses are effective.

Combinations: Usually combination of aluminum and magnesium compounds are used; because aluminum causes constipation, whereas magnesium compound causes laxative effects. Aluminum ions causes relaxation of GI smooth muscles so there is constipation. After administration, $MgSO_4$ dissociates into Mg^{+2} and SO_4^{-} ions. They are not absorbed from the intestine and create an osmotic effect. Prevents the water absorption and also draws fluid from intestinal capillaries and increase the bulk of intestinal content. There is mechanical stimulation of intestinal wall and increase motility and painless evacuation.

Depending on Solubility and Intestinal Absorption Antacids May be—

1. Systemic, i.e. $NaHCO_3$, $KHCO_3$, Na^+-citrate, because they are soluble

and completely absorbed in the systemic circulation and produce systemic alkalosis.
2. Nonsystemic, i.e. $Al(OH)_3$, $Mg(OH)_2$ as they are water-soluble and not absorbed in the system.

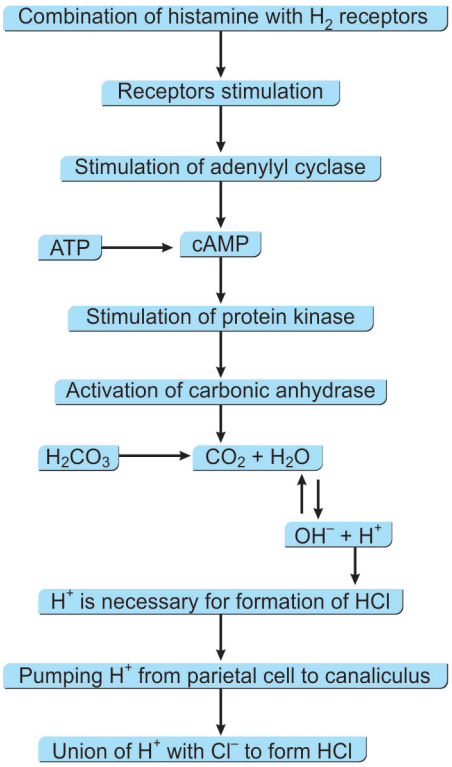
Antisecretory Agents

H_2 receptors blockers

- Name
- Mechanism of action
- Clinical use
- Maintenance therapy
- Superiority of Ranitidine over Cimetidine.

Name: Cimetidine, Ranitidine, Famotidine and Nizatidine

Mechanism of action: H_2 receptors are found in the parietal cells, uterine muscles and atrial muscles of heart. Combination of histamine with the H_2 receptors in the stomach leads to secretion of HCl.



H_2 blockers competitively block the H_2 receptors on the parietal cells, so that there is powerful inhibition of gastric HCl secretion

Clinical uses

1. They are used against duodenal and gastric ulcer
2. They are also used in reflux esophagitis
3. They may be used to prevent gastroduodenal bleeding in some stressful condition like burns trauma or renal failure
4. Prophylactically, they may be used in subjects receiving NSAIDs
5. They are also used in preanesthetic medication to prevent GER → aspiration into the lungs.

Maintenance therapy

1. Elderly subjects where complications like bleeding episodes are likely to be dangerous
2. Where the patient is unable to give up smoking
3. Where H. pylori eradication program cannot be implemented
4. Particularly repeated occurrence of complications, i.e. bleeding.

Superiority of ranitidine over cimetidine

1. Ranitidine contains a furan ring instead of an imidazole ring.
2. Cimetidine can penetrate the BBB, producing some CNS symptoms and some effects on hypothalamus like low production of GnRH leading to gynecomastia. But ranitidine has remarkably low CNS side effect.
3. Unlike Cimetidine, Ranitidine has little effect on hepatic P-450 MFO system, so that Ranitidine has little or no action on the metabolism of other drugs.

Proton pump inhibitors

Name

1. Omeprazole
2. Lansoprazole.

Mechanism of action: H^+ produced from HOH is pumped into the canaliculus within the parietal cells by H^+- K^+ ATPase which is also called the proton pump. Inhibition of H^+ - K^+ ATPase, therefore would result in no pumping of H^+ into the canaliculus no HCl will be formed. Thus a complete inhibition of proton pump must inhibit all HCl formation.

Uses: Clinically omeprazole can be used in:

1. Peptic ulcer, where H_2 blockers have failed
2. GER
3. Zollinger–Ellison syndrome
4. MED (multiple endocrine diseases).

SECTION-V AMEBIASIS AND ITS MANAGEMENT

- Cause
- Presentation of the disease
- Classification of drugs
- Life cycle
- Individual drug.

CAUSE

It is an infectious diseases caused by the protozoan parasite entamoeba histolytica. The parasite exists in trophozoites or active form and cysts or inactive form.

PRESENTATION OF THE DISEASE

Amebiasis may be presented as—
1. Severe intestinal infection (dysentery)
2. A mild to moderate symptomatic intestinal infection
3. An asymptomatic intestinal infection
4. As an ameboma
5. Liver abscess or other type of extraintestinal infection.

CLASSIFICATION OF DRUGS

The choice of drugs depend on A. Clinical presentation
B. Desired site of action.

A. Clinical presentation	1st choice of drugs	Alternative drugs
Asymptomatic intestinal infection	Diloxanide fiuroate	Iodoquinol
Mild to moderate intestinal infection	Metronidazole plus diloxanide furoate	Diloxanide furoate plus tetracycline followed by choloroquine
Severe intestinal infection	Metronidazole plus diloxanide furoate	Metronidazole plus Diloxanide furoate followed by chloroquine or emetine
Hepatic abscess	Metronidazole plus diloxanide furoate followed by chloroquine	Emetine followed by chloroquine plus diloxanide furoate
Ameboma	As for hepatic abscess excluding chloroquine	Same as hepatic abscess excluding chloroquine

B. Desired site of action:

1. Tissue amebicides: These are drugs which act on bowel wall, liver

and other extraintestinal sites, i.e. nitroimidazole (metronidazole, tinidazole, ornidazole) Emetine and dihydroemetine.

2. **Luminal amebicides**: These are drugs which act on GI. lumens, i.e. dichloracetamides, diloxanide furoate, teclozan, clefamide and etofamide.
   Halogeneted quinolones, i.e Hydroxyquinole iodoquinol,
3. **Antibiotics**: That is tetracycline, paromomycin and erythromycins.

LIFE CYCLE

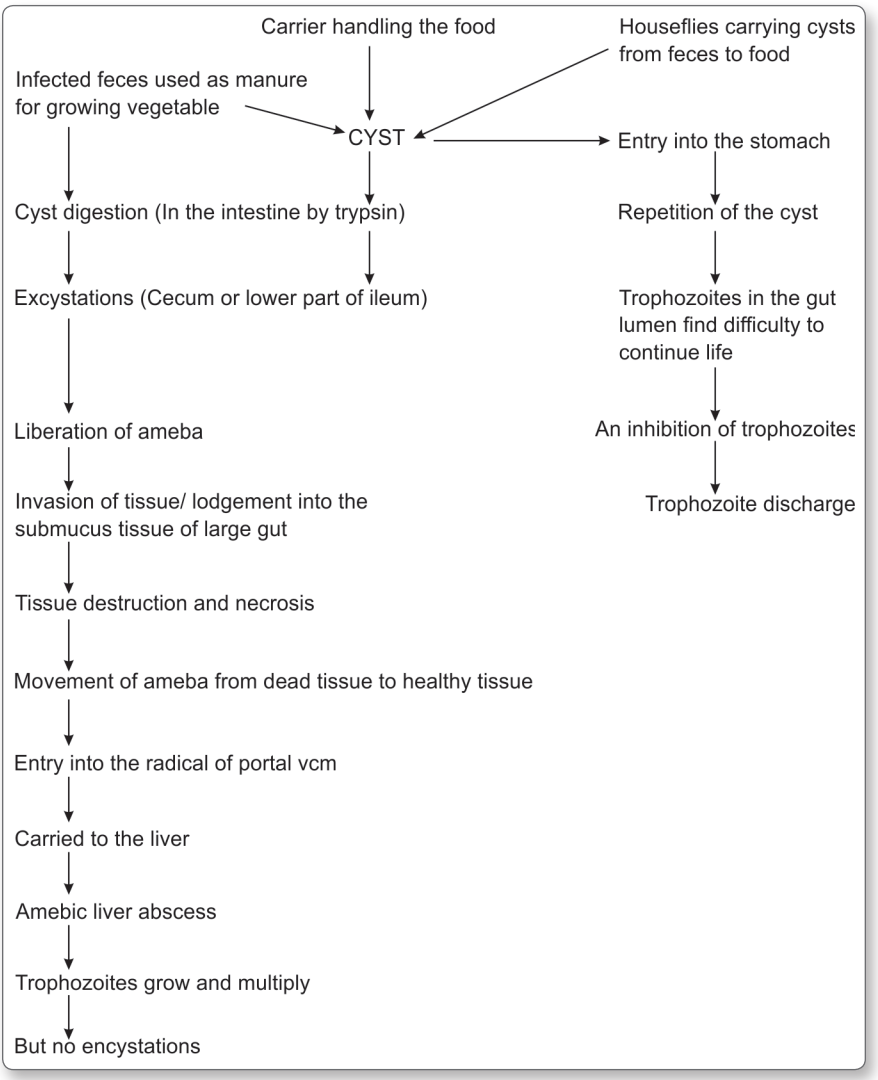


Fig. 4.4: Life cycle of Entamoeba histolytica

INDIVIDUAL DRUG

Metronidazole

- Introduction
- Chemistry
- Pharmacokinetic
- Mechanism of action
- Clinical uses
- ADRs
- Drug interaction
- Contraindications and cautions.

Introduction

It is extremely useful in the treatment of extraluminal amebiasis. It effectively eradicates amebic tissue infection (liver abscess, intestinal wall and extraintestinal infection) but a luminal amebicide must be used with it to achieve satisfactory cure rates for luminal infectious. Metronidzole kills trophozoites but does not kill cysts of E. histolytica.

Chemistry

It is a nitroimidazole compound.

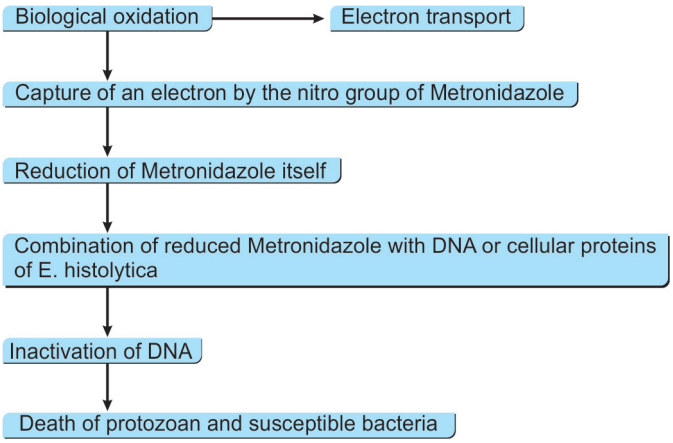
Pharmacokinetics

Oral metronidazole, is readily absorbed and permeates all tissues by simple diffusion including CSF, breast milk and alveolar bone, intracellular concentration rapidly approaches extracellular levels. The half-life of unchanged drug is 7.5 hour. The drugs and its metabolites are excreted in the urine. Plasma clearance of metronidazole is decreased in patients with impaired liver function.

Mechanism of action

It is active against— a. Anaerobic bacteria.
b. Parasites like protozoa.

Exact mechanism of action of metronidazole is not clear. Within anaerobic bacteria, nitro group of metronidazole is chemically reduced by ferrodoxin linked enzymes. The reduced products appear to be responsible for killing the organism by reacting with various intracellular macromolecules. Thus reduction is responsible for the drugs bactericidal action against anaerobic bacteria. In vitro, it is active against most obligate anaerobes or obligate aerobes. It has also a radiosensitizing effect on tumor cells. With its antibacterial action, the mechanism appears to be dependent on relative hypoxia in the target cells and may involve interaction with free radicals.



Clinical uses

1. Anaerobic infection, i.e. enterococcal and clostridial infection
2. Amebiasis
3. Giardiasis
4. Trichomoniasis
5. Balantidiasis
6. Gingivitis
7. Gardnerella vaginalis infection.

ADRs

Nausea, headache, dry mouth or a metallic taste in mouth occur commonly. Urine may be dark or reddish brown. Infrequent ADRs includes vomiting, diarrhea, insomnia, weakness, dizziness, stomatitis, rash withdrawal burning, vertigo and paresthesia.

Drug interaction

It has a disulfiram like action, so that nausea and vomiting occur if alcohol is consumed while the drug is still in the body. Mutagenicity and carcinogenicity have been reported in case of animals but not in humans.

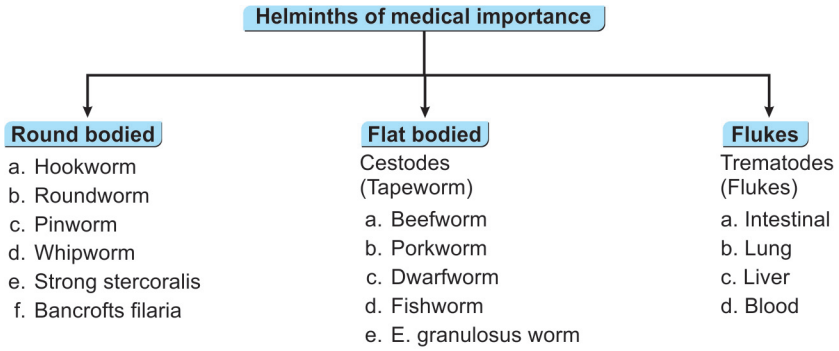
Contraindications and cautions

1. History of blood dyscrasias
2. Pregnant women (specially in the first trimester)
3. Nursing mother
4. Young children.

SECTION-VI DRUGS USED AGAINST HELMINTHS

Rationality of Considering Anthelmintics as Chemotherapeutics

Anthelmintics attack the parasitic cells, but they do not attack the human (or rather mammalian cells). This is why they are chemotherapeutic agents.



BIOCHEMICAL BACKGROUND OF HELMINTHS

a. Nematodes living in the intestine have muscles for their locomotion and the muscles are supplied by nerves. But in mammals, ACh is the neurotransmitter and receptors are nicotinic in the neuromuscular junction.

The neuromuscular junction of the nematodes have both cholinergic and GABAergic nerves. Cholinergic nerves being the excitatory and GABAergic being the inhibitory neurons. However, this cholinergic receptors, unlike those of man, are ganglionic nicotinic receptors, their homologous in man are nicotinic muscular (N/M) types of receptor.

Pyrantel pamoate and some other drugs act here as ACh receptor agonist → a sort of depolarizing block is produced → worm is paralyzed.

GABAergic nerves are found in man too, but only in the brain and not in the peripheral nerves as in the nematodes. Anthelmintic drugs cannot reach the human brain because, they fail to penetrate the BBB, though the drugs can reach the peripheral tissue.

b. Piperazine is a GABA agonist but fails to cross the human BBB → **neuromuscular paralysis of the nematode** → **the parasite** fails to **cling the intestinal wall** → **rejected**, via **feces**.

Ivermectin can stimulate the GABAergic neurons of worm but cannot cross the human BBB, which is extensively used in West Africa for onchocerciasis.

Microtubules: All animal cells contain cytoskeletal structure. It includes such structures like microfilament, microtubules and so forth, containing contractile elements like actin and myosin. This contractile elements are present in structures called tubulin. The finer structure of

the chemistry of tubulin of parasite differs to some extent form those of mammals.

Mebendazole and some other drugs can destroy the microtubules of parasites but not those of man, that is why they are considered as chemotherapeutic agents.

Microtubules and microfilaments are required for various functions of the cell and without their presence the cell dies. Mebendazole ultimately, thus kills the intestinal cells of many nematodes → the nematodes in question, i.e. Ascaris lumbricoides dies.

c. Calcium influx into any muscle cell causes more intense contraction of the muscle in question. Praziquantel cause more intense Ca^{+2} influx into the muscle. It is possible that the targets of praziquantel, viz. schistosomes and tapeworms are killed because of an effect which is related to this Ca^{+2} influx.

COMMONLY USED ANTHELMINTIC

1. Mebendazole
2. Pyrantel pamoate
3. Thiabendazole
4. Diethylcarbamazine
5. Praziquantel
6. Niclosamide
7. Levamisole
8. Ivermectin
9. Piperazine
10. Albendazole.

INDIVIDUAL DRUG

Mebendazole

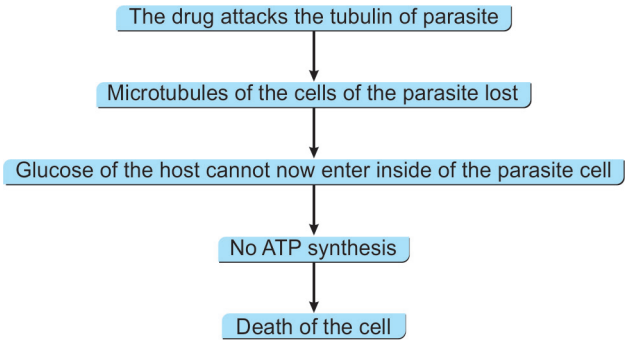
- Introduction
- Mechanism of action
- ADRs
- Clinical use

Introduction

Mebendazole is a synthetic benzimidazole compound. It is very popular, because it has two advantages—

1. Low toxicity
2. Wide spectrum of anthelmintic effect.

Mechanism of action



ADRs

Only 10% of the drugs given orally is absorbed. Therefore, it has few systemic pharmacological effect. Toxicity includes diarrhea, abdominal pain. In animals it is embryotoxic, but not in human being, even, it is safer to avoid the drug during pregnancy.

Clinical use

1. Roundworm
2. Hookworm
3. Pinworm
4. Whipworm (all nematodes)
5. Against some tapeworm (cistodes)
6. Capillaria (controversial).

Levamisole

This drug is used against Ascaris lumbricoides. Worms are paralyzed and then expelled, via feces. The drug also has immunomodulating efficiency, it increases the T. lymphocytic efficiency for which it is also used, as a supplementary drug, in colonic cancer.

ADRs are mild and include nausea, vomiting and giddiness. The drug may also be used for long duration and high doses in rheumatoid arthritis where more severe ADRs can develop.

CHAPTER

5

Endocrine Pharmacology

SECTION-I INTRODUCTION

Almost all secretion by the pituitary gland is controlled by either hormonal or nervous signals from the hypothalamus. Secretion by the anterior pituitary gland is controlled by hypothalamic 4 releasing and 2 inhibitory hormones. These hormones reach the anterior pituitary through hypothalamic-hypophyseal portal vessels. The hypophyseal branch

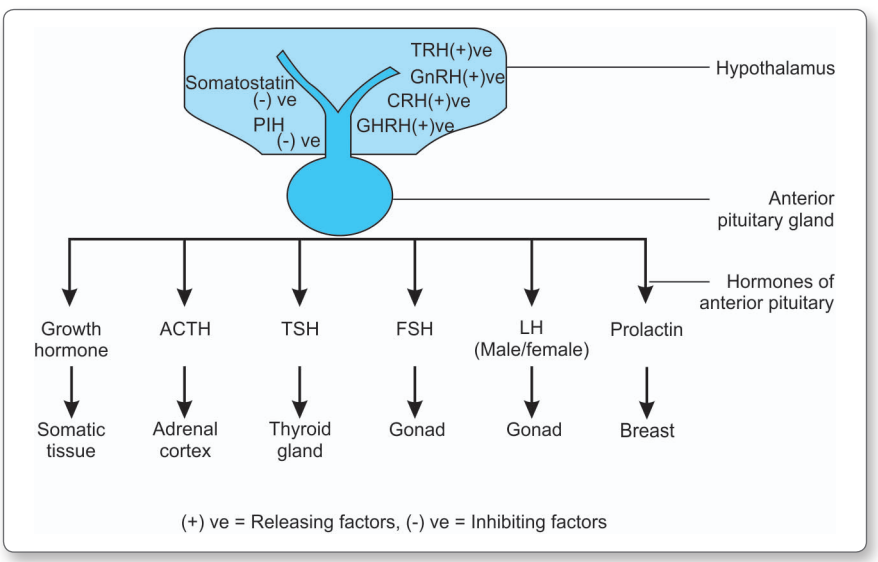


Fig. 5.1: Release of hormone by hypothalamus and pituitary

(+ve)= Releasing factors
(–ve) = Inhibiting factors

of internal carotid artery supplying the lower part of hypothalamus, median eminence and infundibulum does by forming a plexus. This capillary plexus is drained by long portal veins which pass into anterior pituitary and end by forming sinuses which supply the cells of the gland. Therefore, the releasing hormones pass through this vascular connection and control the secretion of anterior pituitary. Secretion from the posterior pituitary is controlled by the nerve signals that originate in the hypothalamus and terminate in the posterior pituitary.

The four releasing hormones of the hypothalamus are:
1. Growth hormone releasing hormone (GHRH)
2. Corticotropin releasing hormone (CRH)
3. Thyrotropin releasing hormone (TRH)
4. Gonadotropin releasing hormone (GnRH).

The two inhibiting hormones of hypothalamus are:
1. Somatostatin
2. Prolactin inhibiting hormone (PIH).

In addition to these six hormones the hypothalamus also synthesizes two other hormones in connection with posterior pituitary and they are:
1. ADH (vasopressin)
2. Oxytocin.

HORMONES OF THE ANTERIOR PITUITARY

1. Growth hormone, GH or somatotropin
2. PRL (prolactin)
3. ACTH (adrenocorticotropic hormone or corticotropin)
4. TSH (thyroid stimulating hormone or thyrotropin)
5. FSH (follicle-stimulating hormone) and LH (luteinizing hormone). FSH and LH together is called gonadotropic hormone.

Growth Hormone: Properties

1. Source—It is produced by somatotrophs by anterior pituitary
2. Chemistry—It is a peptide hormone
3. Function—Most of the growth hormone acts as a prohormone
4. Conversion—It is converted in the liver into somatomedin, also called (IGF-1) insulin like growth factor. Which stimulates growth.

Roles of growth hormone

GH deficiency produces dwarfism (pituitary dwarf). Conversely presence of access GH before the epiphyses close, manifests as gigantism (pituitary gland). If there is excess GH after 18 years the condition developed is called acromegaly. GHRH of the hypothalamus stimulates the synthesis

and release of GH. Somatostatin of the hypothalamus inhibits the production of GH.

Somatostatin

1. Source—It is produced mainly by hypothalamus and also by other organs like GIT.
2. Function—Hypothalamic somatostatin inhibits the production of GH. GIT somatostatin causes inhibition of insulin secretion and gastric hydrochloric acid. In addition it reduces blood flow to abdominal viscera.

Prolactin (PRL) and PIH

i. Source—Lactotrophs of anterior pituitary
ii. Function—It causes synthesis of milk by the breast alveolar epithelium and high prolactin level causes loss of libido, amenorrhea, lack of ovulation and impotence in male.

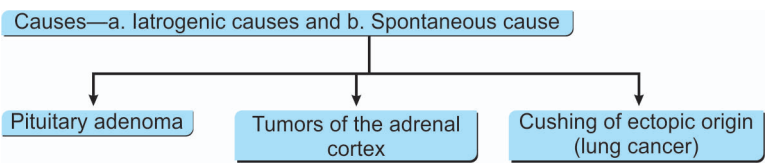
PIH

i. Source—Hypothalamus
ii. Chemistry—Chemically it is dopamine
iii. Availability—Pituitary lactotrophs where it combines with DA_2 receptors. This combination inhibits PRL secretion. DA antagonists—e.g. Chlorpromazine increase PRL concentration (hyperprolactinemia).

CRH, ACTH

Cushing syndrome

It is a condition where there is high level of cortisol occurs.



- Differentiation between Cushing of ectopic origin and pituitary adenoma.
  After CRF injection, if the plasma cortisol level does not rise, then the case is Cushing of ectopic origin.
- Differentiation between Addison's disease and adrenocortical insufficiency due to pituitary failure.
  If ACTH (cosyntropin) injection produces a rise of plasma cortisol level, conclusion is that the adrenal cortex is intact, this symptoms are due to failure of ACTH secretion by the pituitary, or if cosyntropin fails to elevate plasma cortisol level, the patient is a case of Addison's disease (atrophy of the adrenal cortex).

GONADOTROPINS

FSH and LH together is called gonadotropic hormones because they stimulate the gonads (testes/ovary).

They are:

i. Pituitary gonadotropins—FSH and LH
ii. Urine of menopausal women is called hGH
iii. Placental gonadotropins—hCG—has only LH activity
iv. Menotropins—It contains both FSH and LH
v. Urofolitropin is FSH.

SECTION-II HORMONE-PRELIMINARIES

- Definition of hormone
- Characteristics
- Clarification and source
- Classification
- Mechanism of action of protein and steroid hormone
- Feedback mechanism of hormonal action.

DEFINITION OF HORMONE

Hormones are the chemical substances produced by the ductless glands, poured into the venous blood, produce their actions and become the target of different fates.

CHARACTERISTICS

1. Hormones are protein, steroid and polypeptide in nature.
2. Secreted from one or a group of cells.
3. They have the physiological control effect on other cell of the body.
4. They are circulated through blood in the body because they have no duct for circulation.
5. Some are secreted from ending of nerves.
6. Perform their action far away from their site of secretion.
7. Action occurs slowly.
8. Some control the secretion of some other hormone.
9. They have specific receptor in target cell and bind with this receptor for performing action.
10. It can be stored in the body for long time.

CLARIFICATION AND SOURCE

Adrenaline is a hormone produced mainly by the adrenal medulla, released into the suprarenal vein, causes bronchodilatation, CNS stimulation, cardioacceleration and finally reuptaken mainly and some

portion is metabolized by COMT and MAO into VMA and excreted by the kidneys.

Different endocrine glands produce different hormones, i.e.

1. Oxytocin and vasopressin is produced by paraventricular and supraoptic nucleus of hypothalamus.
2. Thyroxin from thyroid gland.
3. Insulin and glucagon from pancreas.
4. Estrogen and progesterone from ovaries.
5. Testosterone from testis.

CLASSIFICATION

Chemically, the hormones are either protein or steroidal in nature. Oxytocin vasopressin, thyroxin are protein in nature whereas aldosterone, hydrocortisone, estrogen and testosterone are steroidal in nature and their mode of actions also differ.

MECHANISM OF ACTION OF PROTEIN AND STEROID HORMONE

Usually protein hormones combine with receptors located on the outer surface of the cell membrane. After combining with the receptor they activate an enzyme, adenylate cyclase which converts the intracellular ATP to cAMP in presence of Mg^{+2}. This cAMP produce effects.

On the other hand, after entry, steroid hormones combine with the receptors located on the cytoplasm of the target cells. The combined steroid receptor complex then transported into the nucleus of the cell and activates the transcription process of specific genes to form mRNA. This mRNA defuses into the cytoplasm and promotes the translation process at the ribosome to form new protein. This new proteins form a special enzyme, ATPase which converts cytoplasmic ATP to 3,5 cAMP. This 3,5 cAMP acts as a 2nd messenger.

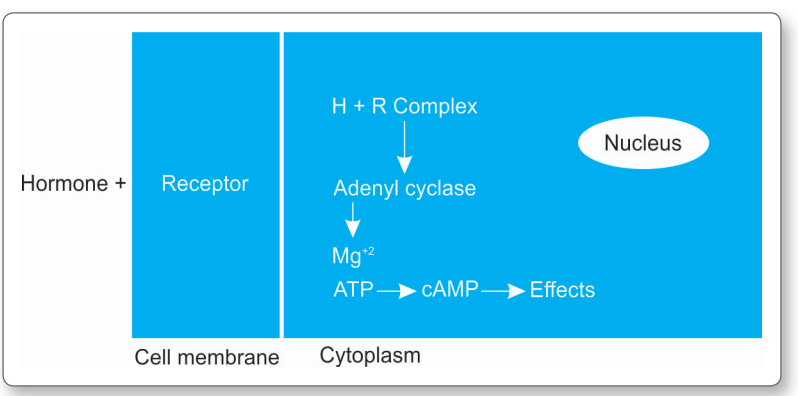


Fig. 5.2: Mechanism of action of protein hormone

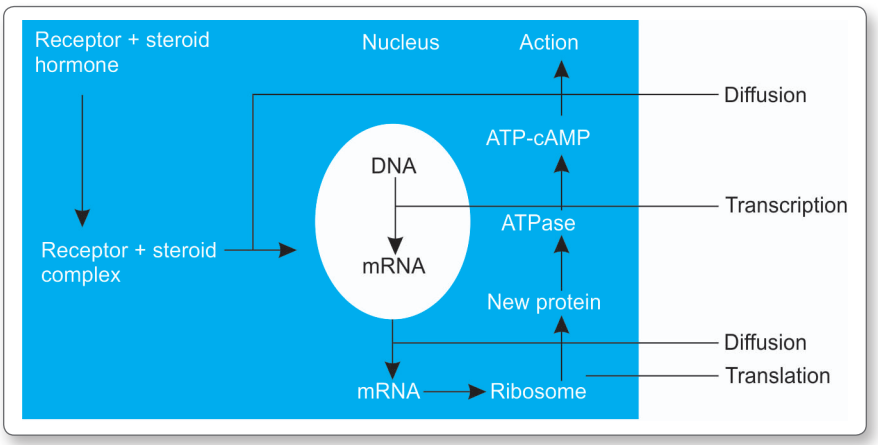


Fig. 5.3: Mechanism of action of steroid hormones

FEEDBACK MECHANISM OF HORMONAL ACTION

It is a phenomenon, where within a physiological limit, any rise or fall of any hormone in blood can inhibit or stimulate the release of hormone from the gland. It is of two types—

1. Negative feedback
2. Positive feedback.

Negative Feedback

Negative feedback mechanism is very important in control of hormone secretion. The hormone has a negative feedback activity to prevent over secretion of the hormone or over activity at the target tissue. After a stimulus causes release of the hormone, conditions or products resulting from the action of the hormone tend to suppress its further release. When the target tissue activity rises to an appropriate level will feedback signals to the endocrine glands become powerful enough to slow further secretion of the hormones.

Positive Feedback

It occurs when the biological action of the hormone causes additional secretion of hormone, e.g. the surge of LH that occurs as a result of the stimulatory effect of estrogen on the anterior pituitary before ovulation.

Hypothalamus releases CRF which stimulates the anterior pituitary to secrete ACTH. This ACTH then stimulates the adrenal cortex for secretion of cortisol which inhibits hypothalamus to release CRF. If there is higher level of cortisol in blood, CRF release will be less, the phenomenon is known as negative feedback and if less cortisol, CRF release will be more, known as positive feedback mechanism of hormone release.

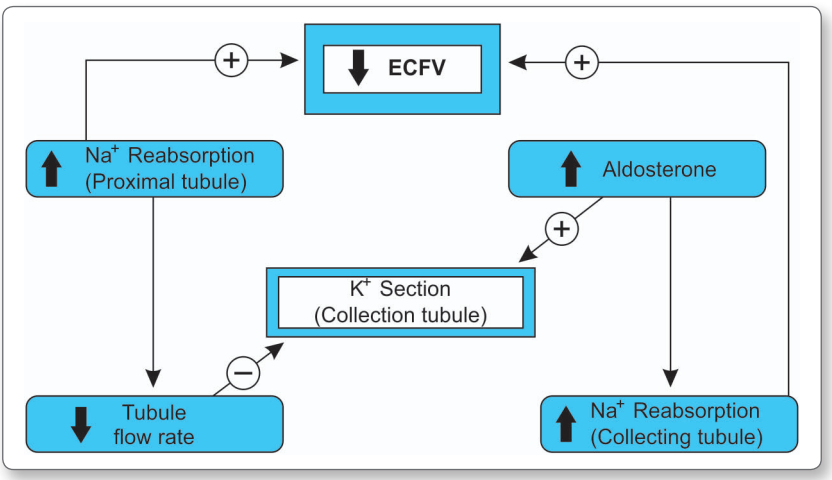


Fig. 5.4: Feedback mechanism regulating aldosterone secretion

SECTION-III ENDOCRINE PANCREAS

- Definition of DM and its mechanism
- Types
- Complications
- Some terms related to DM—
  a. Glycation
  b. Glycosylation
  c. Advanced glycated end products
  d. Significance of glycated hemoglobin (Hb. A_{1c})
- Treatment goal
- Drugs used in DM
  - OHA*
  - Insulin
    - Source
    - Chemistry
    - Route and time of administration
    - Mechanism of action
    - Units
    - Systemic effects
    - ADRs.

* OHA—Oral hypoglycemic agents

DEFINITION OF DIABETES MELLITUS AND ITS MECHANISM

Diabetes mellitus is a symptom complex due to absolute or relative lack of insulin characterized by polyuria, polydipsia, polyphagia, muscle wasting and hyperglycemia with or without glycosuria.

Keywords

1. Polyuria—Due to hyperglycemia; there is excess glucose in renal tubules; so there is osmotic diuresis and polyuria.
2. Polydipsia—As there is excess loss of water due to polyuria; so severe dehydration and compensatory polydipsia.
3. Wasting—As there is hindrance of carbohydrate utilization so the muscles and fats of the body are utilized and increased neoglucogenesis to provide energy and nutrition supply, hence wasting.
4. Polyphagia—To compensate wasting.
5. Hyperglycemia—Due to absolute or relative insulin lack.
6. Glycosuria—Due to crossing of renal tubular maximum of glucose.

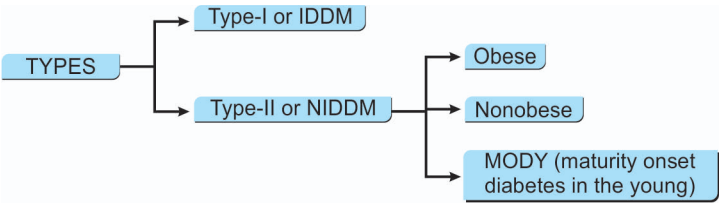
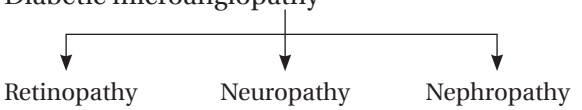


Table 5.1 Differences between type-I (IDDM) and type-II (NIDDM)

Points	Type-I (IDDM)	Type-II (NIDDM)
Age of onset	Usually <20 years	Usually >40 years
Body weight at onset	Normal or low	Obese
Plasma insulin	Absolute deficiency	Relative deficiency
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Ketoacidosis	Common	Rare
Family history	May be absent	May be present
Autoantibodies	Autoimmunity, immune pathogen mechanisms	Insulin resistance
Treatment with insulin	Only treatment	Occasionally required
Islet cell atrophy	Marked atrophy and fibrosis is seen	Focal atrophy, amyloid deposits found
β-cell depletion	Marked	Mild

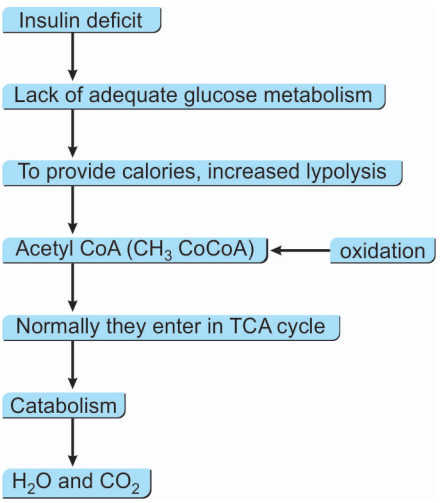
COMPLICATIONS

1. Ketosis
2. Atherosclerosis
3. Diabetic microangiopathy



Ketosis or Diabetic Ketoacidosis

Description



But in uncontrolled DM acetyl CoA molecules cannot be removed by TCA cycle so that acetyl CoA molecules accumulate and form acetoacetic acid and β-hydroxy butyric acid, from which acetone can develop. Acetone, acetoacetic acid and β-OH butyric acid are known as ketone bodies. Their accumulation in the body is called **ketosis** or diabetic ketosis which may cause acidosis, coma and death.

Atherosclerosis

Incidence of death due to atherosclerotic lesions in DM is very high. DM increases the proneness to develop atherosclerosis, but why?

In normal person, LDLs are native LDL molecules. Normally they can enter the vascular endothelium via their receptors and are eventually catabolized. In a person who is developing atherosclerosis, the LDLs are no longer native LDLs but are oxidized. These oxidized LDLs are not recognized by their receptors, they enter the vascular endothelium by other means and eventually binds and all are deposited in the subintimal layer. In experimental animals, it has been shown that diabetes enhances the oxidation of LDLs.

Diabetic Microangiopathy

Retino and nephropathy

In diabetic microangiopathy the basement membrane of the capillary endothelium is thickened. What causes this thickening is not very clear. In DM, there is chronic hyperglycemia. Some of the glucose molecules are reduced to from sorbitol. Sorbitol formation in some unknown way, helps the thickening of the basement membrane. Also conjugation of protein with glucose (seen in DM) contribute to the thickening of basement membrane of the capillary. Thickening of the basement membrane leads to narrowing of the vessel so there is deficiency of the perfusion of the tissue.

Diabetic neuropathy

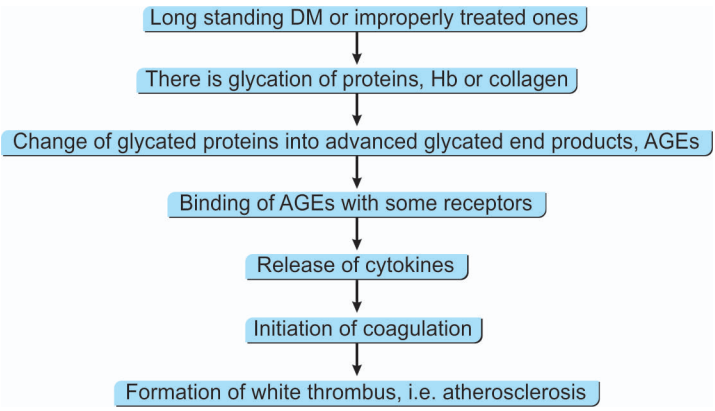
Both autonomic and somatic nervous systems are affected due to:

a. Nerve fiber degeneration
b. Demyelination
c. Microangiopathy of interneuronal fine blood vessels and may be presented as—
    1. Autonomic manifestation, i.e. impotence, gastroparesis, distended bladder, cardiac abnormalities and so on.
    2. Somatic manifestation, i.e. peripheral neuritis, diabetic tabes.

SOME TERMS RELATED TO DM

a. Glycation
b. Glycosylation
c. Advanced glycated end products
d. Significance of glycated hemoglobin (Hb. A_{1c}).

By the term glycation and glycosylation is meant addition of sugar (glucose fructose) to such agents or structures like proteins collagens hemoglobins WBCs. But glycation is not enzymatic, while glycosylation is an enzymatic procedure.



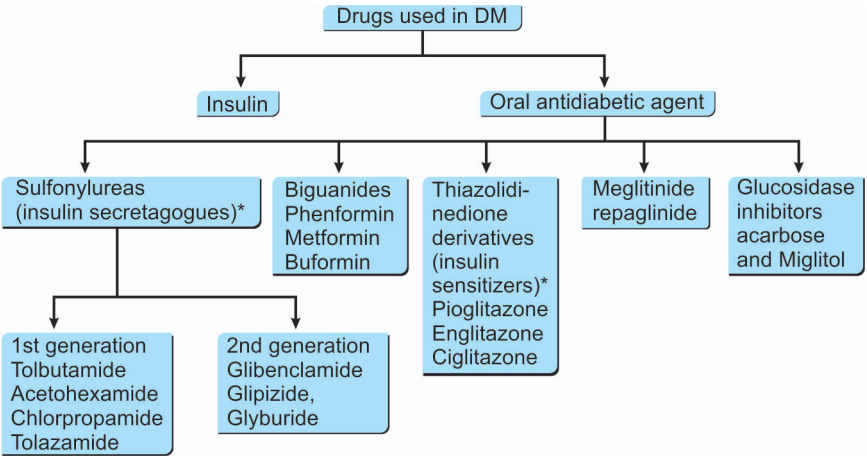
In addition glycated LDLs produce atherosclerosis. In the tissues where there is plenty of glucose, some glucose molecules are converted into sorbitol, which is a poison to tissues. Long continued stay of sorbitol may be the major cause of retinopathy, nephropathy and neuropathy. Therefore untreated DM leading to long drawn hyperglycemia produces twin chemicals AGEs and sorbitol.

Hb. A_{1c} is more reliable index of mean blood sugar than occasional isolated blood sugar samples. High GHb is associated with increased chances of microvascular complications (retinopathy-nephropathy and neuropathy). A 6% GHb is equivalent to a mean blood sugar value of 110 mg%. A 1% rise of GHb means about 36 mg% rise of mean blood sugar value. Thus GHb 7% is roughly equivalent to mean blood glucose level of 146 mg%.

TREATMENT GOAL

A. Diabetic has to be treated by—
   1. Dietary restrictions
   2. Obesity reduction
   3. Regular physical exercise
   4. Prevention of complications
   5. Educating the patient on DM.

B. Drug therapy



INSULIN

Source

4 polypeptides (insulin is secreted from B cell, glucagon is secreted from A cell, somatostatin is secreted from C cell and PPP is secreted from D cells) come from islands of Langerhans of pancreas.

Chemistry

Insulin consists of 51 amino acids arranged in two chains of A and B.

Chain A contains 21 AA and B 30 AA. connected by two disulfide bridges. The chain A means acidic, B means basic chain. A chain starts with glycine and ends with phenylalanine and B chain starts with threonine and ends with arginine.

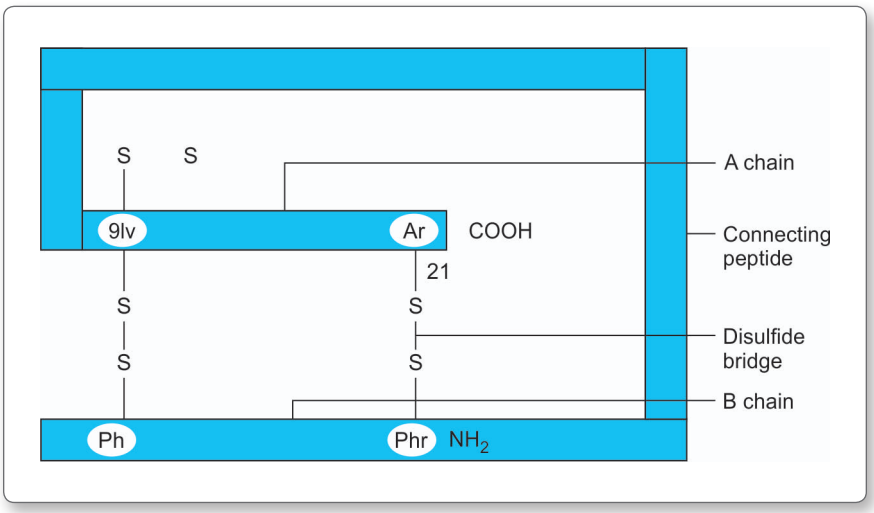


Fig. 5.5: Chemistry of human insulin

- **Monocomponent insulin**: Insulin free from biological impurities (like C-peptide proinsulin) and hence less antigenic and having the capacity to produce (mono or one) upward deflexion in chromatography with less chance of development of resistance are knwon asmonocomponent insulin.

Route and Time of Administration

Insulin is usually given subcutaneously, half an hour before meal, in case emergency, IV route is used.

Mechanism of Action

Insulin receptor has 2 parts. Each part consists of one α and β unit. So the complete receptor has ααββ unit. The α unit is rounded and projects outside the cell membrane and catches insulin molecule. The β unit totally confined within the cell membrane. There is link between α and β and a units themselves also. β units contains an enzyme tyrosine kinase.

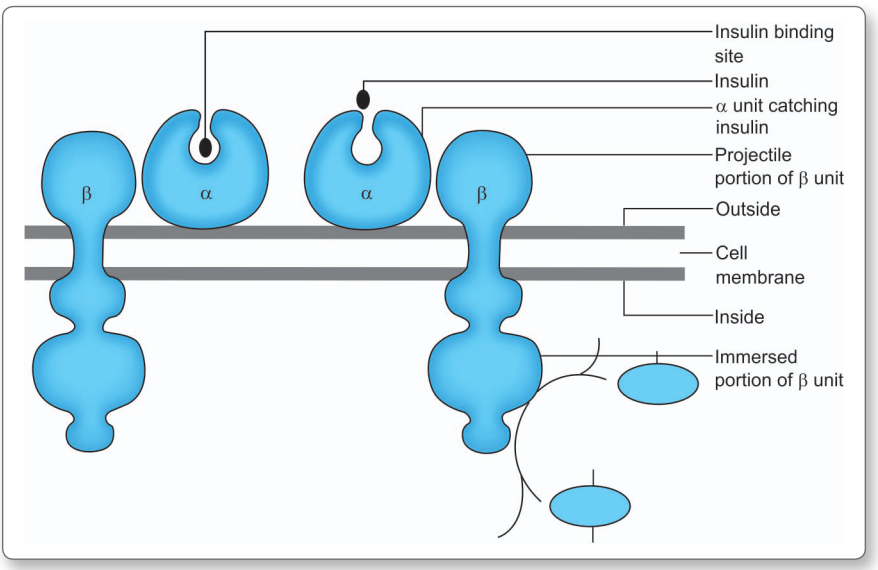
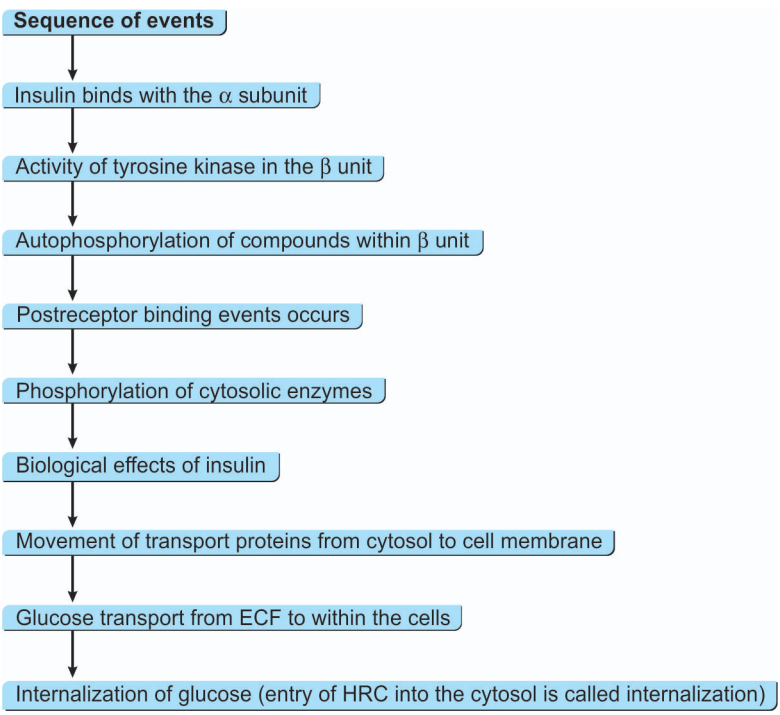


Fig. 5.6: Insulin receptor



After internalization, the net actions which occur are:

a. Cytosolic glucose transporting proteins are translocated to the cell membrane.

b. Influence of some genes and there is more production of the corresponding enzymes like hexokinases and thereby glucose metabolism is intensified.
c. Similarly insulin can inhibit some DNA transcription. Inhibition of DNA transcription of specific genes so that an enzyme facilitating gluconeogenesis is no longer produced. Finally inhibition of gluconeogenesis occurs.
d. **Unit of insulin**: Amount of insulin which is needed to reduce blood glucose 45% of a 2 kg rabbit, after keeping it 24 hours fasting.

Systemic Effects

On liver cells

1. It prevents gluconeogenesis and hepatic glycogenolysis leading to hypoglycemia.
2. It promotes uptake of glucose by the liver cells however glucose can enter liver cells independent of insulin.
3. Promotes glycogenesis.

On muscle cells

1. Stimulates glucose uptake and glucose molecules are metabolized
2. Muscle glycogenesis is facilitated.

Inhibition of gluconeogenesis production or input of raw materials for gluconeogenesis,(i.e. glycerol, lactic acid, alanine and so on) are reduced due to insulin.

On fat cells

Uptake of glucose into the fat cells and fat synthesis within the cells stimulated.

ADRs

- Hypoglycemia
- Allergic reaction
- Lipodystrophy
- Edema
- Weight gain
- Insulin resistance

Hypoglycemia

It may develop due to excess dose of insulin or due to omission of meals and so on. Brain depends solely on glucose as fuel. Therefore hypoglycemia causes dysfunction of brain. Compensatory mechanism stimulates the sympathoadrenal system therefore symptoms of hypoglycemia are a combination of CNS dysfunction, i.e. confusion, coma, convulsion and sympathetic overactivity, i.e. tachycardia, palpitation, cardiac pain, anxiety and sweating.

Allergic reactions

In the past only older preparations of insulin were used and allergic reactions were common due to—1. Amino acid pattern of bovine insulin is different from that of human. 2. Older preparations contained many impurities like proinsulin which were immunogenic.

Lipodystrophy

If insulin injections are taken sc daily on the same spot, then—1. In some patients there occurs atrophy of local fat known as lipoatrophy. 2. In some others there is local excess deposition of fat called lipohypertrophy may develop. Lipoatrophy is a form of local allergy to insulin whereas lipohypertrophy is an expression of local lipogenesis due to insulin.

Edema

When a dehydrated and metabolically broken down case of diabetic is first treated with insulin and promptly corrected dehydration, some Na^+ and fluid retention, resulting in rapid weight gain and even pitting edema can develop. This also may cause edema of the lense causing temporary error of refraction (needs to change reading glass).

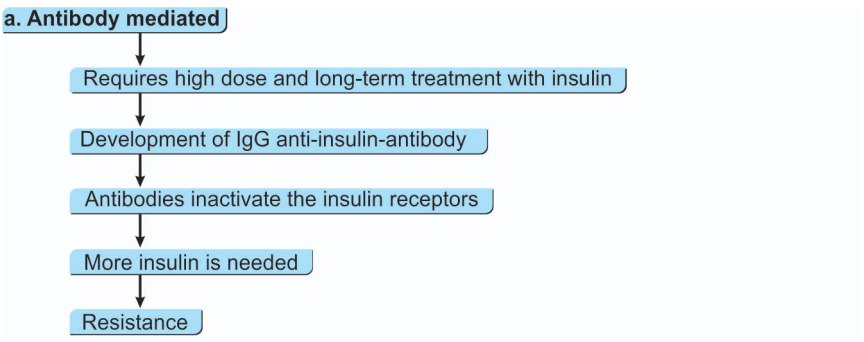
Weight gain

Insulin prevents lipolysis, is an anabolic hormone, prevents wasting due to hyperglycemia, causes weight gain.

Insulin resistance

Insulin resistance is a condition where daily requirement of insulin exceeds 200 units per day. Insulin resistance can be due to resistance at (i) prereceptor, (ii) receptor, and (iii) postreceptor sites.

Mechanism



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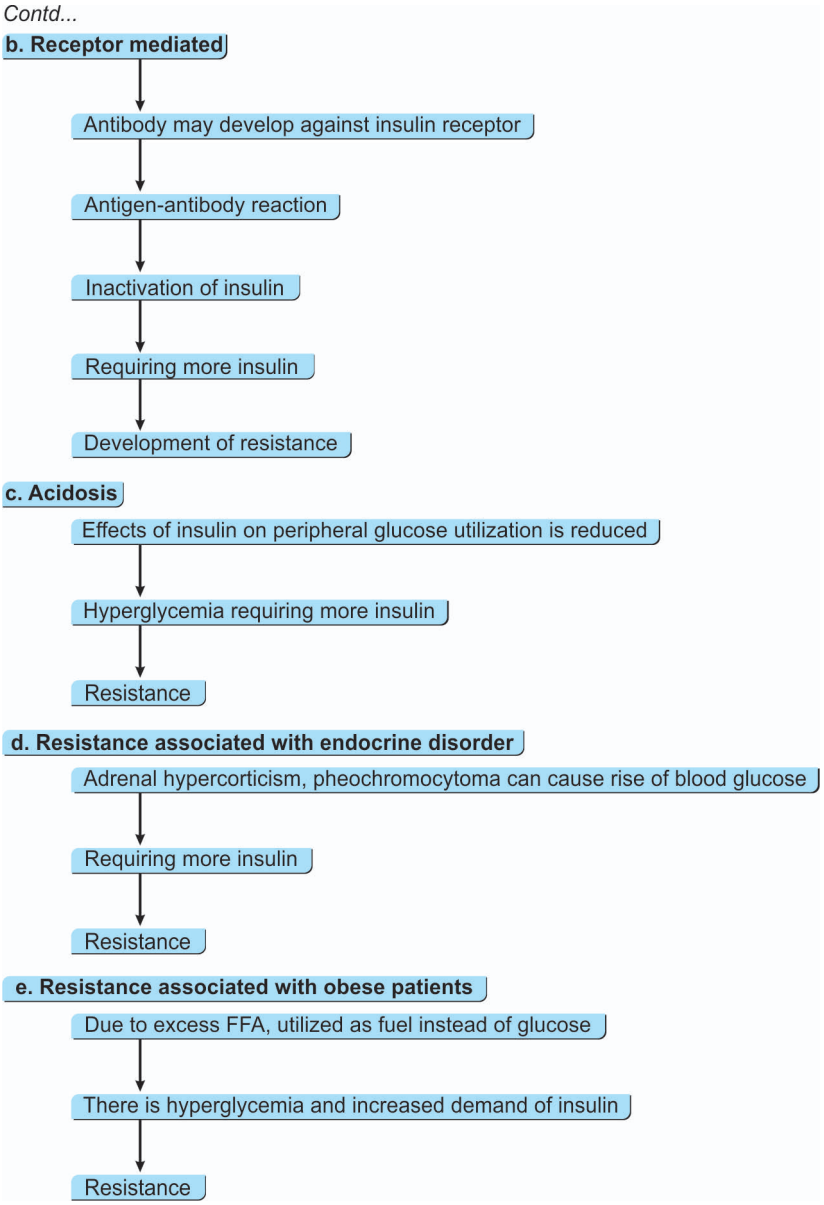


Treatment

1. Change of preparation of insulin
2. Administration of sulfonylurea
3. Administration of glucocorticoids
4. Reduction of obesity
5. Correction of endocrine disorder and ketoacidosis.

ORAL HYPOGLYCEMIC (ALSO CALLED ANTIHYPERGLYCEMIC) AGENTS

There are several groups of oral hypoglycemic agents (OHA) mentioned earlier.

Sulfonylureas

There are several subgroups of drug within the group of drugs called sulfonylurea. Drugs included in the category of sulfonylurea are divided into two generations.

MOA of sulfonylureas

All sulfonylureas act via same mechanism of action they—

i. Stimulate the release of insulin from the β cells
ii. Potentiate the action of insulin on target cells
iii. Decrease the serum glucagons level.

Adverse effects of sulfonylureas

i. Hypoglycemia
ii. Weight gain
iii. Hyperinsulinemia.

Meglitinides

Both Sulfonylureas and Repaglinide stimulate insulin release form β cells of pancreas and thus lower blood sugar level. Hence both Sulfonylureas and Repaglinide are called "**insulin secretagogues**".

Biguanides

Metformin is an euglycemic agent rather than a hypoglycemic agent.

Mechanism of action

Mechanism of action of metformin is not clear. Apparently, it acts by several mechanisms as follows—

i. It decreases the intensity of hepatic gluconeogenesis—This may be the principal mechanism.
ii. It intensifies the glycolysis in the tissues.
iii. It decreases the serum glucagons level.
iv. It decreases the rate of glucose absorption from the gut.

The Great Pharmacological Effects of Metformin are—

i. Metformin can improve serum lipid profile. That is use of metformin can raise serum HDL cholesterol, but lower LDL cholesterol and

triglyceride levels, we know diabetics are prone to suffer from serum dyslipoproteinemia.
ii. It prevents weight gain.
iii. It does not practically cause hypoglycemia.
iv. Its effects does not depend upon the cell mass of pancreas.

Adverse effects

i. GI upset is a common problem.
ii. Lactic acidosis—In gluconeogenesis, lactic acid is an important substrate. That is, one example of hepatic gluconeogenesis is conversion of lactic acid to glucose in the liver, because, Biguanides inhibit hepatic gluconeogenesis, lactic acid accumulation that is, lactic acidosis, can occur.

Thiazolidinediones

These drugs are also collectively called "glitazones".

The "glitazones" are "insulin sensitizers", that is they diminish insulin resistance. This means, for these drugs to become effective exogenous or endogenous insulin must be present. When used as a monotherapy, hypoglycemia does not occur. Viewed in this way, it is an "euglycemic" drug.

Glucosidase Inhibitors

A glucosidase inhibitors delay the digestion of polysaccharides and hence the absorption is delayed this blunts the sharp rise of postprandial blood sugar level.

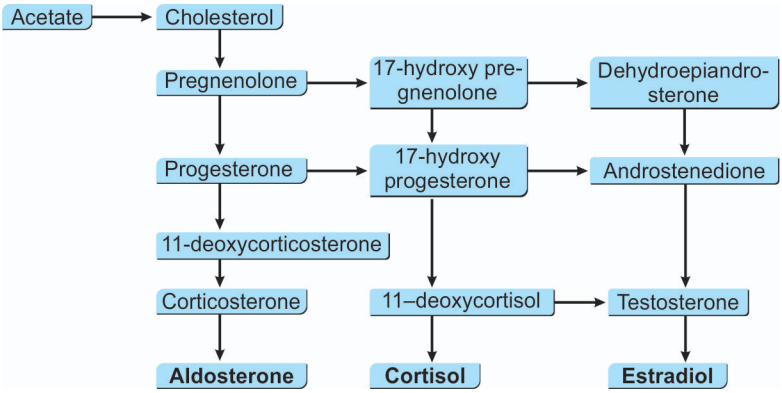
SECTION-IV CORTICOSTEROIDS

- Definition
- Biosynthesis
- Classification
- SAR (structure activity relationship) and supersteroid
- Mechanism of actions
- Principles of steroid therapy (Henoctis discovery)
- Clinical uses of glucocorticoids
- Adverse actions of glucocorticoid therapy
- Principles of withdrawn
- Contraindications
- Steroids and tuberculosis
- Anabolic steroids.

DEFINITION

Steroids are the carbon containing unsaponificable lipid fraction, which are insoluble in water and soluble in lipids and possesses the common perhydrocyclopentanophenanthrene nucleus.

BIOSYNTHESIS



CLASSIFICATION

Table 5.2 Classification of steroid hormones

Organ	Hormones	Source (Natural/ synthetic)	Examples	Duration of action (Half-life)
Adrenal cortex	Glucocorticoids	Zona fasciculata synthetic	Cortisol (Hydrocotisone) Cortisone (N) Dexamethasone (S) Betamethasone (S) Paramethasone (S) Triamcinolone (S) Prednisolone (S) Methyl prednisolone (S) Cortisone cortisol fludrocortisone	36–72 hours long acting 12–36 hours intermediate acting 8–12 hours short acting
Adrenal cortex	Mineralocorticoids	Zona glomerulosa synthetic	Aldosterone (N) 11-desoxycorticosterone (N) Fludrocorticosterone	
Adrenal cortex	Sex hormones	Zona reticularis	Androgen in male (S)	
Testes	Sex hormones	Interstitial cells of Leydig	Testosterone (N)	
Ovaries	Sex hormones	Graafian follicle	Estrogen and progesterone (N)	

SAR (STRUCTURE ACTIVITY RELATIONSHIP) AND SUPER STEROIDS

Corticosteroids may be viewed as derivatives of cholesterol. Cholesterol has a (cpp) Cyclopentanoperhydrophenanthrene nucleus with a long side chain attached at c-17 and it is a c-27 carbon compound. By contrast corticosteroids have a cpp nucleus but a short side chain and hence of c-21 carbon structure.

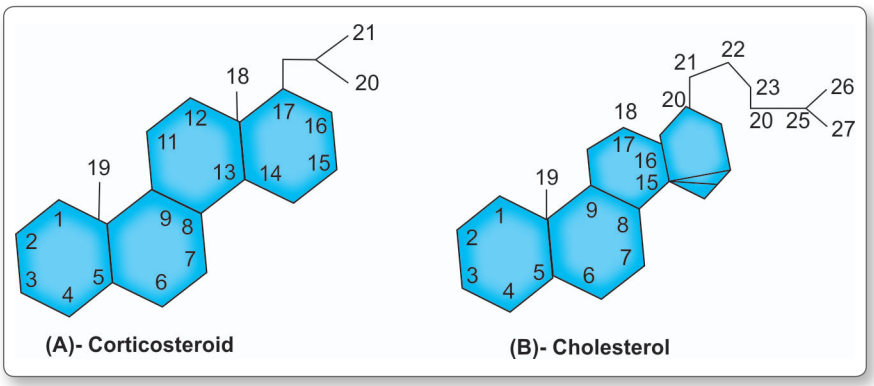


Fig. 5.7: Corticosteroid and cholesterol skeleton

1. Corticosteroid nucleus itself is inactive.
2. To exist corticosteroid activity C_2 or halogen must be present on C_{11} position.
3. Presence of halogen atom at C_6 or C_9 position increases the glucocorticoid activity.
4. Presence of OH^- or CO^- at C_{17} position increases the glucocorticoid activity.
5. Presence of an alkyl group at C_{16} also increases the glucocorticoid potency.
6. Addition of OH^- group at C_2 increases the water (Na^+ retaining capacity) mineralocorticoid activity.

Dexamethasone and betamethasone are prednisolone containing a methyl and fluoro group at 9 and 16 position respectively. In addition, there is a double bond in between C_1 and C_2 instead of C_3 and C_4 hence, they are called super steroids.

MECHANISM OF ACTION (SEE SECTION-I)

Systemic Effects

Three terms—a. Physiologic, b. Pharmacologic, and c. Permissive actions are popular, concerned with corticosteroid activity. However the distinction between physiologic and pharmacologic actions are too artificial. There is a good deal of overlapping.

Physiologic actions are those seen due to endogenous corticosteroids in physiologic state, although they all can be reproduced by their synthetic analogue.

Pharmacologic actions are those which are seen when heavier or (supraphysiologic) doses of corticosteroids are given but they are not seen with physiologic doses. That is why anti-inflammatory and immuno-suppressive actions are seen only when heavier doses are used but not physiologic ones.

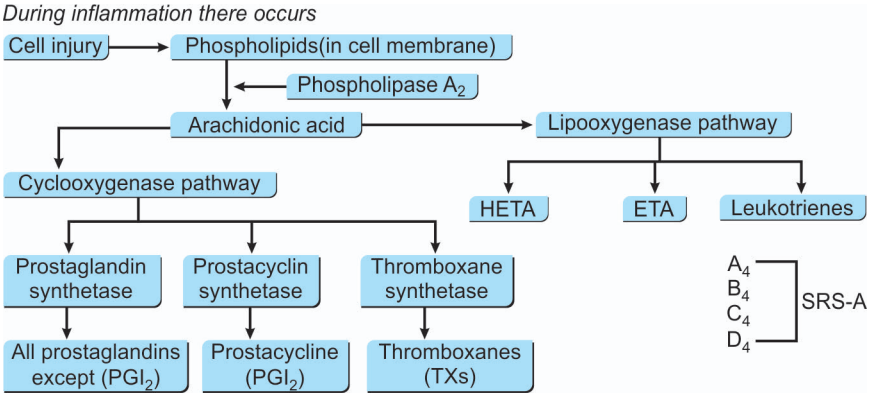
Permissive actions are some actions of other hormones like vaso-constrictor activity, lipolysis by NA are seen only when some cortisol is present in the tissue. Absence of cortisol in the tissue leads to the failure of NA induced vasospasm; but presence of excess cortisol does not lead to excess vasospasm. This is permissive action.

Metabolic Effects

a. **Carbohydrate metabolism**: There is increased i. glycogenesis and neoglucogenesis and decreased peripheral utilization of glucose so net effect is hyperglycemia.
b. **Fat metabolism**: Redistribution of fat is seen. That is fat accumulates in the face and shoulder region producing "moon face" and "buffalo hump" respectively. In addition beta adrenergic stimulated lipolysis is intensified; an example of permissive action.
c. **Protein metabolism**: Catabolism is increased leading to increased availability of amino acids. Thus more amino acids and glycerol from lipolysis becomes available for gluconeogenesis.
d. **Electrolyte metabolism**: The endogenous hormone cortisol has some Na^+ retension and K^+ ejection effect.
e. **Effects on organ systems**:
   i. Bones develop osteoporosis, continued therapy makes the bone susceptible to fracture.
   ii. Lymphoid tissues regress.
   iii. Heavy dose can cause muscle wasting.

Anti-inflammatory Effects

During inflammation there occurs



Glucocorticoids inhibit phospholipase A_2, thereby reducing the formation of mediators of inflammation.

1. Reduction of transudate and exudate formation, by opposing capillary permeability.
2. By their permissive action in conjunction with catecholamines they cause vasoconstriction and reduces the chances of developing of septicemic shock.
3. They inhibit fibroblastic activity, fibroblasts "wall-off" or "cordon" the bacterially infected site and thus prevent the dissemination of the invading bacteria. Use of steroid, therefore, can lead to conversion of a localized infection into a generalized septicemia. Yet in some clinical settings, the fibroblastic wall has to be broken otherwise the antibiotic may fail to reach the spot.
4. It suppress phagocytosis by inhibition of monocytes.

Immunosuppressive action

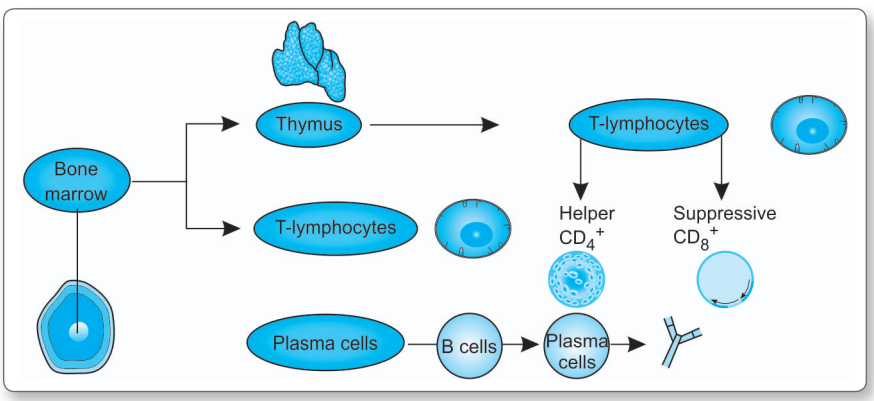


Fig. 5.8: Mechanism of immunity

Specific immunity may be —

a. Cell mediated immunity (CMI)
b. Humoral immunity (HI).

CMI is achieved by the actions of T-lymphocytes and macrophages, whereas humoral immunity is achieved by B-lymphocytes and macrophages. B-lymphocytes after coming in contact with the antigen, proliferate and are converted into plasma cells, which produce immunoglobulins (Igs).

PRINCIPLE OF STEROID THERAPY (HENOCTIS DISCOVERY)

1. For each disease and each patient dose should be adjusted by trial and error basis.
2. A single large dose is usually harmless.
3. Therapy for few days is usually harmless.
4. Taking large dose for prolonged period is harmful.

5. They are not used as curative agent. It can be used as adjuvant therapy (except Addison's disease). Palliative therapy is done due to its anti-inflammatory effect.
6. After prolonged therapy, they should not be stopped abruptly, which may lead to acute adrenal insufficiency.

CLINICAL USES OF GLUCOCORTICOIDS

1. **Primary adrenocortical deficiency or Addison's disease**: In this disease, there is bilateral destruction of adrenal cortex by such conditions like—
   a. Autoimmune disease
   b. Fungal infection
   c. TB and others.

   These are due to deficiency of glucocorticoids + mineralocorticoids + adrenal androgens and excess ACTH (Law of –ve feedback) ACTH causes the characteristic pigmentation, seen in the disease so, main drug therapy in this condition is corticosteroids replacement as well as treatment of the cause.
2. **Anti-inflammatory use**: This is the most common use, corticosteroids only reduce the changes of inflammation but not the cause, so treatment should be accordingly—
   a. Topical uses in various inflammatory disease of skin, eyes in these cases however systemic administration may also be needed. Eczema—Clinically very pruritic, papulovesicular with lots of oozing (weeping eczema) microscopically there are signs of inflammation spongeogenesis with edema of the epidermal cells and so on. Atopic dermatitis and contact dermatitis are the examples. Treatments are topical adrenocorticosteroids.
   b. In rheumatoid arthritis—They are popular but not controversial. In RA, steroids cannot cure but reduce the progress of the disease and relieves symptoms.
   c. In osteoarthritis or in rheumatoid arthritis—They may be injected within the affected joint. Osteoarthritis changes are due to degeneration rather than inflammation.
   d. In IBD—(Chronic ulcerative colitis) retention enema of prednisolone or hydrocortisone is very popular.
   e. In inflammation due to microbes—Steroids are risky.
   f. In bronchial asthma inflammation plays a big role for bronchospasm in asthma. Steroids in asthma act chiefly as an anti-inflammatory agent to relief from bronchospasm.
3. **In immunosuppression**: Depression of circulating lymphocytes or antibodies are the mechanism by which corticosteroids in high doses

act as immunosuppressants. That is why they are used in SLE where the aim is to suppress immunity and in autoimmune disorders, rheumatoid arthritis and so forth.

4. **Allergy**: In acute life-threatening emergencies, demanding immediate action, as in anaphylactic shock or acute life-threatening angioneurotic edema for immediate lifesaving purpose, drug of choice is adrenaline.
5. **Miscellaneous**: They are used in—
   a. Nephrotic syndrome
   b. Postoperative phase of brain surgery to reduce cerebral edema
   c. Malignant exophthalmos and so on.

ADVERSE ACTIONS OF GLUCOCORTICOID THERAPY

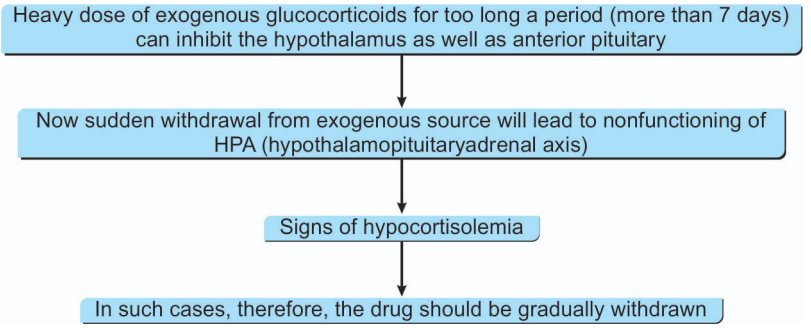
These are, as a rule, extension of their physiological effects.

Cushing's syndrome can appear in gross over used cases and it can be detected by—

   a. Moon face—That is face becomes more round little puffy. Particularly the women becomes delighted because she now looks better, thinning of extremities, appearance of facial hair in woman can develop.
   b. Buffalo hump—Due to deposition of fat in the supraclavicular region.
   c. Hypertension—Due to some water and sodium retaining capacity.
   d. Hyperglycemia—Due to increased neoglucogenesis.
   e. Osteoporosis—Due to increased osteoclastic and decreased osteoblastic activity.
   f. Euphoria—It is common but depression even tendencies to suicide also can occur.

1. Aggravation of peptic ulcer—By inhibition of PGEs synthesis and making the mucosal resistance weak.
2. Hypertension—Due to its Na^+ retaining capacity.
3. Cardiovascular embracement in CCF—By increasing preload.
4. Masking of bacterial infections—May be disastrous.
5. Posterior subcapsular cataract and glaucoma—Resultant glaucoma may respond only poorly to β-blocker eyedrop.
6. Psychosis—They increases the activity of MAO so that there is excessive degradation of adrenaline and deficiency of adrenaline in the sympathetic synaptic neurotransmission manifested as psychosis.
7. Muscle wasting – Due to more catabolic effects on protein metabolism.
8. Growth retardation – Not responding to growth hormone due to excessive catabolism of protein.

PRINCIPLES OF WITHDRAWN



Contraindications

a. Absolute

Cushing syndrome—It can develop in continued high dose of glucocorticoids therapy

b. Relative

1. Peptic ulcer—Due to decreased mucosal resistance offered by PGE_h
2. Hypertension—Due to expansion of fluid volume resulting from sodium retention
3. Diabetes mellitus—Glucocorticosteroid therapy is very risky arising from hyperglycemia
4. CCF—It is because of increased preload
5. Myocardial infarction—Due to increased preload

STEROIDS AND TUBERCULOSIS

In pulmonary tuberculosis, a corticosteroid may be given to severely ill patients particularly tuberculosis of the hollow viscus, e.g. pleura, GIT, etc. It reduces the reaction of the body to tuberculoprotein and buys time for the chemotherapy to be effective. It also causes the patient to feel better much more quickly. In the absence of effective chemotherapy an adrenal corticosteroid will cause tuberculosis to extend and it should never be used alone or for another disease, if tuberculosis is suspected.

ANABOLIC STEROIDS

Introduction

Nandrolone is an injectable anabolic agent having protein-sparing and anticatabolic effects as well as its favorable effects on calcium metabolism in cases of increased calcium excretion and osteoporosis.

Uses

It can be used as an adjunct to specific therapies and dietary measures in pathologic conditions characterized by a negative nitrogen balance, e.g. (i) During chronic debilitating disease. (ii) During prolonged glucocorticoid therapy. (iii) During radiotherapy and after major surgery or trauma. (iv) It produces marked relief of clinical symptoms of osteoporosis, particularly that with dorsolumbar pain. (v) It is also used for the palliative treatment of selected cases of disseminated mammary carcinoma in women.

Contraindications

It is contraindicated in—
i. Pregnancy
ii. Carcinoma of prostate or testes
iii. Mammary carcinoma in the male.

Adverse Reactions

i. Virilization in some sensitive women.
ii. Hoarseness of voice may be the first symptom of vocal change which may lead to irreversible lowering of the voice.
iii. There may be increased frequency of erections and phallic enlargement in prepubertal males and clitoral hypertrophy.
iv. Increase of pubic hair may occur in girls.

Precautions and Warnings

Hypercalcemia or hypercalciuria may develop either spontaneously or as a result of therapy in patients with certain tumors, especially mammary carcinoma hypernephroma and bronchial carcinoma. Patients with myocardial, hepatic or renal dysfunction, migrains, epilepsy, hypertension or a history of coronary artery disease should be observed carefully, since anabolic steroids may cause sodium and water retention. Alterations in glucose tolerance may occur, requiring surveillance for latent diabetes and possible changes in control for diabetic patients.

SECTION-V DRUGS INFLUENCING UTERINE CONTRACTION AND TOCOLYTICS

- Introduction
- Drugs
- Labor and its stages
- Initiation of labor pain
- Ecbolics – Oxytocin, Ergometrine
- Tocolytics – Ritodrine.

INTRODUCTION

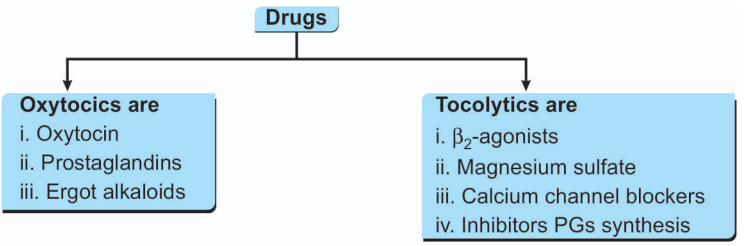
The uterus contracts rhythmically in its virgin state. This rhythmic contraction does not depend upon the nerve supply because the contraction survives after denervation. The contraction can be influenced by—

1. Nerves—Sympathetic and parasympathetic—It can be ignored.
2. Chemicals—Drugs and hormones.

α_1 and β_2-receptors have been demonstrated in the myometrium. β_2 stimulation leads to relaxation of myometrium. Adrenaline causes contraction of pregnant uterus but in nonpregnant uterus it causes relaxation.

Oxytocin—It causes uterine contraction.

Prostaglandins—Facilitate uterine contraction.



DRUGS

Two types of drugs are clinically important—

i. Oxytocics—Which cause stimulation of uterine contraction.
ii. Tocolytics—Which cause relaxation of uterine muscles.

LABOR AND ITS STAGES

- **First stage or stage of dilatation**: Signaled by onset of labor pain upto full dilatation of cervix.
- **Second stage or stage of expulsion**: Extends from full dilation of cervix upto the delivery of the fetus.
- **Third stage or stage of delivery of secundines**: From delivery of the fetus upto the delivery of placenta and membranes.

INITIATION OF LABOR PAIN

It has been suggested that the release of $PGF_{2\alpha}$ from the fetal and maternal placenta at an appropriate point in fetal development is the initiating factor for parturation. There is evidence to suggest that fetal corticosteroids, which are synthesized and released in appropriate amounts at about the time of parturitions, inhibit the synthesis of progesterone and increase the synthesis $PGF_{2\alpha}$ by the placenta. The $PGF_{2\alpha}$ further inhibits progesterone synthesis and stimulates estrogen

synthesis. Estrogen further stimulate $PGF_{2\alpha}$ synthesis. The responsiveness of myometrium is increased by the change in hormonal balance. Uterine contractions are induced by $PGF_{2\alpha}$ and these are reinforced by oxytocin, released from the maternal postpituitary resulting in expulsion of fetus.

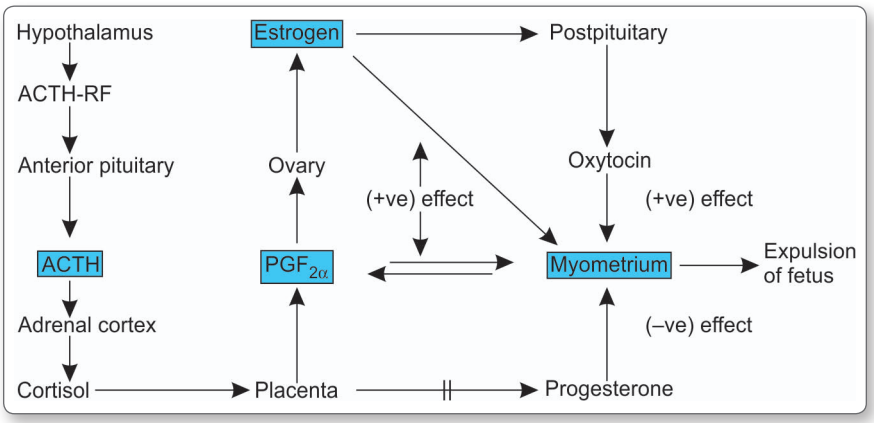


Fig. 5.9: Mechanism of imition of labor pain

ECBOLICS

Oxytocin

- Chemistry
- Source
- Clinical uses
- ADRs
- Contraindication.

Chemistry

It is a nonapeptide.

Source

The preprohormone is synthesized in the hypothalamus and the final hormone is released from the neurohypophysis.

Clinical uses

Synthetic oxytocin (1 unit/ml syntocinon).

1. To induce labor at terms because it causes contraction of body and fundus, making cervical dilatation.
2. To overcome unterine inertia during labor.
3. After labor to prevent postpartum hemorrhage.

4. To induce therapeutic abortion during 2nd and 3rd trimester of pregnancy.
5. As an intranasal spray prior to breastfeeding to promote milk ejection when lactation is deficient in nursing mother.

ADRs

1. Water intoxication
2. Rupture of uterus
3. Tetanic contraction but little or no relaxation of uterus leading to fetal anoxia. (Because circulation through placenta stops) fetal death.

Contraindications

1. Previous cesarean section or other uterine operation
2. Cephalopelvic disproportion
3. Abnormal fetal presentation
4. Parity greater than 4.

Ergometrine

It causes contraction of the uterus, the site and nature of contraction of which, are the whole uterus (whereas oxytocin causes contraction of the body and fundus of the uterus and dilatation of cervix) and tonic type without relaxation. This can result in fetal hypoxia and rupture of uterus, if it is used to induce labor, that is why ergometrine today is not used to induce labor. But for prevention of postpartum hemorrhage.

ADRs

1. Hypertension
2. Gangrene due to peripheral vasoconstriction.

TOCOLYTICS (UTERINE RELAXANTS)

These are agents which cause relaxation of uterine muscle → uterus fails to expel its contents. They are, clinically, used where the aim is to prevent a premature birth or an abortion is threatened.

Ritodrine

It is the drug of choice in premature labor, if not available, then Terbutaline Salbutamol or Fenoterol can be used. Ritodrine is used as IV as well as orally.

If, its use is decided then start IV Ritodrine with very small dose, observe whether ADRs develop or not, if not, use Ritodrine drip in heavier conc. until the labor pain + uterine contraction. Then continue

the drug at this dose for 12 hours or more, eventually switch on to oral preparation.

ADRs

1. Tachycardia—Due to β_2-agonist induced fall of BP. (Compensatory mechanism).
2. Fluid retention—Due to renin angiotensin overactivity leading to salt retention.
3. Hyperglycemia β_2-induced hepatic glycogenolysis.
4. Hypokalemia—Due to renin—Aldosterone angiotensin overactivtiy.

SECTION-VI HORMONAL CONTRACEPTIVES

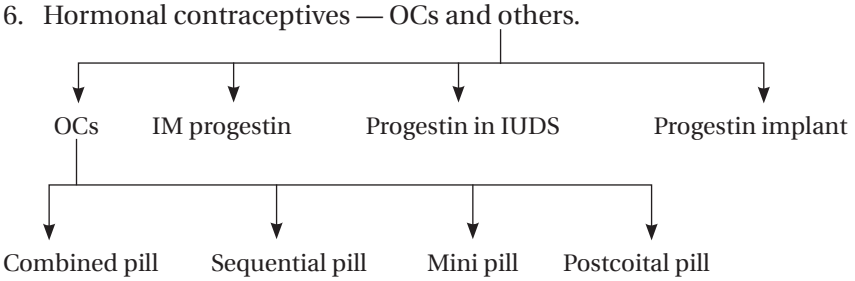
- Definition of contraception
- Recent popular methods of contraception
- OCs and progestin preparations.
  - OCs composition and schedules
  - Combined pill mechanism of action
  - ADRs of oral contraceptives
  - Indications of contraceptive pills
  - Contraindications
  - Drug interactions.

DEFINITION OF CONTRACEPTION

Prevention of conception is called contraception.

RECENT POPULAR METHODS OF CONTRACEPTION

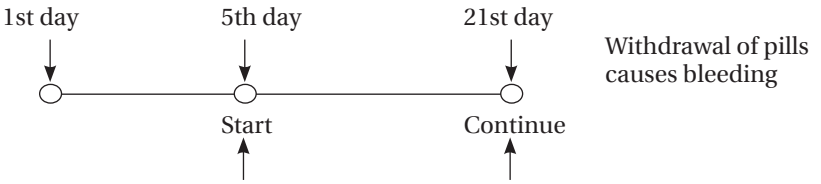
1. Sterilization (vasectomy/ligation)
2. Observation of safe period
3. Condoms
4. Spermicides
5. IUDs
6. Hormonal contraceptives — OCs and others.



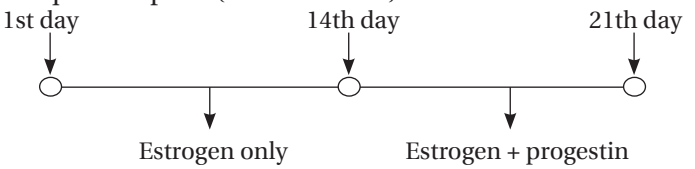
OCs AND PROGESTIN PREPARATIONS

OCs Composition and Schedule

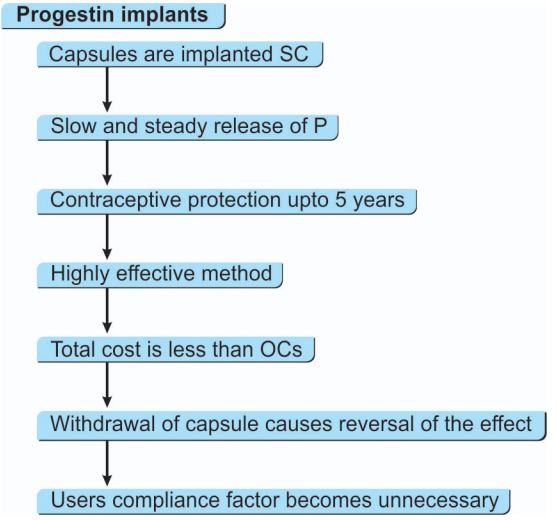
a. Combined pill—Both estrogen and progesterone.
(ethinyl estradiol (e)+ norethindrone acetate (p)



b. Sequential pill—(Now obsolete)



c. Mini pill (progesterone only) taken daily on uninterrupted basis.
d. Postcoital pill (morning after pill)
- Diethylstilbestrol (DES)
- Within 72 hours after the coitus
- In a dose of 25 mg BD for 5 days.



IM progestins

- Depot-Medroxy progesterone acetate
- Protection against upto 87 days.

IUD progestin

IUD (progestin) inserted through vagina—
1. It has high range efficacy
2. It is effective for 1 year
3. It acts purely locally
4. It is now available.

Combined Pill—Mechanism of Action

It is not fully clear in spite of the volume of research in the last five decades. Hormonal contraceptives act in several ways including:
1. When combined pills are used, there is no maturation of graafian follicle and no ovulation.
   (Estrogen inhibits FSH → No follicular maturation →No ovulation).
2. E and P exert a –ve feedback on the anterior pituitary. Due to the E's –ve feedback FSH secretion become poor—No maturation of follicle results. LH secretion is defective and the LH surge (which causes ovulation) does not occur.
   (Progesterone → Inhibits LH → No preovulatory LH surge → No ovulation).

In addition progestin causes:
1. Increases the thickness of cervical mucus so prevents the movement of spermatocytes.
2. Abnormal contraction of fallopian tube of uterus and expulsion of blastocyst.
3. Inhibits implantation by changing the endometrial environment.

ADRs of Oral Contraceptives

It depends upon the (i) age of the user, who are more than > 35 years of age are more susceptible, (ii) contents of progesterone and estrogen, and (iii) habit of smoking and other factors.
1. **Thromboembolic disorder**: Includes—
   a. Deep vein thrombosis
   b. Pulmonary embolism
   c. Cerebral thrombosis—It can occur particularly in users having pills containing high dose of estrogen.
2. **Thrombophlebitis**: Due to estrogen.
3. **Hepatic function**: OCs may produce signs of liver damage, manifested as a rise in plasma levels of hepatic enzymes SGOT and SGPT and falls in plasma cholinesterase and albumin. All these are reversible.
4. **Anemia**: Tendency to an increased incidence of macrocytic anemia amongest the OCs users has been reported and there is evidence for a

reduction in plasma level of vitamin B_{12}. On the other hand there is a much reduced incidence of iron deficiency anemia which is probably explained by the decrease in menstrual blood loss.

5. **Glucose tolerance**: OCs may impair glucose tolerance without affecting resting blood glucose values. The effects appears to be an anti-insulin action. But the DM is an absolute contraindication to the use of OCs.
6. **Weight gain**: It occurs commonly either due to an anabolic action or fluid retention or both may be involved.
7. **Hypertension**: There is small risk of development of hypertension or exacerbation of existing hypertension has been attributed to activation of renin angiotensin aldosterone system by estrogen.
8. **Amenorrhea and ovulation**: Generally normal menstrual cycles with ovulation occur within 3 months of discontinuance of an OCs preparation but it may persist for 6 months or more after cessation of treatment.
9. **Headache**: Women who are liable to have attacks of premenstrual migraines headache may have this symptom aggravated by OCs.
10. **Mood changes**: Depression, tiredness, loss of libido and irritability have all been reported. The undergoing mechanism is thought to be an increase in MAO in response to catecholamines.
11. **Carcinogenicity**: There is no evidence of an increased incidence of carcinoma in women user of OCs. In fact, there is protective effects against benign neoplasia of the breast and possibly against development of ovarian cysts.

Indications of Contraceptive Pills

1. Contraception
2. To reduce premenstrual tension
3. Functional ovarian cyst
4. Benign breast diseases
5. To regulate menstruation
6. To reduce menstrual bleeding
7. Dysmenorrhea.

Contraindications

1. Liver disorders
2. Cancer breast
3. Ca-endometrium
4. Thromboembolic disorder with a(+ve) history
5. Marked hypertension
6. CVA and MI
7. Diabetes mellitus

8. Eczema
9. Hyperlipoproteinemia.

All the above been explained under adverse reaction.

Drug Interactions

Specially contraceptive failure can occur if concomitantly drugs like Rifampicin, Carbamazepine or Phenytoin enzyme inducers or antibiotics which inhibit the intestinal bacterial flora are taken.

SECTION-VII ANTITHYROID DRUGS

- Hormones of thyroid glands
- Chemistry
- Synthesis
- Function
- Hyperthyroidism
- Treatment.

HORMONES OF THYROID GLANDS

They are—

1. Thyroxin
2. Tri-iodothyronine
3. Calcitonin.

CHEMISTRY

Thyroxin and Tri-iodothyronine each contains two phenyl rings linked by ether bridge. In thyroxin there are four iodine atoms whereas in Triiodothyronine there are only three iodine atoms.

SYNTHESIS

This consists of five steps. These are—

1. Iodide trapping
2. Iodide oxidation by peroxides
3. Organification of iodine – Attachment of tyrosine with iodine
4. Coupling of DIT with DIT or TIT with MIT
5. Freed and release of thyroxin from thyroglobulin by proteolysis.

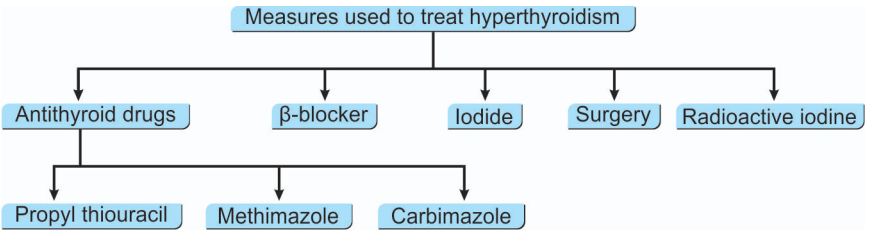
FUNCTION

1. Helps in growth of the body
2. Helps in physical and mental development
3. Regulates metabolism of foods
4. Regulates body temperature.

HYPERTHYROIDISM

It is a state where there is excess of thyroid hormons. About 75% of hyperthyroidisms are due to Graves disease, some 14% due to multinodular goiter and 5% are due to autonomous solitary toxic nodule. Usually in the treatment of Graves disease, Carbimazole is used, in toxic multinodular goiter large dose of radioactive iodine therapy is useful. In toxic adenoma surgery or radioactive iodine therapy is the treatment of choice.

TREATMENT



Mechanism of action of (antithyroid drugs)—Carbimazole and Methimazole

They act by inhibiting the synthesis of thyroid hormones by—

1. Peroxidase enzymes
2. Iodine organification
3. Coupling of iodotyrosine molecules.

In addition propylthiouracil can prevent conversion of thyroxin into tri-iodothyronine in the periphery. But the Carbimazole cannot block the iodide trapping or release of thyroid hormones. As a result, the release of stored hormone is not blocked, Carbimazole administration does not give immediate relief. The relief counts only when the stored hormones are depleted and the clinical improvement does not begin before three weeks.

Use of β-blockers in Hyperthyroidism

Logic

1. In hyperthyroidism there is excessive secretion of catecholamines β-blockers blunt the effects of catecholamines.
2. The effects of β-blockers start immediately; whereas the clinical benefits of Carbimazole takes three weeks.
3. In Graves disease, population of β_1-receptors increase in number.
4. In thyroid storm, use β-blockers may be lifesaving.
5. A popular β-blocker used in hyperthyroidism is Propranolol.
6. In presence of asthma, where propranolol cannot be used, Verapamil or Diltiazem can be used.
7. β-blockers is an adjunct therapy in hyperthyroidism.

SECTION-VIII CALCIUM HOMEOSTASIS BONE REMODELLING AND OSTEOPOROSIS

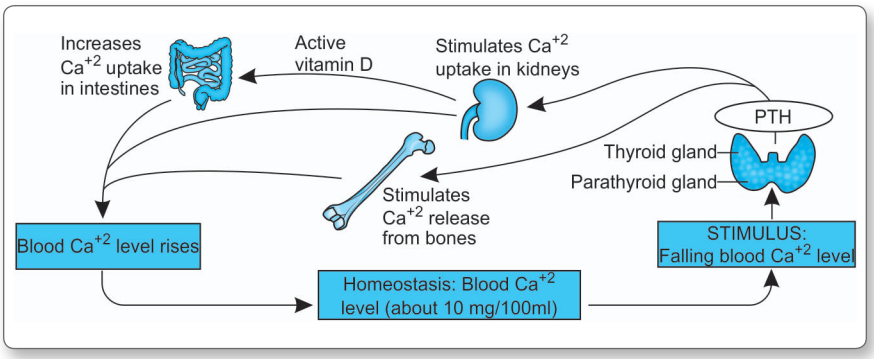


Fig. 5.10: Outline of calcium homeostasis

CALCIUM HOMEOSTASIS

If the concentration of serum Ca^{++} tends to fall, Ca^{++} from bone is mobilized and enter the serum thus preventing fall of serum Ca^{++} level. Or, when the level of serum Ca^{++} tends to rise, Ca^{++} ions of serum leave the serum to enter the bone—Thus elevation of Ca^{++} level of serum is prevented.

BONE REMODELLING

Normal bone undergoes remodelling: Simultaneously, in several sites of the skeletal structure, tiny cavities are formed by osteoclastic activity. Osteoclasts (a kind of bone—Thus creating the cavity. Afterwards, osteoblasts (another kind of bone cells) invade the cavity region and lay down new bone to replenish what was lost by osteoclastic activity. This is bone remodelling. Bone remodelling goes on for whole of the life. Each time, a tiny cavity is filled by osteoblastic bone laying, some bone matter is lost.

OSTEOPOROSIS

In osteoporosis due to relentless bone remodelling, good deal of bone mass is lost and thus the clinical state of osteoporosis is developed.

Factors Effecting Osteoporosis

i. Activity of interleukins—It increases the activity of osteoclasts
ii. Lack of estrogen—As seen in menopausal women
iii. Lack of physical activity—Decreased activity potentiates osteoporosis.

iv. Lack of exposure to sun—Vitamin D is converted into its active form called calcitriol in the sun. Calcitriol facilitates increased absorption of calcium in the intestine. Calcitriol stimulates both osteoclastic and osteoblastic activity, but because of the fact that under calcitriol's influence intestinal calcium absorption increases greatly, there is ultimately a net deposition of calcium in the bone.
v. Lack of calcium
vi. Excess use of glucocorticoids
vii. Hyperparathyroidism—As a result of PTH, the osteoclasts are activated → bone absorption → mobilization fo bone calcium → elevation of serum calcium level occurs.

CHAPTER

6

Pharmacology of Nervous System

SECTION-I PHARMACOLOGY OF NERVOUS SYSTEM

- Overview
- Neuro and psychopharmacology differences
- Anatomical layout of nervous system
  a. Difference between sympathetic and parasympathetic system
  b. Synapse and ganglia
     i. Pre and postganglionic fibers
     ii. Cholinergic and adrenergic fiber.
  c. Sympathetic and parasympathetic target cells
  d. Neurotransmission
     i. Cholinergic
     ii. Adrenergic.
  e. Neurotransmitters
     i. Definition
     ii. Types
     iii. Properties
     iv. Role of neurotransmitter in some diseases.
  f. Some tracks in the psychopharmacology
  g. Effects of stimulation of ANS (in brief).

OVERVIEW

Our body function is regulated and integrated by the two systems:
1. The endocrine and 2. The nervous system. The endocrine system sends signals to target tissues by varying the levels of blood borne hormones. In contrast, in the nervous system, more than 10 million neurons that constitute the human nervous system communicate with eACh other

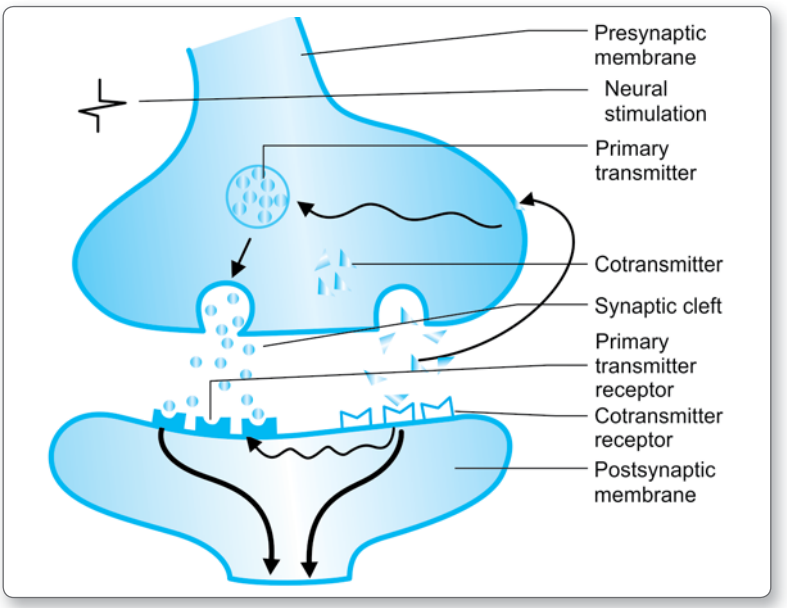


Fig. 6.1: Protoplasmic continuity

through chemical mediators not by protoplasmic continuity between the adjacent neurons.

They also exert their effects on peripheral structures by release of neurotransmitters. The pharmacology of nervous system can be discussed as:

NEURO AND PSYCHOPHARMACOLOGY DIFFERENCES

i. **Neuropharmacology** deals with drugs that produce their primary therapeutic effects by mimicking or affecting the functions of the autonomic nervous system are called autonomic drugs. These autonomic agents act either by stimulating portions of the autonomic nervous system or by blocking the action of the autonomic nervous system.
ii. **Psychopharmacology** deals with those drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process "Drugs affecting the CNS" may act presynaptically by influencing the production, storage, release and termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors.

However, several major differences exist between neurons in **neuropharmacology** (the peripheral autonomic nervous system) and those in **psychopharmacology** (the CNS) like—

i. The circuitry – In the CNS is much more complex than that of the autonomic nervous system.

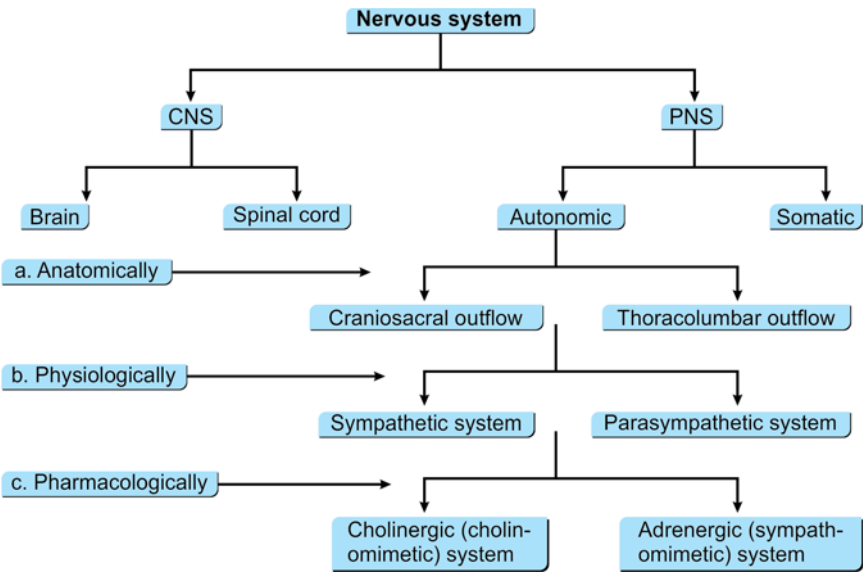
ii. The number of synapses in the CNS is greater.
iii. Powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission is prominently found in the CNS.
iv. Number of communicating neurotransmitters—The CNS communicates through the use of more than 10 (and perhaps as many as fifty) different neurotransmitters. In contrast the autonomic system uses only two primary neurotransmitters, e.g. acetylcholine and noradrenaline.

All these NTs combine with their receptors and regulates the physiological functions, but any form of deficiency or excess can cause many diseases, e.g.

i. Overactivity of DA in the mesolimbic—Mesocortical tract can cause **schizophrenia**.
ii. Either cholinergic overactivity or dopaminergic deficiency occur in **parkinsonism**.
iii. In depression, there is deficiency of **serotonin and/or noradrenaline**.
iv. In epilepsy, **NMDA** mediated overactivity or **GABA** underactivity is seen.
v. Patients with **Alzheimer's** disease have a significant loss of cholinergic neurons in the temporal lobe.

ANATOMICAL LAYOUT OF NERVOUS SYSTEM

Nervous system can be schematically classified as follows



The autonomic nervous system is "autonomic" because it is not under the influence of volition or will, by contrast the somatic fibers are often controlled by the will. The sympathetic and parasympathetic system are the two main divisions of autonomic nervous system.

Differences Between Sympathetic and Parasympathetic System

The sympathetic system is also called "thoracolumbar outflow". The "preganglionic fibers", originate from all (i.e. from all the twelve) thoracic segments plus the two or three upper lumbar segments of the spinal cord relay in the "sympathetic ganglia". From the sympathetic ganglia, "postganglionic fibers" arise and terminate in their target cells.

The parasympathetic system is also called "craniosacral outflow" because the nerves arise:

i. Either from the brain and conveyed via IIIrd, VIIth, IXth and Xth cranial nerves.
ii. Or from the IInd, IIIrd and IVth segments of sacral segments of spinal cord.

Points of difference	Sympathetic system	Parasympathetic system
Origin (other name)	Thoracolumbar	Craniosacral
Distribution	($T_1 \rightarrow L_3$)	(III, VII, IX, X S2 $\rightarrow$ S4)
Distribution ganglia	Wide	Limited to head and neck
Length of postganglionic fiber	Long, away from organs	Short on or close to the organ
Fiber ratio (pre: postganglionic fiber ratio	1:20 $\rightarrow$ 1:100	1: 1 $\rightarrow$ 1:2
Released transmitter	NA (major), ACh (minor)	ACh
Transmitter stability	NA stable, diffuses for wider action	ACh rapidly destroyed locally by cholinesterase
Purpose	Tackling stress and emergency	Assimilation of food and conservation of energy

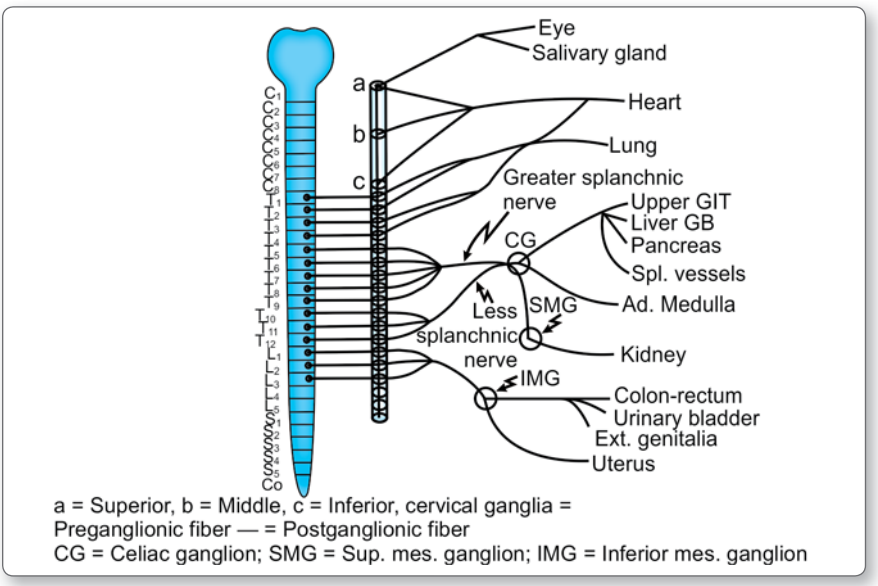


Fig. 6.2: Sympathetic system

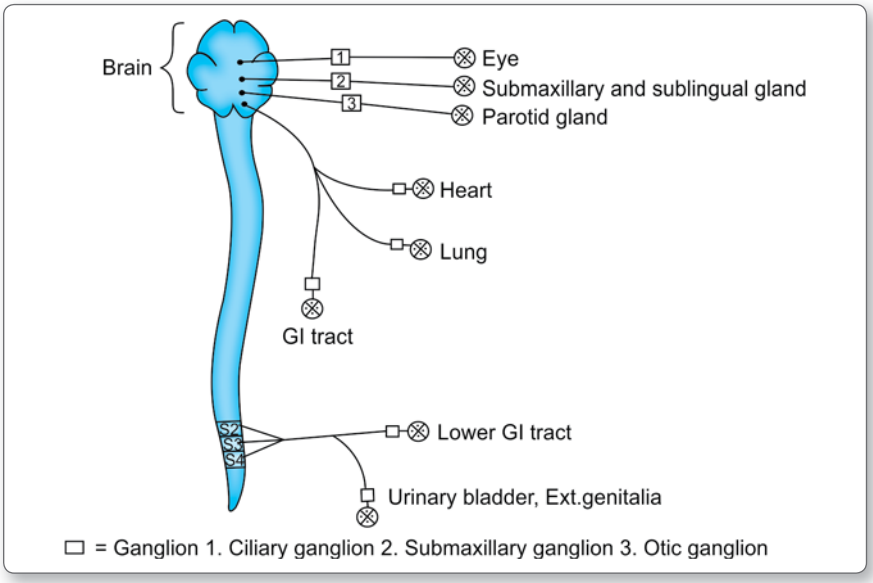


Fig. 6.3: Parasympathetic system

Synapse and Ganglia

Synapse is the junctional region between two neurons where one neuron relays the impulse to other so that the impulse is transmitted.

Ganglion—It is the site where the axons of the preganglionic fibers make synapse with the neurons of the postganglionic fibers.

Pre and postganglionic fibers

In both the sympathetic and parasympathetic system, there are preganglionic fiber, ganglia and postganglionic fibers. Thus there are sympathetic and parasympathetic ganglia. Most of the sympathetic ganglia are in the sympathetic chain. Some other ganglia (celiac superior mesenteric and inferior mesenteric) are situated away from the sympathetic chain.

In the parasympathetic system the preganglionic fibers make the synapse with the postganglionic fibers at the parasympathetic ganglia. The postganglionic fibers arise from the parasympathetic ganglia (not like the sympathetic chain) and terminate in the target cells.

Cholinergic and adrenergic fibers

Cholinergic fibers are those which release acetylcholine on stimulation. They are—

i. All preganglionic fiber (both sympathetic and parasympathetic)
ii. Postganglionic parasympathetic fiber

iii. Postganglionic sympathetic fibers supplying sweat gland and piloerector muscle
iv. Nerve supplying to adrenal medulla
v. Skeletal neuromuscular junction
vi. Some CNS neurons.

Adrenergic fibers are those which release noradrenaline on stimulation. They are—

i. All postganglionic sympathetic fibers accept those supplying to sweat glands.

Sympathetic and Parasympathetic Target Cells

Sympathetic system

i. Vascular smooth muscles
ii. Visceral smooth muscles
iii. Cardiac muscles (both atria and ventricles)
iv. Dilator pupillae of the eye.

Parasympathetic system

i. Exocrine gland
ii. Smooth muscles of viscera
iii. Atrial muscles (not ventricular)
iv. Constrictor pupillae of the eye.

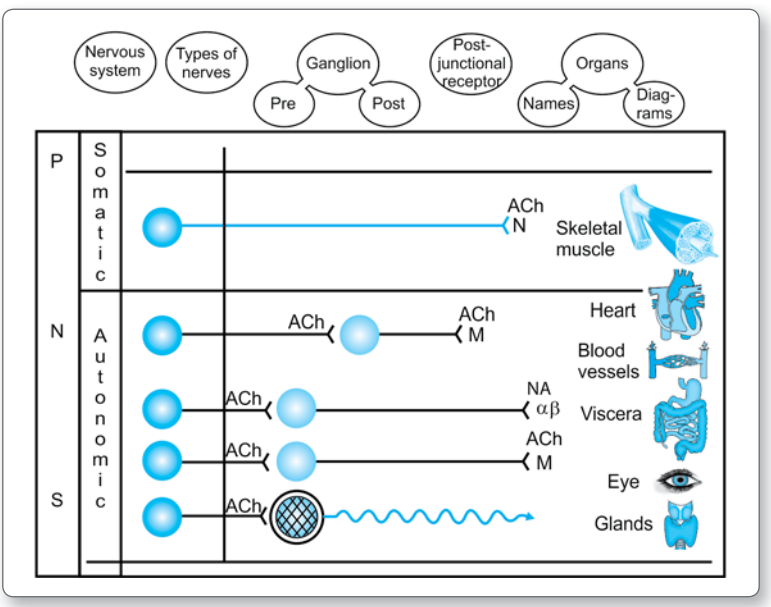


Fig. 6.4: Target organs

Neurotransmission

Neurotransmission in **cholinergic neurons** involves six steps. The first four—synthesis, storage, release and binding of the acetylcholine—to a receptor, are followed by the fifth step, degradation of the neurotransmitter in the synaptic gap (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs) and the sixth step, the recycling of choline.

Cholinergic transmission

ACh is a major neurohumoral transmitter at cholinergic nerves.

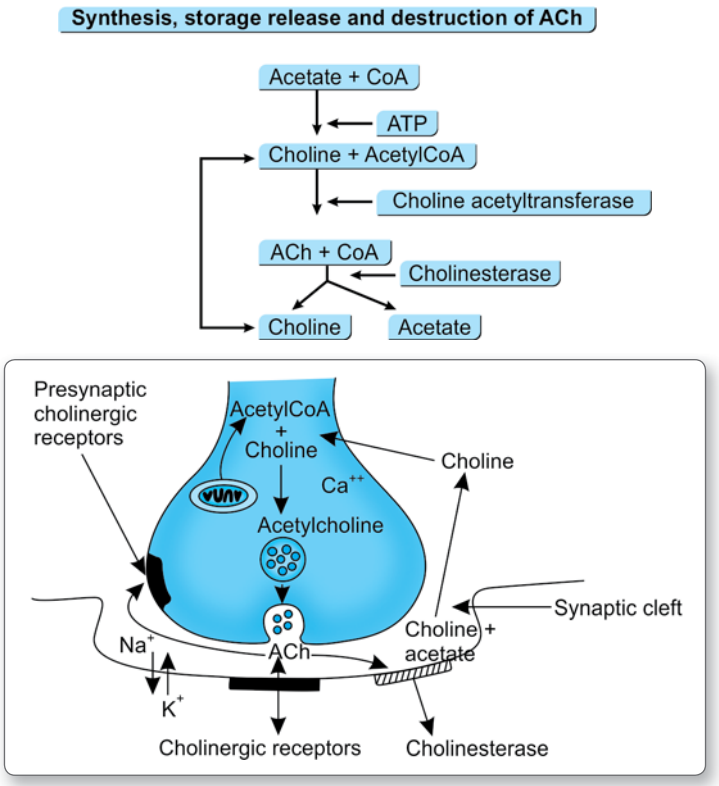


Fig. 6.5: Cholinergic transmission

Synthesis—ACh is synthesized locally in the cholinergic nerve endings by the above pathway. Choline is actively taken up by the axonal membrane and acetylated with the help of ATP and coenzyme A by the enzyme acetylcholine transferase, present in the axoplasm.

Storage—Most of the ACh is stored in ionic solution within small synaptic vesicles, with ATP and chromogranin.

Release—Release of ACh from nerve terminals occur by exocytosis. Immediately after release, ACh is hydrolyzed by the enzyme cholinesterase into acetate and choline and is recycled.

Destruction—Acetylcholinesterase (AChE or true cholinesterase) and butyrylcholinesterase (or pseudocholinesterase) are the two enzyme system responsible for the destruction of cholinesterase occurs in the body. Important differencs between these two enzymes are given below:

Point of difference	Acetylcholinesterase	Butyrylcholinesterase
Distribution	All cholinergic sites RBC, gray matter	Plasma, liver, intestine white matter
Hydrolysis	ACh → very fast Butyrylcholine → not hydrolyzed	Hydrolyzed
Inhibition	More sensitive to physostigmine	More sensitive to organophosphorus compound
Function	Termination of ACh, action	Not known

Adrenergic transmission

In adrenergic neurons closely resembles that already described for the cholinergic neurons, except that norepinephrine is the neurotransmitter

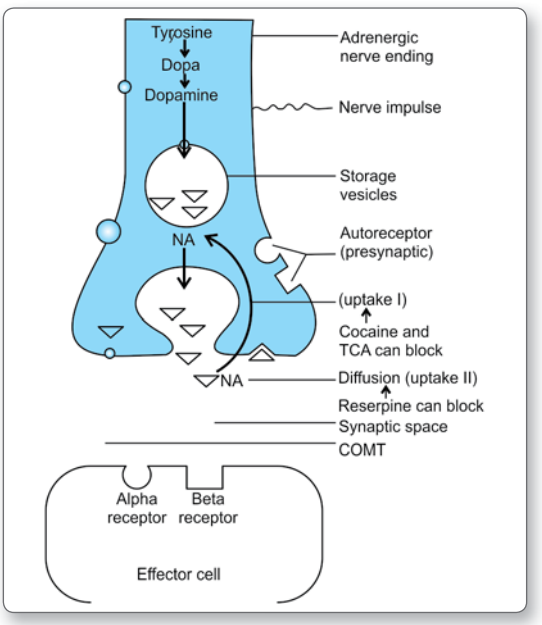


Fig. 6.6: Varicosities of sympathetic nerves

instead of acetylcholine. Neurotransmission takes place at neurons bead-like enlargements called varicosities. The process involves five steps: the synthesis, storage, release and receptor binding of the norepinephrine, followed by removal of the neurotransmitter from the synaptic gap.

Synthesis, Storage, Release, Reuptake and Metabolism of Catecholamines

a. **Synthesis**—Catecholamines are synthesized from the amino acid phenylalanine as shown above. Tyrosine hydroxylase is the rate limiting enzyme and its inhibition by a methyltyrosine results depletion of CAs. It can be used in pheochromocytoma before surgery and in inoperable cases. Synthesis of AD. occurs only in the adrenal medullary cells.

b. **Storage**—NA is stored in synaptic vesicles or granules within the adrenergic nerve terminal. The granular membrane activity takes up DA from the cytoplasm and the final step of synthesis of NA takes place within the granule which contains DA (3 hydroxylase. NA is then stored as a complex with ATP, which is adsorbed on a protein chromogranin. In the adrenal medulla, the NA thus formed within the chromaffin granules diffuses out into the cytoplasm, is methylated and AD so formed is again

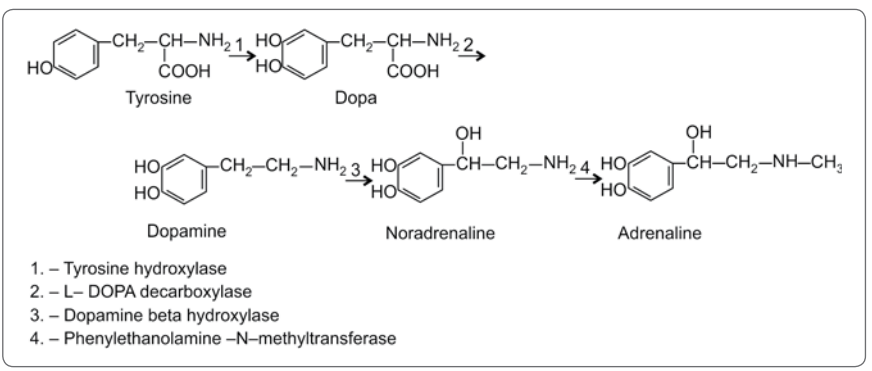


Fig. 6.7: Steps of synthesis of catecholamines

taken up by separate granules. The cytoplasmic pool of CAs is kept low by the enzyme monoamine oxidase (MAO) present on the outer surface of mitochondria.

c. **Release**—The nerve impulse coupled release of CA takes place by exocytosis and all the granular content, i.e. NA, AD, ATP, dopamine hydroxylase and chromogranin are poured out. The release is modulated by presynaptic receptors, of which an inhibitory control is dominant. Certain drugs also induces release of NA but they do so by displacing NA from the cytoplasmic pool and not from the granules. This process does not involved Ca^{+2}.

d. **Reuptake**—There is a very efficient mechanism by which (70% to 90%) NA released from the nerve terminal is recaptured. This occurs in two ways.

Table 6.1 Differences between uptake I and uptake II

	Uptake I	Uptake II
Site	Neuronal uptake	Extraneuronal uptake
Dependence	It is energy, carrier and temperature dependent	Not so
Requirements	Presence of Na^+ and low conc. of K^+ is required for the process	Ca^{+2} is necessary
Concentration of Na^+	Cone. of Na is small<39 mg/dl	High>40 mg/dl
Selectivity of the process	Specific process for AD NA and DA	Specific for Isoprenaaline and Amphetamine
Inhibitors	Inhibited by cocaine and Procaine	Inhibited by Reserpine

e. **Metabolism of Catecholamines**: The pathways of metabolism of CAs is shown below:

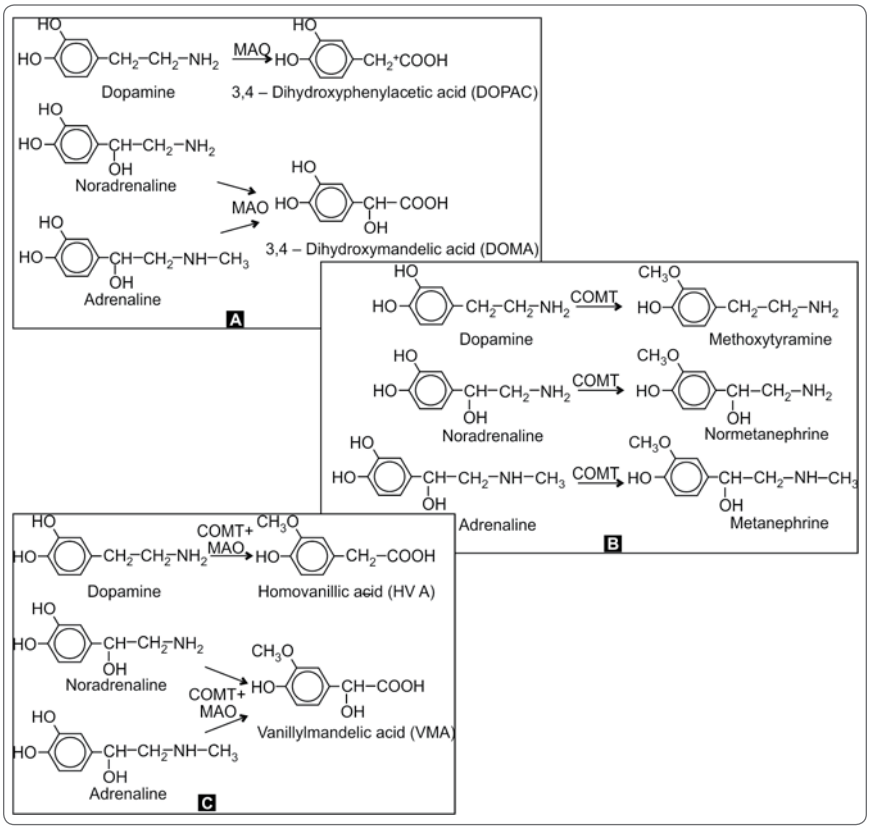


Fig. 6.8: Metabolism of catecholamines

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

Table 6.2 Differences between α and β-receptors

Receptors	Rank order of potency of agonist	Antagonist	Effectors pathway	Autoreceptor activity
α- receptor	Ad $\alpha_1+\alpha_2$ NA $\alpha_1+\alpha_2$ ISO–no α action	α_1– Prazosin α_1– Yohimbine	IP_3/DAG/ cAMP ↓	Dominant
β- receptor	Ad $\beta_1+\beta_2$ weak β_3 activity NA $\beta_1+\beta_3$ but no β_2 activity ISO– $\beta_1+\beta_2$	β_1– Atenolol selective β_2– Butoxamine selective Propranolol (nonselective)	cAMP $Ca+^{2}$↑	Less

Table 6.3 Differences between β_1-and β_2-receptors

Receptors	Location	Selective agonist	Selective antagonist	Potency of NA as agonist	Potency of ISO as agonist
β_1-receptor	Heart and kidney	Dobutamine	Atenolol	Strong	Moderate
β_2- receptor	Bronchial tree, blood vessels, uterus, GI and urinary tract	Terbutaline	α_1- methyl propanolol	No action	Present

Table 6.4 Differences between α_1-and α_2-receptors

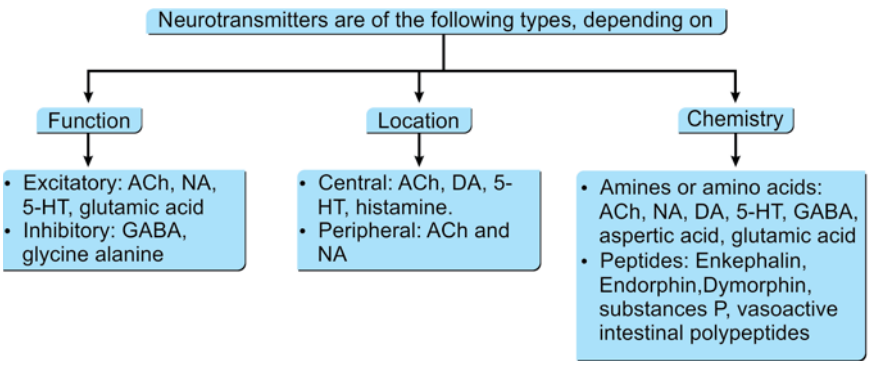
Receptors	Location	Function	Selective agonist	Selective antagonist	Effector pathway
α_1-receptor	Postjunctional/ effector organ	• Smooth muscle contraction • Gland secretion • Gut relaxation	Phenylephrine	Prazosin	IP_3/DAG
α_2-receptor	Prejunctional or nerve ending	• Inhibition of transmitter release • Vasoconstriction • Decreased central sympathetic flow	Clonidine	Yohimbine	↓ CAMP

Neurotransmitters

Definition

Neurotransmitter and neurotransmission chemical substances which transmit impulses from one neuron to another neuron or from neuron to effector organ is called neurotransmitter and the process is known as neurotransmission.

Types



Properties

They have—

1. Precursor(s)
2. Synthesizing enzymes
3. Storage vesicles
4. Release by neural stimulation
5. Postsynaptic receptors
6. Specific antagonists
7. Degrading enzymes.

Clarification

Points	Cholinergic NTs	Adrenergic NTs
Precursor (s)	Acetate and choline	Phenylalanine
Enzyme for synthesis	Acetyltransferase	Tyrosine hydroxylase → Methyltransferase
Storage	With ACh+ATP+ Chromo-granin	With NA + ATP + proteoglycan
Release	By exocytosis	By exocytosis
Postsynaptic receptors	Either nicotinic on muscarinic receptor	Either α or β
Specific antagonists	• Atropine on muscarinic receptors • d-tubocurarine on nicotinic receptors	• Prazosin on α-receptors • Propranolol on β-receptors

Contd...

Contd...

Points	Cholinergic NTs	Adrenergic NTs
Degrading enzymes	Cholinesterases • True • Pseudo	• Monoamine oxidase • Catechol–O– methyl-transferase

From the above consideration, it is clear that among others ACh and NA are the best classical examples of neurotransmitters.

Role of neurotransmitters in some diseases

All the NTs combine with their concern receptors and in normal cases, produce the (physiological) desired effects. Deficiency or excess of activity of these NTs may occur in many diseases, e.g.

1. Overactivity of dopamine is seen in schizophrenia.
2. Either cholinergic overactivity or dopaminergic deficiency occur in parkinsonism.
3. In depression, there is deficiency of serotonin and/or noradrenaline.
4. In epilepsy, NMDA mediated overactivity or GABA underactivity is seen.
5. Loss of cholinergic neuron may be the cause of Alzheimer's diseases.

Some Tracts in the Psychopharmacology

1. **Noradrenergic tracts**
   They maintain—
   a. Healthy mood
   b. Healthy sleep and wakefulness
   c. Healthy appetite.
2. **Dopaminergic tracts**
   a. Nigrostriatal pathway—It maintains extrapyramidal activity.
   b. Mesolimbic pathway—It maintains normal psychic activity.
   c. Tuberoinfundibular pathway—It causes inhibitions of prolactin secretion.
   d. Medullary paraventricular pathway—It concerns with eating behavior.
   e. Incertohypothalamic pathway—Its function is yet unknown.
3. **Cholinergic tracts**
   a. They are necessary for memory
   b. They perhaps maintain a state of wakefulness.
4. **Serotoninergic tract**
   a. Concerned with maintenance of sleep wakefulness and mood (deficiency of 5-HT causes depression), temperature regulation, development of hallucination, appetite control and neurohumoral control. Another group of serotoninergic fiber are concerned with endogenous pain inhibiting system.
5. **Glutamate receptors**
   NMDA receptors have drawn wide attention:
   a. They are concerned with learning and memory.

b. They are important for nerve cell injury.
c. When a nerve cell is injured, say, due to cerebrovascular thrombosis—Anoxia. NMDA receptors play important role in the extension of such injuries. Thus serious attempts have been made and considerable progress achieved in developing drugs which can block NMDA receptors. If this attempt becomes successful, it will be possible to minimize neuronal damage in cerebral thrombosis.

Effects of Stimulation of ANS (in brief)

Ultimately, it has become a tradition that during discussing the anatomy and physiology in neuropharmacology that all textbook contains the ANS stimulatory effects at organ level. Either in brief or detail, so the same is placed in the text also in the same area of discussion.

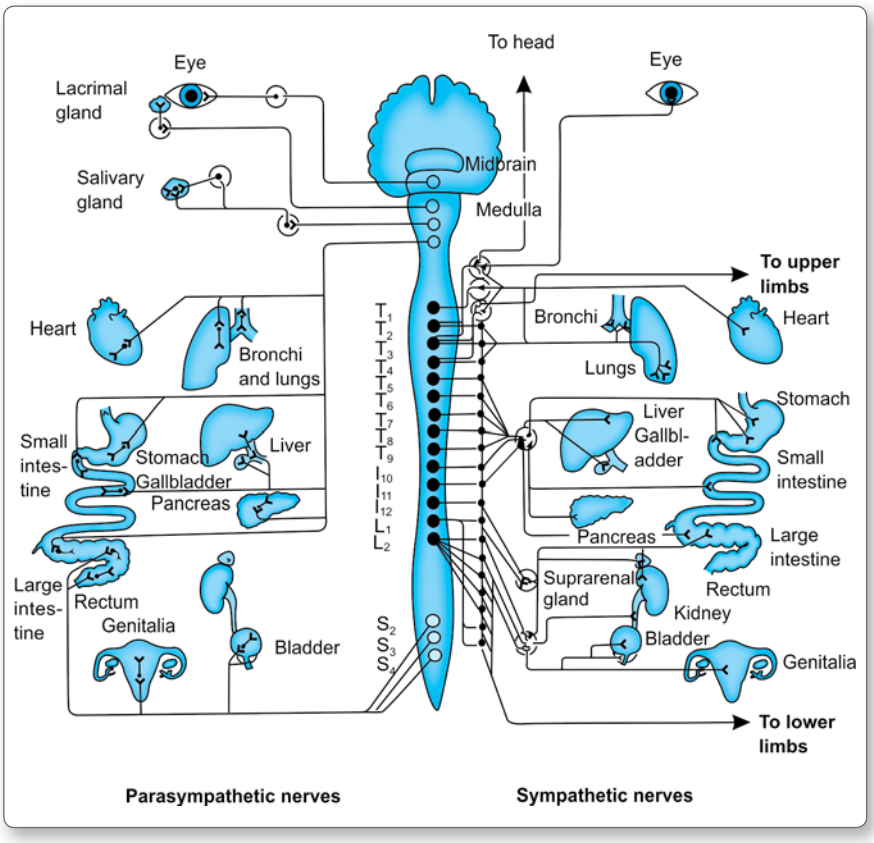


Fig. 6.9: The effect of stimulation of ANS

Table 6.5 Gross effects of ANS stimulation at organ level

Organ	Sympathetic	Parasympathetic stimulation
1. Heart • Rate • Force • Conduction velocity • Cardiac output	 • + ve chronotrophic effect • + ve ionotrophic effect • Increased • Increased	 • – chronotrophic effect • – ve ionotrophic effect • Decreased • Decreased
2. Blood vessels	Constriction of arterioles and veins rise in BP (α_1+α_2 activation) Dilation of arterioles and veins→fall in BP (β_2 action)	No effect on arterioles, except erectile tissue – Vasodilatation → erection vasodilatation
3. Bronchial tree • Smooth muscles • Glands	 • Relaxation (bronchodilatation) • ± or decreased or increased secretion	 • Constriction • Relaxation • Increased secretion
4. GI tract • General smooth muscle • Sphincters • Exocrine glands	 • Relaxation, →↓ peristalsis • Contraction • ±	 • Contraction,→↓peristalsis • Relaxation • Increased secretion
5. Eye	Pupillary dilatation	Pupillary constriction
6. Kidney	↑Renin production, ↓renal vasoconstriction	±
7. Uterus	Usually contraction in pregnancy and relaxation in nonpregnant uterus	Unpredictable
8. Urinary bladder	Sphincter contraction and detrusor relaxation	Evacuation of bladder
9. Male sex organ	Contraction of the vas and ejaculation	Erection of penis
10. Liver	Glycogenolysis	±
11. Skin • Hair • Sweat glands	 • Piloerection • Sweating	±

[↑ = increase; ↓ = decrease; ± = effect]

NEUROPHARMACOLOGY

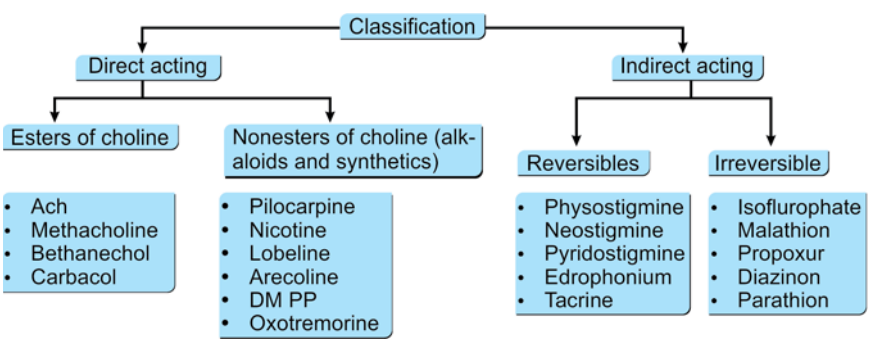
SECTION-II (A) CHOLINERGIC DRUGS

- Definition
- Classification
  a. Direct acting—Acetylcholine
     i. Synthesis
     ii. Storage
     iii. Release
     iv. Binding
     v. Degradation
     vi. Recycling – from point (i to vi) have been discussed in Section I. Here the remaining part of discussion from (vii to xi) is given.
     vii. Mechanism of action of cholinesters
     viii. Pharmacological action
     ix. Drug interactions
     x. Toxic effects
     xi. Contraindications.
  b. Indirect acting—Anticholinesterase
     i. Definition
     ii. Names
     iii. Chemistry
     iv. Mechanism of action
     v. Pharmacological effect
     vi. Physostigmine and Neostigmine—Comparison
     vii. Idea on myasthenia gravis
     viii. Anticholinesterases poisoning
     ix. Management.

DEFINITION

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

CLASSIFICATION



Direct Acting Drugs—Acetylcholine

- **Direct acting**—Drugs are called 'cholinergic agonists'. They (direct acting drugs) combine with AChR (acetylcholine receptor) and act as agonists of AChR.
- **Indirect acting**—The indirect acting drugs inhibit the cholinesterase enzyme and thus increases the stay of ACh in the local region.
- **Reversible binding**—Cholinomimetic drugs bind with enzyme cholinesterase by weak bonds (H-bond, van der Waals bonds). The bond may be broken down.
- **Irreversible binding**—Cholinomimetic drugs bind with enzyme cholinesterase by strong bonds (covalent bond). The bonds may not be broken down.

Mechanism of action of cholinesters

Through activation of muscarinic and nicotinic receptors (Hypothetical mechanisms involved in the combination of an acetylcholine molecule with a muscarinic receptor).

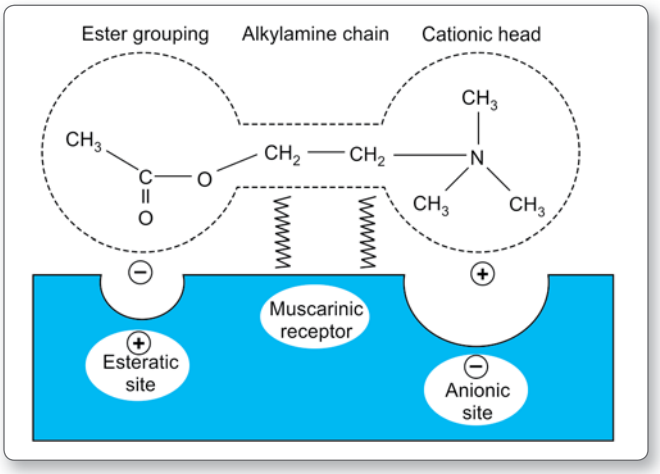


Fig. 6.10: Mechanism of action of cholinesters

Table 6.6 Effects of stimulation of muscarinic receptor

Stimulation of M_1 – receptor	**Stimulation of M_2 – receptor**	**Stimulation of M_3 – receptor**
Increase formation of IP_3 and DAG ↓ Membrane depolarization	Inhibit generation of intracellular cAMP, opens K^+ channels of heart ↓	Increase IP_3 formation Increase intracellular calcium

Contd...

Contd...

Stimulation of M_1–receptor	Stimulation of M_2–receptor	Stimulation of M_3–receptor
↓ Excitatory action (e.g. gastric secretions) ↓ Agonist: Oxotremorine ↓ Antagonist: Pirenzepine	↓ Agonist: Methacholine ↓ Antagonist: Methoctramine	↓ Excitatory action ↓ Agonist: Bethanechol ↓ Hexahydrosila difenidol

Pharmacological action

Muscarinic

1. **Heart**—ACh. hyperpolarizes the SA nodal cells and decreases the rate of diastolic depolarization. As a result rate of impulse generation is reduced, bradycardia or even cardiac arrest may occur. At the AV node and His Purkinje fibers refractory period (RP) is increased and conduction is slowed. PR interval increases and partial to complete AV block may be produced. The force of atrial contraction is markedly reduced and RP of atrial fibers is abbreviated.
2. **Blood vessels**—Blood vessels are dilated, though only few (skin of face, neck) receive cholinergic innervation. Thus fall in BP and flushing, specially in the blush area occurs. Muscarinic receptors are present on vascular endothelial cells. Vasodilatation is primarily mediated through the—(1) release of an endothelium dependent relaxing factor (EDRF). (2) It may also be due to inhibitory action of ACh on NA release from tonically active vasoconstrictor nerve endings.
3. **Smooth muscle**—Smooth muscles in most organ is contracted. Tone and peristalsis in the GIT is increased and sphincters relax—abdominal cramps and evacuation of bowel. Peristalsis in ureter is increased. The detrusor contracts while the bladder, trigone and sphincter relaxes → voiding of bladder.

   Bronchial muscle constrict, asthmatics are highly sensitive → dyspnea, precipitation of an attack of bronchial asthma may occur.
4. **Glands**—Secretion from all parasympathetically innervated glands is increased sweating salivation, lacrimation tracheobronchial and gastric secretion. The effect on pancreatic and intestinal glands is not marked. Secretion of milk and bile is not affected.
5. **Eye**—Contraction of constrictor pupillae → miosis. Contraction of ciliary muscle → spasm of accommodation, increased outflow facility, reduction in intraocular tension. [Contraction of dilator pupillae by sympathetic stimulation causes → mydriasis].

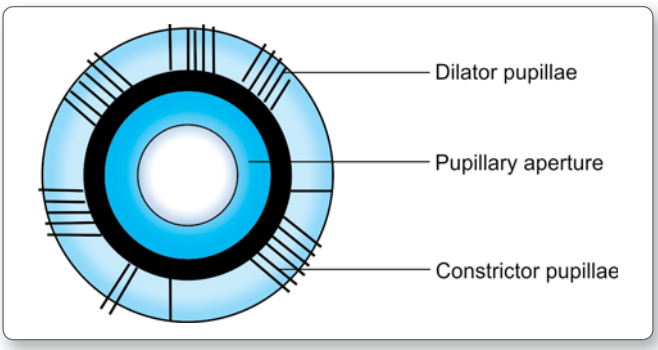


Fig. 6.11: Effects of sympathetic and parasympathetic stimulation on eye

Nicotinic

1. **Autonomic ganglia**: Both sympathetic and parasympathetic ganglia are stimulated. This effect is manifested at higher doses. High dose of ACh given after Atropine causes tachycardia and rise of BP.
2. **Skeletal muscle**: Application of ACh to muscle end plate causes contraction of the fibers, intra-arterial injection of high dose can cause twitching and fasciculation but IV injection is generally without any effect (due to rapid hydrolysis of ACh).
3. **Adrenal medulla**: Nicotine acts on chromaffin cells of adrenal medulla, these cells are homologus to sympathetic ganglia.

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

Drug interactions

Anticholinesterases potentiate action of ACh markedly.

Toxic effects

These are based on the pharmacological actions → flushing, sweating, salivation, cramps, belching, involuntary micturition and defecation, fall in BP, fainting and cardiac arrest may occur.

Contraindications

a. In angina pectoris ←It may reduce coronary flow by causing fall in BP
b. Peptic ulcer←It increases gastric secretion; symptoms are accentuated
c. Bronchial asthma ← It worsened due to bronchoconstriction
d. Hyperthyroidism ← Cardiac arrhythmias may be precipitated.

Uses and dose

Cholinesters are rarely used. ACh is not used because of its diversity and transient action.

Indirectly Acting Drugs—Anticholinesterase

Definition

Anticholinesterases are agents which inhibit ChE, protect ACh from hydrolysis. It produces cholinergic effects in vivo and potentiate ACh both in vivo and in vitro.

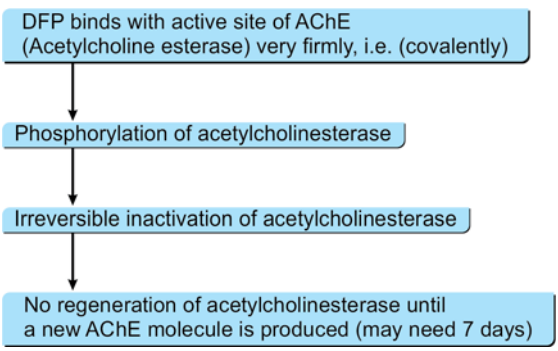
Names

(See in the indirectly acting cholinergic drugs).

Chemistry

Anticholinesterases are either esters of carbamic acid or derivatives of phosphoric acid.

Mechanism of action



Role of pralidoxime—Ageing AChE and DFP bind with eACh other strongly but the bond can be broken by the drug pralidoxime, provided pralidoxime is given sufficient early, i.e. befeore '**agening**' occurs.

Ageing—It means loss of one isopropyl group from the phosphorylated acetylcholinesterase. Once the isopropyl group is lost, pralidoxime fails to break the bond between AChE and DFP. For DFP ageing starts within 6–8 hours but in case of nerve gases may require only a few minutes.

Pralidoxime's action is to reactivate AChE which has been inactivated through phosphorylation by DFP and others. The drug is given by slow IV or infusion in a dose of 1to 2 gm.

Pharmacological effect

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

Physostigmine and neostigmine—Comparison

Points	Physostigmine	Neostigmine
Source	Natural alkaloid, Physostigma, venenosum	Synthetic compound
Chemistry	Tertiary amine	Quaternary compound
Oral absorption	Good	Poor
CNS action	Present	Absent
BBB crossing	Can cross	Cannot due to large size
Corneal penetration	Penetrates cornea	Poor penetration
Action on cholinoceptors	No direct action	Direct action
Prominent action	Autonomic effector	Skeletal muscle
Important use	Miotic (glaucoma)	In myasthenia gravis
Duration of action	Systemic (4 to 6 hour) in eye—6 to 24 hours	3 to 4 hours

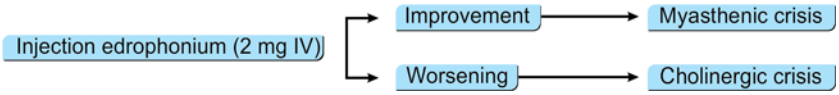
Idea on myasthenia gravis

It is an autoimmune disorder due to development of antibodies directed to nicotinic receptors at the muscle end plate → reduction in number of NM cholinoceptors and structural damage to the neuromuscular junction → weakness and easy fatigue ability. Neostigmine and its congeners improve muscle contraction by allowing ACh released from prejunction endings to accumulate and act on receptor over a larger area, and by directly depolarizing the end plate.

Treatment: It is usually started with neostigmine 15 mg orally 6 hourly dose and frequency is then adjusted according to response. Corticosterod is afford considerable improvement in such cases by their immunosuppressant action, but their long-term use has problems of its own.

Thymectomy produces gradual improvement in majority of cases. Even complete remission can be achieved. It is becoming increasingly popular. Overtreatment with anti AChEs also produce weakness by causing persistent depolarization of muscle end plate, this is called cholinergic crisis or weakness.

The two types of weakness require opposite treatments. They can be differentiated by edrophonium test.



Anticholinesterase poisoning

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

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

1. Irritation of eye
2. Lacrimation
3. Salivation
4. Sweating
5. Copious tracheobronchial secretion
6. Miosis
7. Blurring of vision
8. Breathlessness
9. Colic
10. Involuntary defecation and urination
11. Fall in BP
12. Tachycardia
13. Cardiac arrhythmias
14. Vascular collapse
15. Muscular fasciculations
16. Weakness
17. Respiratory paralysis
18. Excitement
19. Ataxia
20. Convulsions
21. Coma and death.

Management

General

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

Specific

1. **Atropine** is highly effective in counteracting the muscarinic symptoms, but higher doses are required to antagonize the central effects. All cases of anti ChE poisoning must be promptly given atropine 2 mg IV repeatedly every 10 minutes till pupil dilates (upto 100 mg has been administred in a day).
2. **Cholinesterase reactivators** These are used to restore neuromuscular transmission in case of organophosphorus anti ChE poisoning. The phosphorylated ChE reacts very slowly or not at all with water. However, if more reactive OH groups in the form of oximes is provided, reactivation occurs more than a million times faster.

Pralidoxime (2-PAM) has a quaternary nitrogen: Attach to the anionic site of the enzyme which remains unoccupied in the presence of organophosphate inhibitors. Its oxime end reacts with the phosphorus atom attached to the esteratic site; the oxime phosphonate so formed, diffuses away leaving the reactivated AChE. It is ineffective as antidote to carbamate anti AChEs (Physostigmine, Neostigmine, Carbamyl, Propoxur) in which case the anionic site of the enzyme is not free to provide attachment to Pralidoxime. It is rather contraindicated in Carbamate poisoning because not only it does not reactivate Carbamylated enzyme, it has weak anti AChE activity of its own. Pralidoxime causes more marked reactivation of skeletal muscle AChE, than at autonomic sites and not at all in CNS. Rx should be started as early as possible, before the phosphorylated enzyme has undergone '**ageing**' and become resistant to hydrolysis. Doses may be repeated according to need.

Other oximes are Obidoxime (more potent than Pralidoxime) and Deacetyl monooxime (DAM). DAM lacks quarternary nitrogen and is lipophilic. It combines with free organophosphate molecule in the body fluids, rather than with those bound to the ChE. It is therefore, less effective, but reactivates ChE in the brain as well.

SECTION-II (B) ANTICHOLINERGIC DRUGS

- Introduction
- Classification
- Site of action
  - Antimuscarinic – Atropine
    - Source
    - Mechanism of action
    - Pharmacological action
    - Clinical uses
  - Antinicotinic
    - Ganglion blocker—It is used is obsolete nowadays.
    - Neuromuscular blocker

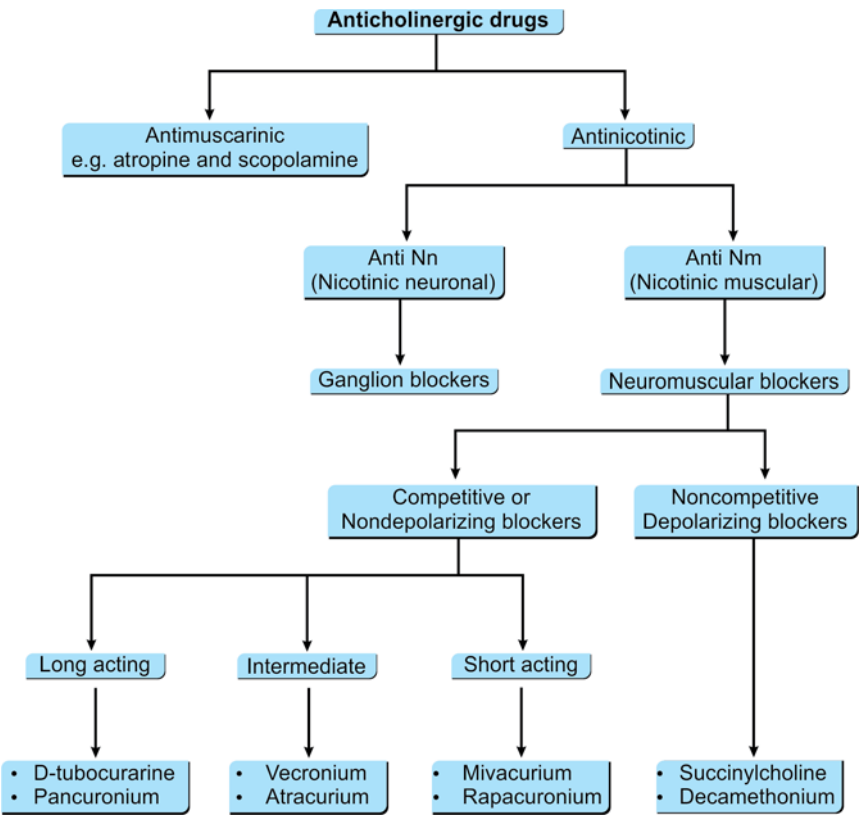
a. Definition
b. Properties
c. Mechanism of action
d. Difference between competitive and noncompetitive blockers
e. Toxicities of succinylcholine and their management.

INTRODUCTION

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

Atropine, the prototype drug of this class, is highly selective for muscarinic receptors. All anticholinergics are competitive antagonists.

CLASSIFICATIONS



SITE OF ACTION

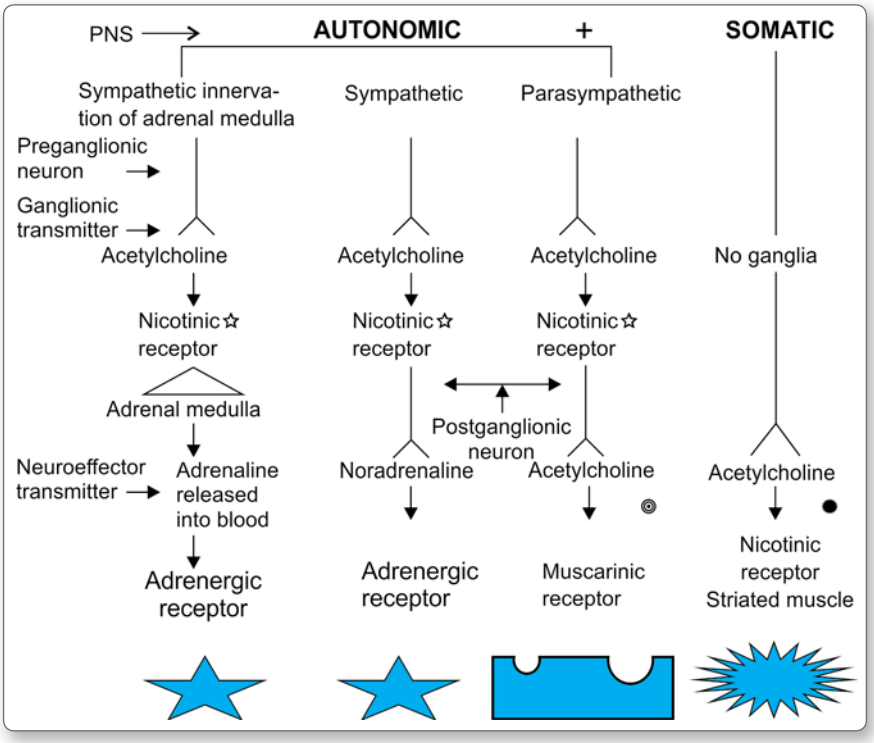


Fig. 6.12: Site of action of ganglionic blockers, antimuscarinic and neuromuscular blockers

Antimuscarinic—Atropine

Source

Atropa belladonna.

Mechanism of action

ACh binds with the M-receptor in the effector cell and increases the intracellular concentration of cGMP. Atropine (as well as hyoscine) binds with the M-receptors, but does not do anything more. That is cGMP concentration within the cell does not rise and therefore concentration of intracellular Ca^{++} does not rise so → no contraction of smooth muscle or glandular secretion occurs following atropine. Further, M-receptors remain occupied and hence ACh cannot act.

Pharmacological actions

1. **CNS**: It has an overall CNS stimulant action. It stimulates many medullary centers, i.e. vagal, respiratory and vasomotor. It depresses

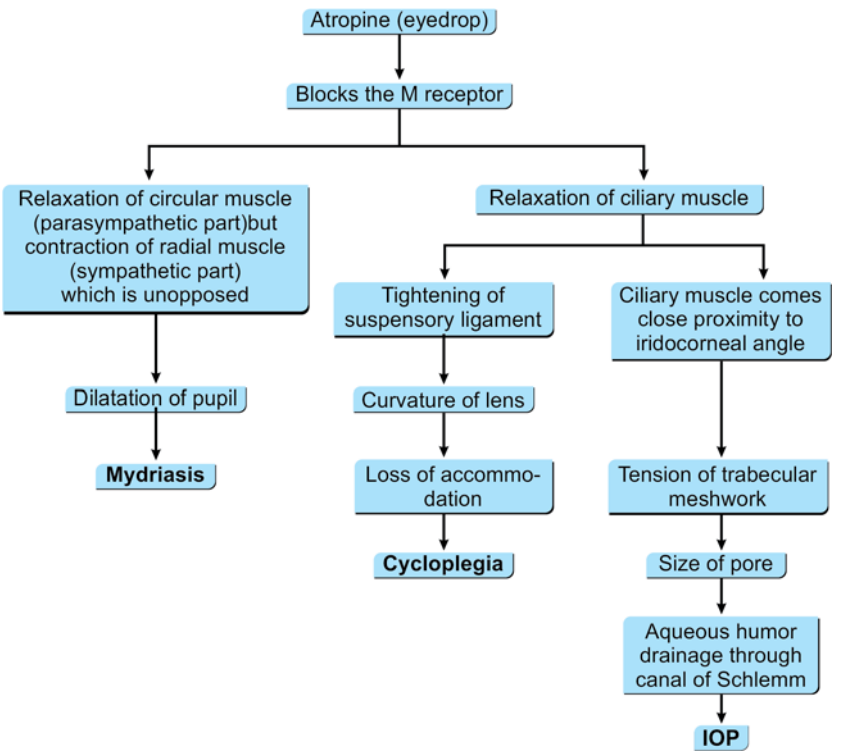
vestibular excitation and has antimotion sickness property. The site of this action is not clear. By blocking the relative cholinergic overactivity in basal ganglia, it suppresses tremor and rigidity of parkinsonism. Majority of the central actions are due to blockade of muscarinic receptors in the brain, but some actions may have a different basis.

2. **CVS**:

a. **Heart**: The prominent effect of atropine is to cause tachycardia. It is due to blockade of inhibitory vagal impulses to the SA node. Higher the existing vagal tone—more marked is the tachycardia. After IM or SC injection transient initial bradycardia may occur due to stimulation of vagal center. Atropine facilitates AV conduction, specially if it has been depressed by high vagal tone and reduces PR interval.

b. **BP**: As cholinergic agent they are not involved in maintenance of vascular tone, atropine does not have any consistent or marked effect on BP tachycardia and vasomotor center stimulation tends to raise BP while histamine release and direct vasodilatation tends to lower BP.

3. **Eye**: Topical installation of atropine causes **mydriasis**, abolition of light reflex and **cycloplegia** lasting 7 to 10 days. This result in photophobia and bluffing of near vision. The **intraocular tension tends to rise**, specially in narrow angle glaucoma.



4. **Respiratory system**: Parasympathetic stimulation causes bronchoconstriction and bronchial secretion. Atropine therefore, ceases bronchodilation and drying of bronchial secretion.
5. **Exocrine glands**: Exocrine glands (salivary, glands of the stomach GIT and so on) produce more secretion when parasympathetic stimulation occurs. Atropine thus opposes this secretion.
6. **GIT**:
a. Salivary secretion is stopped dryness of the mouth results.
b. Gastric secretion is reduced. Telenzepine and Pirenzepine are more effective antimuscarinic drugs (than atropine) that can reduce gastric acid secretion. Without producing dryness of mouth or constipation.
c. Motility of the GIT from stomach to colon is reduced. This causes constipation.
7. **Sweating**: Sweat glands (eccrine) are supplied by sympathetic fibers which are cholinergic. Atropine thus prevents sweating due to rise in environmental temperature leading to rise in body heat.
8. **Urinary tract**: Smooth muscles (detrusor) of the bladder contract when there is parasympathetic stimulation. Atropine therefore, causes relaxation of bladder muscle and may precipitate retention of urine in persons suffering from BHP (benign hypertrophy of prostate).
9. **Body temperature**: Rise in body temperature occurs at higher doses. It is due to both inhibition of sweating and stimulation of temperature regulating center in hypothalamus. Children are highly susceptible to Atropine fever.

Clinical uses

1. **As antisecretory**
    a. **Preanesthetic medication → drug of choice → Atropine**
        1. To check increased salivary and tracheobronchial secretions.
        2. To prevent halothane induced NA- mediated ventricular arrhythmias, which are specially prone to occur during vagal slowing.
        3. It prevents laryngospasm by reducing respiratory secretions that reflexly predispose to laryngospasm.
        4. Vagal attack during anesthesia may also be prevented.
    b. **Peptic ulcer**: Atropine decreases gastric secretion and afford symptomatic relief in peptic ulcer. They have now been largely superseded by specific H_2 blockers → Pirenzipine is the drug of choice.
2. **As antispasmodic** → Hyoscine is the drug of choice
    a. Intestinal and renal colic, abdominal cramps, symptomatic relief is afforded, if there is no mechanical obstruction.

b. Nervous and drug-induced diarrhea → effective in functional diarrhea but not infective diarrhea.
c. Spastic constipation and irritable colon.
d. To relieve urinary frequency and urgency, enuresis in children.
e. To control pylorospasm, gastric hypermotility, gastritis and nervous dyspepsia.
f. Dysmenorrhea.

3. **Bronchial asthma, asthmatic bronchitis** → Ipratropium bromide is the drug of choice.

Atropinic drugs are bronchodilators but less effective than adrenergic drugs. It has additive bronchodilator effect with adrenergic drugs and theophylline. Thus, it has a place in the management of COPD.

4. **As mydriatic and cycloplegic** → Tropicamide is the drug of choice.

For testing error of refraction both mydriasis and cycloplegia are needed. Homatropine is most commonly used in adults because if its brief action. Atropine is very valuable in the treatment of iritis, irridocyclitis, choroiditis, keratitis and corneal ulcer. It gives rest to the intraocular muscles and cuts down their painful spasm.

5. **As cardiac vagolytic** → Atropine is the drug of choice.

Atropine is useful in counteracting bradycardia and partial heart block in selected patients, where increased vagal tone is responsible.

6. **For central action**
   a. Parkinsonism → Procyclidine hydrochloride is the drug of choice.
   b. Motion sickness → Hyoscine is the most effective drug for motion sickness.
7. **To antagonize muscarinic effects of drugs and poisoning**

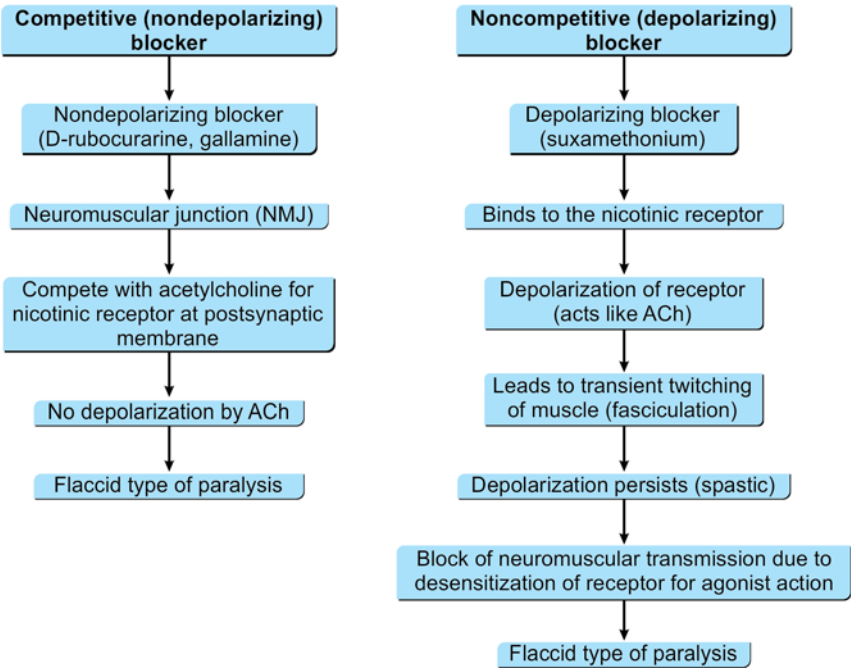
Atropine is the specific antidote for acetylcholine (ACh) and mushroom poisoning.

Antinicotinic Drugs

1. **Ganglionic blockers**—Obsolete nowadays
2. **Neuromuscular blockers**
   a. **Definition**: Drugs which block the transmission of nerve impulse at the neuromuscular junction are called neuromuscular blockers. They are also called skeletal muscle relaxants.
   b. **Properties**:
      i. All nondepolarizing blockers have to be given IV.
      ii. Their onset of action is quick, within a few minutes. However, the onset is quickest with Rocuronium.
      iii. March of paralysis—Fast response muscle is face and diaphragm is the last muscle to be paralyzed.
      iv. Need of Neostigmine—After the operation is over Neostigmine may be given to terminate the effects of the blockers.
      v. Histamine release—d-TC can cause good deal of histamine release.

vi. Ganglion blocking—d-TC can block the Nn of AChR in the ganglia.
vii. Fall of BP—Due to ganglion blocking and histamine release.

Mechanism of action



Differences between competitive and noncompetitive blockers

Points	Nondepolarizing blockers	Depolarizing blockers	
		Phase I	Phase II
Presence of twitch	Nil	Fasciculation	Nil
Mode of action	Competitive antagonist	Prolonged depolarization	Nonsensitivity of motor end plate
Effect of neostigmine	Antagonistic	Augmentation	Antagonistic
Histamine release	Some compounds release and others do not	No relation with histamine release	

Contd...

Contd...

Points	Nondepolarizing blockers	Depolarizing blockers	
		Phase I	**Phase II**
Effect of d-TC addition	Additive	Antagonistic	Augmented
Duration of action	Variable: Long acting	Short acting	
Effect on CVS	Present with some	Cardiac arrhythmia can occur	
Malignant hyperthermia	Nil	Can occur	
Hyperkalemia	Nil	Can occur	
Prototype	d-tubocurarine	Succinylcholine	
Recent use	Obsolete	Other congeners are used	
Toxicities (as a whole)	More	Less	
Lipid solubility	No	(+ve)	

c. **Toxicities of succinylcholine and their management**:

1. Hyperkalemia → cardiac arrest — It can cause, in some patients sudden rise of potassium concentration in the plasma → sufficiently high to produce fatal cardiac arrest.
2. Mailgnant hyperthermia → It is likely to occur particularly when a combination of halothane and succinylcholine is used. However, the condition is rare.

In malignant hyperthermia, the body temperature of the patient rises sharply due to rigidity (sustained contraction) of the skeletal muscles. The contracting muscles produce excessive heat.

Treatment: i. 100% O_2 inhalation, ii. ice packing, iii. injeciton of Dantrolene.

3. Prolonged effect: The effect of succinylcholine can be prolonged, particularly in following conditions:
   a. In the rare congenital condition of pseudocholinesterase deficiency – diaphragmatic paralysis is particularly dreaded.
   b. In presence of hepatic insufficiency. Recall, liver is one of the sources of pseudocholinesterase.

Treatment: Fresh blood transfusion is the treatment as it contains the enzyme pseudocholinesterase.

SECTION-II (C) ADRENERGIC OR SYMPATHOMIMETIC OR SYMPATHETIC DRUGS

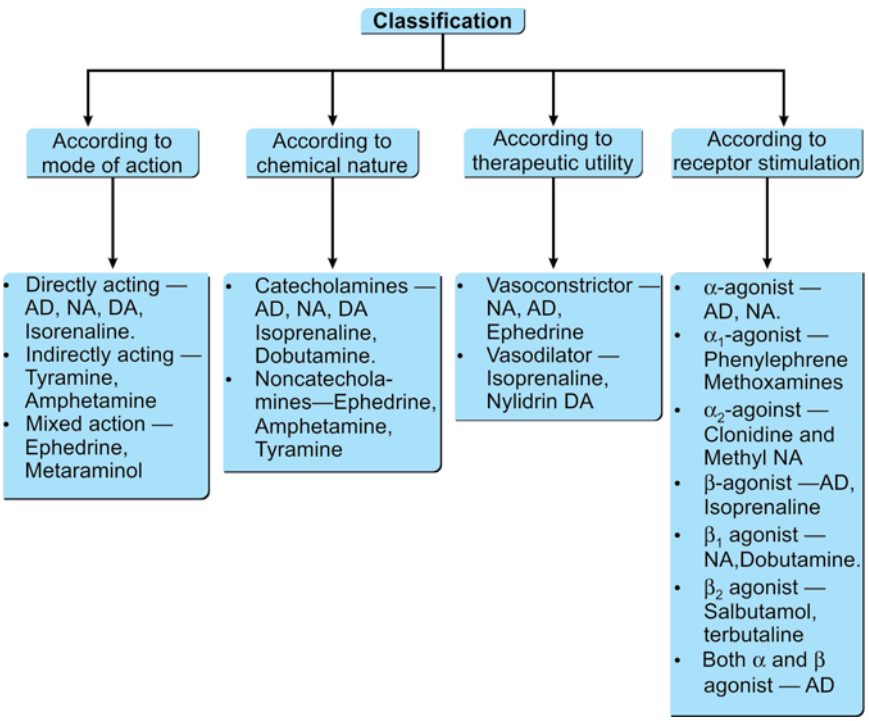
- Definition
- Classification — With basis

- Neurotransmission – a. Synthesis
  b. Storage
  c. Release
  d. Reuptake
  e. Metabolism of catecholamines – (a to e) have been discussed in section-I
- Effect of stimulation of adrenergic receptors
- The overall actions
- Clinical use

DEFINITION

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

CLASSIFICATION



EFFECT OF STIMULATION OF ADRENERGIC RECEPTORS

1. **α_1-receptor, after combining with the agonist**—It produces, within the cytosol, IP_3 and DAG and virtually increased intracellular Ca^{++} ions this→ultimately leads the biological effect (e.g. vasoconstriction).

2. α_2-receptor, after combining with the agonist, causes decreased production of cytosolic cAMP → leading to biologic effect (= inhibition of NA release by the presynaptic membrane, inhibition of insulin release).
3. β_1-receptor, after combining with the agonist, causes increased cAMP in the cytosol → biological effect (e.g. tachycardia), renin secretion).
4. β_2-receptor, after combining with its agonist → causes increased cytosolic cAMP → biologic effect (e.g. bronchodilatation).

THE OVERALL ACTIONS

1. **Heart rate**—It is increased, i.e. (+ve) chronotropic action, force of contraction is increased, i.e. (+ve) ionotropic action.
2. **Blood vessel—**Both vasoconstriction (α) and vasodilatation (β_2) can occur, depending on the drug, its dose and vascular bed. Vasoconstriction occurs through both α_1-and α_2-receptors. Constriction predominates in cutaneous, mucous membrane and renal vessels. Dilatation predominates in skeletal muscles, liver and coronaries. Receptors are activated only by circulating CAs, whereas α-receptors primarily mediate responses to neuronally released NA.
3. **BP**—The effect depends on the amine, its dose and route of administration. NA causes rise in systolic, diastolic and mean BP. It does not cause vasodilatation (no β_2 action) peripheral resistance increases consistently due to action.

   ISO causes rise in systolic but marked fall in diastolic BP (β_1-cardiac stimulation, β_2-vasodilatation). The mean BP generally falls

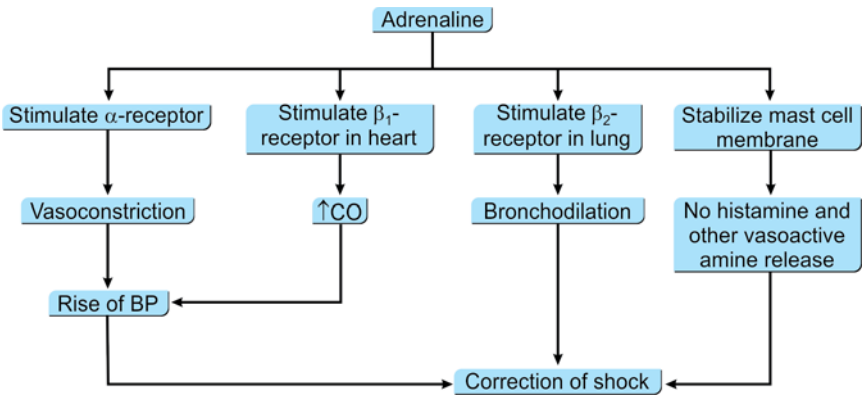
   AD given slow IV infusion or SC injection causes rise in systolic but fall in diastolic BP. Peripheral resistance decreases because vascular β_2-receptors are more sensitive than α-receptors. Mean BP generally rises. Pulse pressure is increased. Rapid IV injection of AD produces a marked increase in both systolic as well as diastolic BP (at high conc. a response predominates and vasoconstriction occurs even in skeletal muscles). The BP returns to normal within a few minutes and a secondary fall in mean BP follows rapid uptake and dissipation, conc. of AD is reduced low conc. are not able to act on α-receptors but continue to act on β_2-receptors.

   When an α-blocker has been given, only fall in BP is seen—**vasomotor reversal of Dale**.
4. **Respirations**—AD and Iso, are potent bronchodilators but not NA. This action is more marked when bronchi are constricted, AD given by acrosol also decongests bronchial mucosa by α action. AD can directly stimulate respiration center but this action is seldom manifest. Bronchodilation by AD is mainly due to β_2 stimulation.
5. **Eye**—Mydriasis occurs due to contraction of radial muscles of iris, the intraocular tension tends to fall; vasoconstriction results decreased aqueous formation and uveoscleral outflow may be increased.

6. **GIT**—Peristalsis is reduced and sphincter are constricted but the effects are brief and of no clinical importance.
7. **Bladder**—Detrusor is relaxed and trigone is constricted tends to inhibit micturition.
8. **Uterus**—Effect of AD varies with species, hormonal and gestation status.
9. **Splenic capsule**—Contracts and more RBCs are poured in circulation. This action is not evident in man.
10. **Skeletal muscle**—Neuromuscular transmission is facilitated through both α and β actions. Release of ACh is enhanced. The direct effect on muscle fiber is exerted through β_2-receptors and differs according to the type of fiber.
11. **CNS**—AD in clinically, used doses not produce any marked CNS effects; because of poor penetration in brain, but restlessness, apprehension and tremor may occur. Injected in the brain, it produces excitation followed by depression. Activation of β_2 receptors in the brainstem results in decreased sympathetic outflow → fall in BP and bradycardia.
12. **Metabolic**—AD produces important metabolic effects. The β actions are mediated through cAMP. This in turn, phosphorylates a number of intracellular cAMP dependent protein kinases and initiates a series of reaction. In the liver and muscle glycogen phosphorylase is activated causing glycogenolysis and glycogen synthetase is inhibited.

CLINICAL USE

1. **Treatment of anaphylactic shock (adrenaline)**

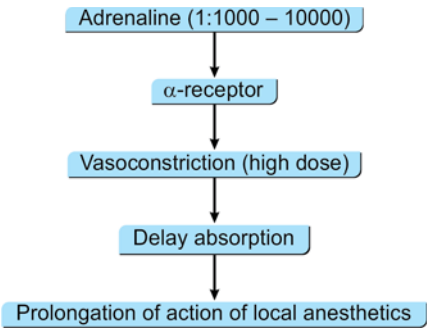


2. **Treatment of cardiogenic shock (Dopamine)—**
   a. Dopamine acts on heart and causes ↑ HR and ↑ force of contractions → So rise of CO and elevation of BP.
   b. It dilates the renal blood vessels by acting on dopamine receptor, so there is no chance of kidney damage.

c. Vasodilation of blood vessel of other vital organs. That is why, Dopamine is used clinically.

3. **Treatment of severe bronchial asthma (Salbutamol)—**
In acute severe-life threatening bronchospasm due to asthma, AD can be used (AD is not used in chronic asthma or where even in acute attack there appears no threat of life, because many good bronchodilators are available which do not have the toxicities of AD like arrhythmia → death). AD injection, if necessary, can be repeated after few hours.

4. **To prolong local anesthetic effects (adrenaline)—**
Adrenaline help in local anesthesia by following ways:



5. **To control local bleeding (epistaxis)**: Adrenline pack is used.
6. **As nasal decongestant (Oxymetazoline, Xylometazoline)—**
In nasal congestion, there is vasodilatation and edema of nasal mucosa. Nasal decongests cause vasoconstriction and they are also antisecretory. So effective in rhinitis, common cold.

SECTION-II (D) ANTIADRENERGIC DRUGS

- Definition
- Difference between receptor and neuron blockers
- Classification of adrenoceptor blockers

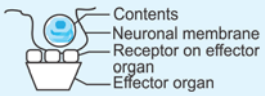
a. α-blockers
   - Definition
   - General effect of α-blockers
   - Therapeutic uses

b. β-blockers
   - Definition
   - Selectivity
   - General effect
   - Individual blocker – Propranolol
     a. Pharmacological action and clinical uses
     b. Difference between propranolol and atenolol
     c. Contraindications
     d. Drug interactions.

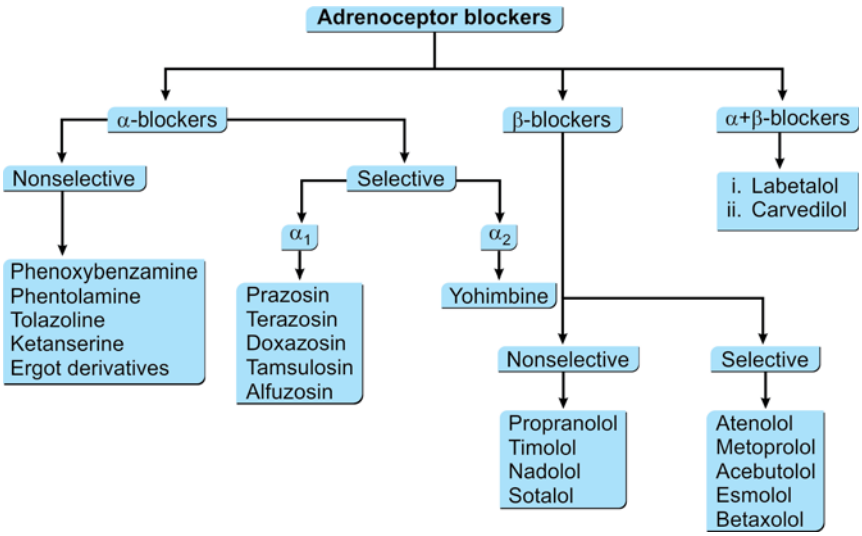
DEFINITION

These are drugs which antagonize the receptor action of adrenaline and related drugs. They are competitive antagonists at α-or β-receptors and differ in important ways from the adrenergic neuron blocking agents. The differences between the two groups are as follows:

Difference between receptor and neuron blockers

Points	Antiadrenergic drugs	Adrenergic neuron blockers
Leveling		
Site of action	Adrenergic receptors on effector cells or neurons	Adrenergic neuronal membrane or contents
Effects of injected adrenaline	Blocked	Not blocked
Effects of adrenergic nerve stimulation	Blocked (less completely)	Blocked (more completely)
Type of effects blocked by a single drug	Either α or β (except labetalol)	Sympathetic function is decreased irrespective of receptor type
Examples	α-Phentolamine β-Propranolol	Reserpine guanethidine bretylium α methyl tyrosine

CLASSIFICATION OF ADRENOCEPTOR BLOCKERS



α-Blockers

Definition

These drugs inhibit adrenergic responses mediated through the adrenergic receptors without affecting those mediated through β-receptors.

General effect of α-blockers

1. Blockade of α-(vasoconstrictor) receptor → reduction of peripheral resistance → pooling of blood in capacitance vessels → reduction of venous return and cardiac output → fall of BP → postural reflex interfered → marked hypotension occurs (on standing) → dizziness and syncope.

   Hypovolemia accentuates the hypotension.They block pressor action of adrenaline which then produces only fall in BP due to β-mediated vasodilatation - Vasomotor reversal of dale, pressure and other actions of selective α-agonists (NA phenylephrine) are also antagonized.
2. **Reflex tachycardia**—It occurs due to fall in mean arterial pressure and increased release of NA due to blockade of presynaptic α_2-receptor.
3. **Nasal stuffiness and miosis**—It results from blockade of α-receptors in nasal blood vessels and in radial muscles of iris respectively.
4. **Intestinal motility**— It is increased due to partial inhibition of relaxant sympathetic influences—Diarrhea may occur.
5. **Hypotension pruduced by α-blockers**—It can reduce renal blood flow → (GFR is reduced and more complete reabsorption of Na^+ and water occurs in the tubules — Na^+ retention and increase in blood volume).
6. **Contraction of vas deferens and related organs**—Which result in ejaculations, are coordinated through α-receptors and α-blockers can inhibit ejaculation, this may manifest as impotence.

Therapeutic uses

1. Chronic hypertension—Prazosin, Trazosin and Doxazosin are used as antihypertensives.
2. Hypertensive emergencies—Phentolamine may be used, safer drugs are now available.
3. BPH – Currently, it is used as guidelines of treatment includes:
   a. Symptom free but big size of the prostate no treatment is needed
   b. If there is complications, surgical treatment is needed
   c. For rest of the case medical treatment is needed.

i. 5 α-reductase inhibitor—Its regular use can cause shrinkage of the volume of prostate.
ii. Selective α_1-inhibitors—This drugs reduced the tone of the smooth muscles at the urinary bladder outlet and prostatic urethra → leading to reduction of the resistance against urinary flow.

β-Blockers

Definition

These drugs inhibit adrenergic responses mediated through the β-receptors.

Selectivity

Selective β_1-blockers are also called cardioselective β_1-blockers, because their effects are almost wholly confined to heart. On the other hand, nonselective β-blockers block both β_1-and β_2-adrenoceptors.

General effect

1. On CVS

i. They reduce the heart rate to produce bradycardia. Bradycardia occurs because of β_1-blocking effects on SAN, AVN and atrial muscles.
ii. Reduce contractility of heart, thereby fall of cardiac output. Cardiac contractility falls because of fall of contractility of myocardium.
iii. Reduce BP in hypertension. How the BP falls in hypertension have been discussed in antihypertensive drugs.

2. On respiratory system: Nonselective β-blockers can produce bronchoconstriction particularly in the asthmatics and other patients suffering from COPD.

3. On eye: Some β-blockers notably, timolol is used as an antiglaucoma drug.

4. Metabolic effect: They can influence both lipid and glucose metabolism. Long-term use of nonselective β-blockers can increase the serum triglycerides and decrease serum HDL. β-blockers block the glycogenolytic effects of adrenaline and reduces glucagon secretion, in hypoglycemia of diabetic patients who are under treatment of insulin or oral hypoglycemic agents.

Individual blocker–propranolol

Pharmacological action and clinical uses

1. CVS

a. **Heart**—Effects are—1. bradycardia, 2. fall of cardiac output, and 3. ECG changes include lengthening of PR interval. All these are due to blocking effect.

b. **BP and peripheral resistance** — Chronic use of β-blockers reduce BP in hypertensives. β-receptors are present in 1. heart 2. juxtaglomerular apparatus of kidney. β-blocking therefore, could lead to bradycardia + reduction of contractility—reduction of CO → fall of BP.

Another major effect of β-blocking is lack of angiotensin Il → fall of body Na^+ concentration and fall of BP.

c. **Angina** —
   1. β-blockers reduce O_2 demands of heart by reducing sympathetic activity on the heart.
   2. They particularly reduce the exercise induced tachycardia, so that chance of angina during effort is reduced.
   3. They reduce the renin angiotensin axis activity; angiotensin II activity is reduced.
   4. They are antihypertensive, which results in reduction of afterload, which inturn contributes to the mechanism of reduction of myocardial O_2 demand.

d. **Cardiac arrhythmia** —
   1. Direct effect → seen with propranolol might have a role, propranolol inhibits Na^+ entry and favors K^+ exit from the cell — leading to the membrane stabilizing effects.
   2. Indirect effect → propranolol acts principally at 4 sites,
      a. SAN, b. AVN, c. His-Purkinje system, and d. working myocardial cell (WMC).

On SAN—The slope of the pacemaker potential becomes flatter → more time is required to reach the firing level, i.e. automaticity delayed. On AVN—The refractory state duration is prolonged → conduction velocity delayed → prevents reentry in the AVN, thus PSVT due to reentry, occurring within the AVN stopped. When it fails to stop AVN entry, there reduces the ventricular rate by producing a partial block at AVN so that the ventricles are spared to some extent.

On His-Purkinje system → delayed automaticity and decreased responsiveness inhibits ectopic focus and triggered activity.

On working myocardial cell (WMC) → it reduces contractile power and has no direct relevancy to its antiarrhythmic property.

e. **Myocardial infarction** (MI) → In MI, β-blockers have been used for two purposes—
   1. Secondary prophylaxis of MI.
      a. By preventing reinfarction.
      b. By preventing sudden ventricular fibrillation during attack of MI.
   2. Myocardial salvage during evolution of MI.
      a. It may limit infarct size by reducing O_2 consumption → marginal tissue, which is particularly ischemic may survive.
      b. It may prevent arrhythmias including ventricular fibrillation.

f. **Pheochromocytoma**—It may be used to control tachycardia, but should not be used unless α-blockers has been given before, otherwise dangerous rise in BP can occur.

g. **Thyrotoxicosis**—It controls symptoms of (palpitation, nervousness, tremor, fixed stare, severe myopathy and sweating) without significantly affecting thyroid status).
   It inhibits peripheral conversion of T_4– T_3 and highly valuable during thyroid storm.

h. **Migraine**—It is the most effective drug for chronic prophylaxis of migraine.

i. **Anxiety**—It exerts an antianxiety effect specially under condition which provoke nervousness and panic, i.e. examination, unaccustomed public appearance.

j. **Essential tremor**—It is also one of the indications.

k. **Glaucoma**—Timolol and Betaxolol are effective and well-tolerated drugs for chronic simple glaucoma; reduce aqueous formation.

l. **Hypertrophic subaortic stenosis**—β-blockers improved CO in these patients during exercise.

Table 6.7 Difference between propranolol and atenolol

Points	Propranolol	Atenolol
Specificity	Nonselective	Cardioselective
Lipid solubility	More	Less
BBB	Can cross	Cannot cross
Bioavailability oral bioavailability	Less 30%	More 50% – 60%
First pass metabolism	Yes	No
Major route of elimination	Hepatic	Renal

Contd...

Contd...

Points	Propranolol	Atenolol
Plasma half-life	3–5 hours	6–9 hours
Dose	40–480 mg/day	50–100 mg/day
Uses in COPD and DM	Risky	Safe
CNS adverse actions	Present	Absent
Membrane stabilizing effect	More (++)	Less (+)
Use in thyrotoxicosis and anxiety	Preferred	Not used

Contraindications

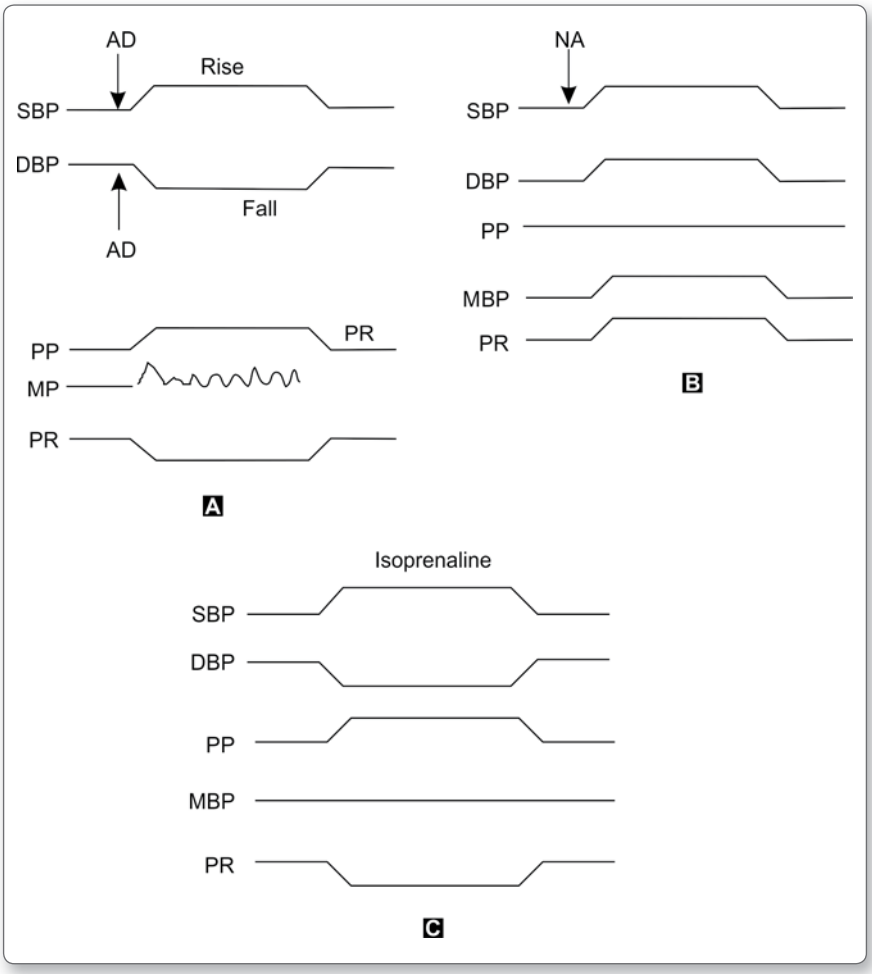
1. **CHF**—It accentuates myocardial insufficiency; can precipitate by blocking sympathetic support to the heart. Propranolol induced chronic reduction in CO results in Na^+ and water retention (due to hemodynamic adjustments) but frank edema occurs only in patients with reduced cardiac reserve.
2. **Bradycardia**—Resting HR may be reduced to bradycardia or less.
3. **COPD**— β-blockers worsens chronic obstructive lung diseases, they can precipitate an attack of bronchial asthma.
4. **Variant (Prinzmetal) angina**—It may be aggravated, due to unopposed α-mediated coronary constriction.
5. **Diabetes mellitus**—It prolongs insulin induced hypoglycemia. At the same time symptoms of hypoglycemia is blocked.
6. **Plasma-lipid profile**—It is altered on long-term use. Total triglycerides and LDL—cholesterol tends to increase while HDL—Cholesterol falls. This may enhance risk of coronary artery diseases.
7. **Heart block**—It is contraindicated in partial and complete heart block—Arrest may occur.
8. **Cold hand and feet**—Worsening of peripheral vascular diseases are noticed due to blockade of vasodilator β_2-receptors.

Drug interactions

1. Digitalis+Propranolol → additive depression of sinus node and AV conduction, cardiac arrest may occur.
2. Insulin+Propranolol → it delays recovery from hypoglycemia to insulin.
3. Phenylephrine, Ephedrine → it can cause marked rise in BP due to blockade + Propranolol of sympathetic vasodilatation.
4. Cimetidine + Propranolol → inhibition of metabolism of Propranolol.
5. Lidocaine+Propranolol → it reduces metabolism of Lidocaine by reducing hepatic blood flow.
6. Chlorpromazine+Propranolol → it increases bioavailability of Chlorpromazine by decreasing the first pass metabolism.

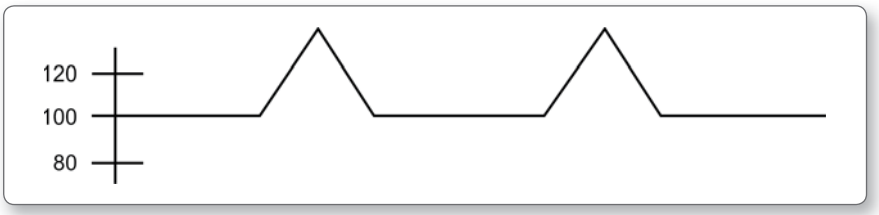
SECTION-II (E) CHYMOGRAPHIC TRACINGS

1. Effect of a. Adrenaline, b. Isoprenaline, and c. Noradrenaline on blood pressure



AD = Adrenaline
NA = Noradrenaline
SBP = Systolic blood pressure
DBS = Diastolic blood pressure
PP = Pulse pressure
MBP = Mean blood pressure
PR = Peripheral resistance

2. Action of Adrenaline on Blood Pressure



Description

This is a Brodie's kymographic tracing showing the effect of adrenaline on blood pressure of a pentobarbitone anesthetized cat. Drug was given by the way of cannulated external jugular vein. After recording of normal mean arterial pressure a dose of Adrenaline was given and a rise of blood pressure was observed. When blood pressure had returned to the baseline then a same dose of Adrenaline was given for the confirmation of the previous dose and the same effect was observed.

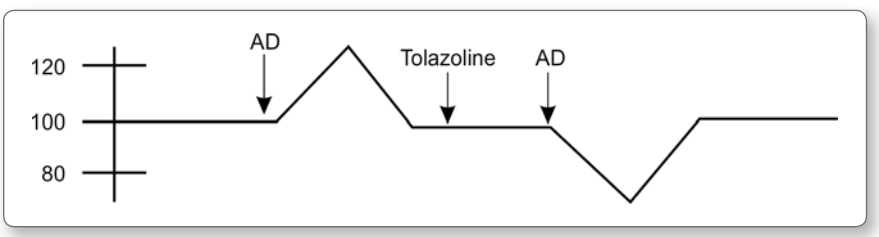
Explanation

Adrenaline raises blood pressure by—

a. Stimulating α-receptors which causes visceral and cutaneous vasoconstriction.
b. Stimulating β-receptors in heart, which increases the force of contraction and heart rate. This action causes an increase in CO and ↑BP (BP = CO × PR).

Blood pressure came to the baseline due to reuptake, metabolic degradation of Adrenaline by MAO and COMT and dilution of the drug by the body fluids.

3. Action of Adrenaline and Tolazoline on Blood Pressure



Description

This is a Brodie's kymographic tracing showing the effects of Adrenaline and Tolazoline on mean blood pressure of a pentobarbitone anesthetized cat preparation. Drugs were given by the way of cannulated external jugular vein. After recording normal mean arterial pressure a dose of Adrenaline was given and rise of blood pressure with secondary fall

was observed. When the blood pressure had returned to normal then a dose of Tolazoline was given and slight increase of blood pressure was observed, when the blood pressure had returned to normal then previous dose of Adrenaline was given. It was found that Adrenaline preceded by a adequate dose of Tolazoline would cause a fall of BP.

Explanation

Adrenaline raises BP by—

a. Stimulating α-receptors which causes visceral and cutaneous vasoconstriction, so rise of peripheral resistance.
b. Stimulating β_1-receptor in heart which increased force of contraction and heart rate. This action caused an increase in CO and BP.

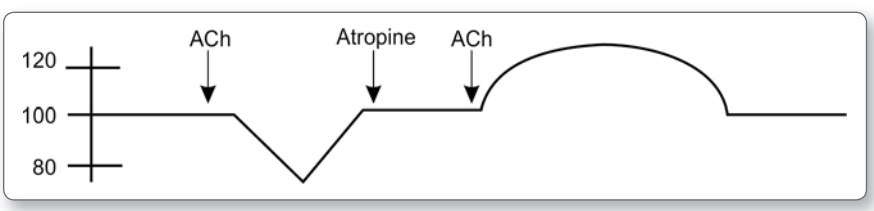
Blood pressure came to the baseline due to reuptake, metabolic degradation of Adrenaline by MAO and COMT and dilution by the body fluids.

Secondary fall of BP was due to stimulation of β_2-receptors at lower concentration.

Slight rise of BP after administration of Tolazoline was due to incomplete or partial blockage of α-receptors and direct cardiotonic action of Tolazoline as it is an imidazole ring containing drug.

Fall of BP by Tolazoline was due to complete blockage of α-receptors and stimulation of only β_2-receptors resulting coronary and muscular vasodilation. This phenomenon is called "**Vasomotor reversal of Dale**". Tolazoline has also histamine-like direct vasodilating action.

4. Action of Acetylcholine and Atropine on Blood Pressure



Description

This is a Brodie's kymographic tracing showing the effects of ACh and Atropine on BP of a pentobarbitone anesthetized cat preparation. Drugs were given by the way of cannulated external jugular vein. After recording a normal mean arterial blood pressure a dose of acetylcholine was given and a fall of BP with secondary rise was observed. When the BP had returned to normal then a dose of Acetylcholine was given for confirmation of the 1st dose and less fall of BP was observed. When the BP had returned to normal a dose of Atropine was given and there was no remarkable change in BP was observed. Then a same dose of Acetylcholine was given and there was gradual rise of BP.

Explanations

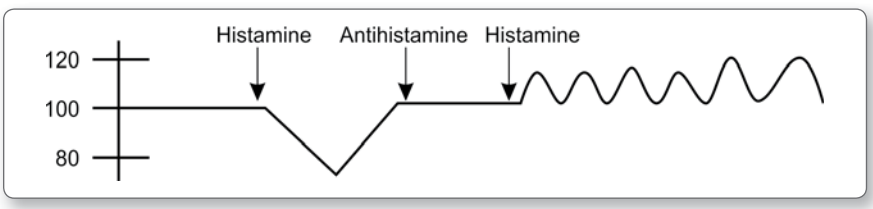
Fall of BP by Acetylcholine was due to stimulation of Muscarinic receptors which causes—

a. ↓ force of contraction, ↓ HR, ↓ conductivity, ↓ automaticity, ↓ SV and CO of heart. So the net effect ↓ BP.
b. Vasodilation ↓TPR →↓ BP.

BP came to the baseline due to hydrolysis of ACh by cholinesterase and dilution of the drug by the body fluid. Secondary rise of BP was due to compensatory mechanism and stimulation of nicotinic receptors which caused release of Adrenaline from autonomic ganglia and adrenal medulla.

Slow and sustained rise of BP was due to nicotinic action of ACh as the administration of Atropine muscarinic action was blocked. The nicotinic action was due to release of Adrenaline and noradrenaline from the sympathetic ganglia and adrenal medulla. Which produced widespread, vasoconstriction and cardioacceleration → all these resulted in slow and steady rise of BP.

5. Action of Histamine and Antihistamine on Blood Pressure



Description

This is a Brodie's kymographic tracing showing the effects of histamine and antihistamine on blood pressure of a pentobarbitone anesthetized cat preparation.

Drugs were given by the way of cannulated external jugular vein. After recording of normal mean arterial pressure a dose of histamine was given and fall of BP with secondary rise was observed. When the BP had returned to normal then a dose of antihistamine, e.g. Promethazine was given and slight fall of BP was observed. Then a same dose of Promethazine was given for the confirmation of the 1st dose and no change of BP was observed. Then previous dose of histamine was given and no further change of BP was observed.

Explanation

Histamine falls BP in two ways—

a. Histamine acts on H_1 receptors in arterioles, capillaries and small veins → causing dilatation ↓ PR ↓ BP.

b. Histamine increased capillary permeability →↑ escape of fluid to ↓ECF compartment →↓Blood volume →↓ CO →↓ BP.

Blood pressure came to baseline due to metabolism and dilution of drug by the body fluid. Secondary rise of BP was due to histamine induced release of Adrenaline from adrenal medulla. The antihistamine drugs are capable of preventing certain actions of histamine. The receptors in the arterioles, capillaries and small veins where histamine acts by dilatation causing a fall of blood pressure are blocked by antihistamine dose, with the result that subsequent doses of histamine will not cause any fall of blood pressure.

Index

AD	-	Adrenaline
AP	-	Action potential
BDZ	-	Benzodiazepines
CAs	-	Catecholamines
CoA	-	Coenzyme A
COMT	-	Catechol-O- methyltransferase
COPD	-	Chronic obstructive pulmonary disease
CTZ	-	Chemoreceptor trigger zone
DA	-	Dopamine
DAG	-	Diacylglycerol
DAβOH	-	Dopamine hydroxylase
DOPA	-	Dihydroxyphenyl alanine
ECF	-	Extracellular fluid
EEG	-	Electroencephalogram
HT	-	Hydroxytriptamine
ICF	-	Intracellular fluid
IP_3	-	Inosine triphosphate
ISO	-	Isoprenaline
M	-	Muscarinic
MARl	-	Monoamine reuptake inhibitor
MAO	-	Monoamine oxidase
N	-	Nicotinic
NA	-	Noradrenaline
NSAIDs	-	Nonsteroidal anti-inflammatory drugs
NO_2	-	Nitrous oxide
NTs	-	Neurotransmitter
PDA	-	Patent ductus arteriosus
PG	-	Proteoglycan
PGs	-	Prostaglandins
PGE	-	Prostaglandin E
SA node	-	Sinoatrial node
SGR	-	Substantia gelatinosa of Rolando
STT	-	Spinothalamic tract
SSRI	-	Selective serotonin reuptake inhibitor
URTI	-	Upper respiratory tract infection
VMA	-	Vinyl mandelic acid

PSYCHOPHARMACOLOGY

SECTION-III (A) ANALGESICS

OVERVIEW

Management of pain in one of the greatest challenge in clinical medicine. Pain is defined as an unpleasant sensation that can be either acute or chronic and that is a consequence of complex neurochemical processes in the peripheral and central nervous system (CNS). It is subjective, and the physician must rely on the patient's perception and description of his or her pain.

Alleviation of pain depends on its type. That is—

i. With headache or mild to moderate arthritic pain, nonsteroidal anti-inflammatory agents are effective.
ii. Neurogenic pain responds best to tricyclic antidepressants or serotonin/norepinephrine reuptake inhibitors rather than NSAIDs or Opioids.
iii. For severe or chronic malignant pain, Opioids are usually the drugs of choice.

Analgesic are drugs with a prominent pain-relieving action differ in groups. Perhaps—

i. The most important distinctions are that only the Opioids have potential for abuse and that tolerance to their actions can develop. Accordingly, Opioids are usually administered for short periods, and precautions are taken to avoid their diversion to illicit use.
ii. Opioids are the more powerful analgesics, but they do not reduce inflammation. In an individual patient with severe pain an Opioid is likely to provide greater relief than a nonopioid.
iii. Opioids undergo sufficient first-pass metabolism that a given dose is more effective by injection than after oral administration.
iv. Opioids act mainly within the central nervous system. Whereas the primary analgesic action of nonopioid is peripheral.
v. The use of Opioid is regulated by the Federal Controlled Substances Act 1970 in USA. Whereas some of the members of NSAIDs are sold as OTC (over the counter drug).
vi. The Opioids have antagonists like Nalorphine which was introduced in 1941 on the other hand NSAIDs have no antagonists.
vii. Use of analgesic is only one approach to pain alleviation, whereas, NSAIDs have other approaches also.

ANALGESICS

Definition

Drugs which relieve pain with or without affecting the level of consciousness.

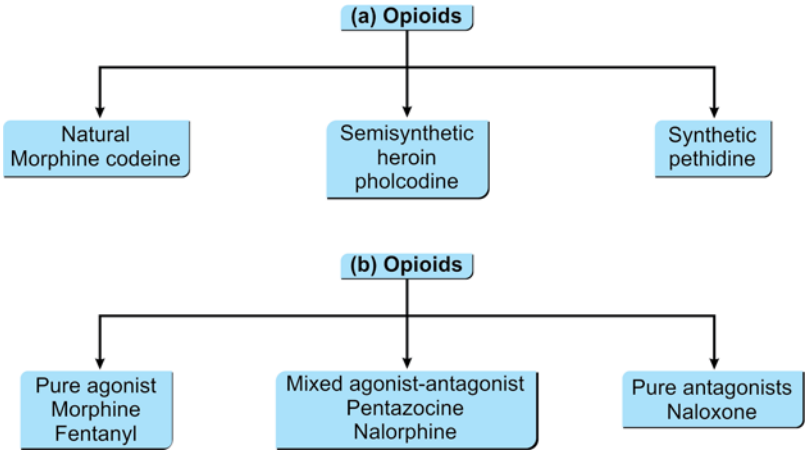
Groups

Two groups of analgesics are—

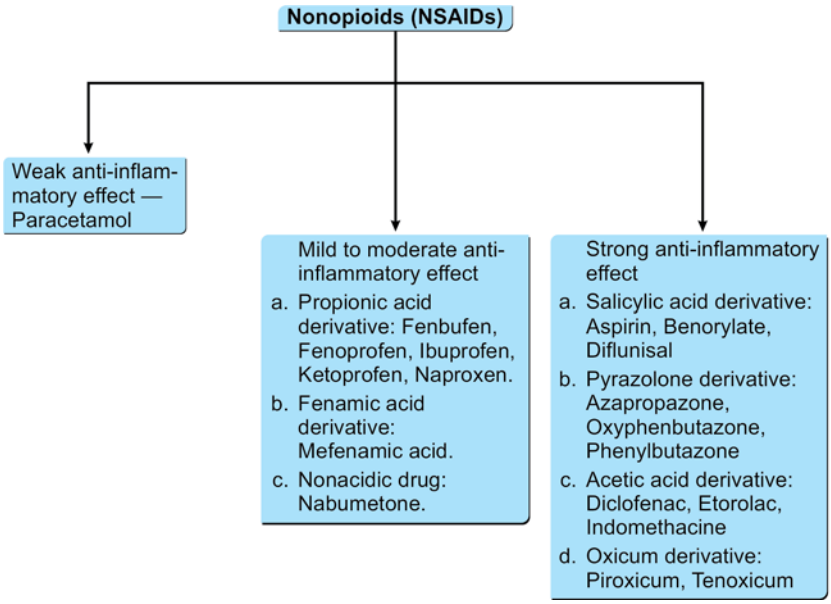
1. **Opioid or narcotic analgesic**: Which relieves pain with affecting the level of consciousness.
2. **Nonopioid or nonnarcotic or nonsteroidal anti-inflammatory drugs**: Which relieves pain without affecting the level of consciousness.

1. **Classification of Opioids**—
   a. According to source
   b. According to receptor activity.

1. Opioids



2. Nonopioids



SECTION-III (B) OPIOIDS

- Introduction
- Some terms
- Morphine
  a. Source
  b. Chemistry
  c. Pharmacokinetics
  d. Pharmacodynamics
  e. Pain pathway its components and analgesia by morphine
  f. Pharmacological effects of morphine
  g. Clinical uses
  h. Cautions
  i. Contraindications
  j. Adverse effects
  k. Antagonist.

INTRODUCTION

Opium is one of the most ancient medicines known to man. Even only before a hundred years, our forefathers did not know about the antibiotic antipsychotics, antidepressants, but they knew of opium. One major use of opium is as narcotic analgesic.

SOME TERMS

a. **Opium** is the juice of unripen seeds of the poppy plant, Papaver somniferum. It contains a large number of alkaloids, called opium alkaloids (e.g. morphine).
b. **Opiates** (a term is now obsolete) means, drugs which is structurally and pharmacologically resembles to morphine. Thus, endogenous opioids (e.g. enkephalins) are not opiates.
c. **Opioids** means drugs which behave like opium. Thus,
   i. Opium alkaloids like morphine
   ii. Endogenous peptides like enkephalins and endorphin
   iii. Semi or synthetic products like pethidine, met hadone are opioids.
d. The second criteria of Opioids is, their pharmacological effects must be antagonized by naloxone.
e. They combine with the opioid receptors. Viewed in this way, Naloxone is an Opioid.

MORPHINE

Source

Juice of unripen capsule of the seeds of Papaver somniferum, known as poppy plant.

Chemistry

Naturally occurring phenanthrene (three ringed) group of opium alkaloid. There are two (–OH) groups; one is at C_3, known as phenolic group and another present in C_6 position called alcoholic group.

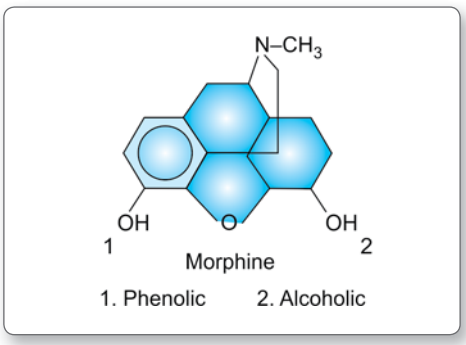


Fig. 6.13: The chemical structure of morphine

Pharmacokinetics

When given orally, absorption suffers considerably due to hepatic first pass effect. Oral parenteral ratio is low, it is well-absorbed from subcutaneous and IM sites as well as from mucosal surface of the nose, mouth and gut. The drug is metabolized by glucuronidation, giving rise to active morphine-6-glucuronide and inactive morphine-3-glucuronide that are excreted primarily in the urine. Both morphine and its glucuronide metabolites undergo enterohepatic recycling, which accounts for the presence of small amounts of morphine in the feces and in the urine for several days after the last dose. A little fraction of absorbed morphine can cross the BBB.

Pharmacodynamics

There are receptors for endogenous Opioid peptides (Mu, Kappa, Sigma, Delta) in our body. These receptors under natural circumstances, can combine with Opioid peptides and can produce analgesia. Exogenous Opioids (Morphine) can combine with these receptors and after combination they produce analgesia.

The control of pain is one of the most important uses of drugs. All types of painful experiences include both the original pain as a specific

sensation, observed by distinct neurophysiological structures, and pain as suffering (the original sensation plus the reaction evoked by the sensation).

Pain Pathway—Its Components and Analgesia by Morphine

Two components of pain perceptions are—

i. **Nociceptive component**: Pain is felt due to the injury, i.e. noxious agent.
ii. **Affective component**: Pain is associated with psychological component of the pain. That is why pain threshold varies among the individual.

The function of the direct spinothalamic system is to carry nociceptive component. The spinoreticular system, on the other hand is concerned with the affective component of pain.

Opioids are effective against both the pain components, whereas NSAIDs (nonopioids) inhibit only the nociceptive component alone.

Endogenous pain inhibiting system: Our body contains a pain inhibiting system which when stimulated, can partly reduce the perception of pain.

Mechanism of analgesic effect of morphine

Analgesic effects of opioids arise from their ability to:

1. Morphine produces a block in pain carriage at the level of SGR → as a result pain cannot reach the brain (thalamus, cerebral cortex). This blocking occurs because the release of the neurotransmitter, substance P, is inhibited. Substance P facilitates transmission of pain from the first neuron to STT (spinothalamic tract).
2. Morphine dulls the perception of pain at brainstem.
3. Morphine by acting on PAG and other areas of descending an inhibitory system, reduces an perception.
4. Morphine probably by influencing limbic system alters affective side of pain. That is, pain is no longer felt as an unpleasant sensation.

Pharmacological Effects of Morphine

On CNS

1. **Analgesia**—(see above).
2. **Euphoria**—Regarding this, very little is known. It is known that excess DAergic activity can produce mania and schizophrenia like symptoms. Opioid receptors (particularly M) are found in these neurons and exogenous opioids can cause DAergic hyperactivity in this tract. Euphoria may be related to these facts.
3. **Miosis**—It is due to combination of morphine with M and K receptors in the Edinger-Westphal nucleus (parasympathetic center of 3rd nerve

nucleus in the midbrain). Stimulation of 3rd nerve nucleus causes release of ACh, which acts on circular muscles (cause contraction) of eye and finally there is constriction of pupil – Miosis.

4. **Respiratory depression**—As the pCO_2 rises, the rising pCO_2 stimulates the medullary respiratory center (i.e. central chemoreceptors) and there is beginning of inspiration. With inspiration pCO_2 falls, and inspiratory drive disappears, and inspiration stops and expiration begins.
   a. Opioids reduce the sensitiveness of medullary respiratory center to CO_2
   b. It has direct depressive effect on respiratory center also.
5. **Cough**— It is also suppressed, because of inhibition of medullary cough center.
6. **Vomiting**— It is produced due to stimulation of CTZ in medulla.
7. **Endocrine effect**—Decreased concentration of testosterone and cortisol due to reduction of GnRH and CRH secretion by Morphine.

On CVS

i. Morphine induced rise in pCO_2 can cause vasodilatation and increased intracranial pressure.
ii. Slight vasodilatation may be due to histamine release and inhibition of baroreceptor reflex and can cause postural hypotension.

On GIT morphine causes

1. Constipation by increasing the tone of smooth muscles of the small and large intestine and reduce motility. All these result in greater transit time in the GIT, more absorption of water and reduction of the amount of water in the intestinal content (in feces).
2. Nausea and vomiting are central effects.
3. Intrabiliary pressure rises, because morphine causes spasm of sphincter of Oddi.

On urinary system

Mild spasm of the ureter or sphincter of bladder can occur; cause complication in patient of enlarged prostate.

On uterus

Morphine may prolong the labor.

Clinical Uses

- Severe and intractable pain (acute and chronic)
- Myocardial infarction

- Acute pulmonary edema
- Adjunct during major surgery
- Postoperative analgesia.

Cautions

- Hepatic impairment—It may precipitate coma.
- Renal impairment—Dose is to be reduced or avoided.
- Hypotension—Morphine-induced histamine can cause fall of PR.
- Hypothyroidism.
- Asthma and decreased respiratory reserve—Potential risk due to histamine release.
- Prostatic hypertrophy—It leads to urinary retention also can inhibit the urinary bladder voiding reflex thus catheterization may be required.
- Pregnancy and breastfeeding—Morphine increases prolacting and growth hormone release by diminishing dopaminergic inhibition.
- Elderly and debilitated (dose reduced).
- Convulsive disorders.
- Dependence.
- Use of cough suppressants containing Opioid analgesics not generally recommended in children and should be avoid altogether in those under 1 year.
- Concurrent administration of other CNS depressants.
- In the control of pain in terminal illness these cautions should not necessarily be a different in the use of Morphine.

Contraindications

- Acute respiratory depression—Severe respiratory depression occurs and can result in death in acute poisoning.
- Acute alcoholism.
- Acute abdomen—Chance of biliary spasm.
- Risk of paralytic ileus—It enhances segmentation movement and inhibits peristaltic movement.
- Raised intracranial pressure or head injury—Repeated used produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of Morphine.
- Pheochromocytoma.

Adverse Effects

- Dependence
- Nausea and vomiting particularly initial stages, constipation
- Drowsiness
- Larger doses produce respiratory depression and hypotension.

- Others include difficulty in micturition.
- Ureteric and biliary spasm.
- Dry mouth, sweating.
- Facial flushing, miosis.
- Rashes, urticaria, pruritus—Due to histamine release.

Antagonists

The Opioid antagonists bind with high affinity to Opioid receptors, but fail to activate the receptor mediated response. Administration of Opioid antagonists produces no profound effects in normal individuals. However, in patients dependent on Opioids antagonists rapidly reverse the effect of agonists, such as heroin, and precipitate the symptoms of opiate withdrawal.

a. Naloxone
b. Naltrexone.

Naloxone

Naloxone is used to reverse the coma and respiratory depression of Opioid overdose. It rapidly displaces all receptor bound Opioid molecules and, therefore, is able to reverse the effect of a heroin overdose. Within thirty seconds of IV injection of Naloxone, the respiratory depression and coma characteristics of high doses of heroin are reversed, causing the patient to be revived and alert.

Naltrexone

Naltrexone has actions similar to those of Naloxone. It has a longer duration of action than naloxone, and a single overdose of Naltrexone blocks the effects of injected herion for upto 48 hours. Naltrexone is hepatotoxic.

SECTION-III (C) ASPIRIN (NSAIDs)

OVERVIEW

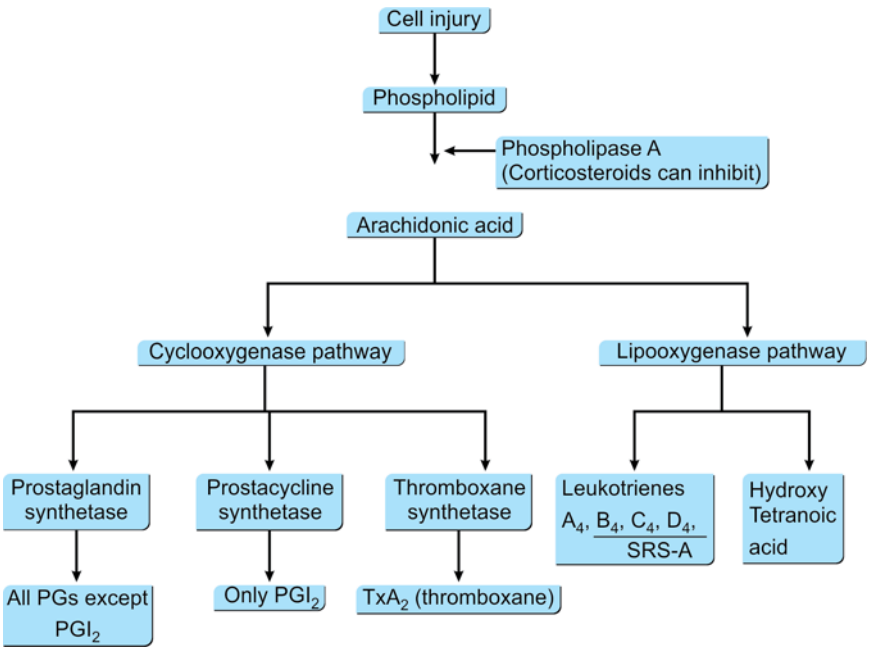
I have already mentioned in the overview of analgesic that opioids are powerful analgesic but they do not reduced inflammation. Inflammation is a normal, protective response to tissure injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate of destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides. However, inflammation is sometimes inappropriately triggered by an innocuous agent, such as

pollen, or by an autoimmune response, such as in asthma or rheumatoid arthritis. In such cases, the defense reactions themselves may cause **progressive tissue injury (shown below)**, and anti-inflammatory or immunosuppressive drugs may be required to modulate the inflammatory process.

Classification (NSAIDs) See section—I

ARACHIDONIC ACID METABOLISM—PATHWAYS

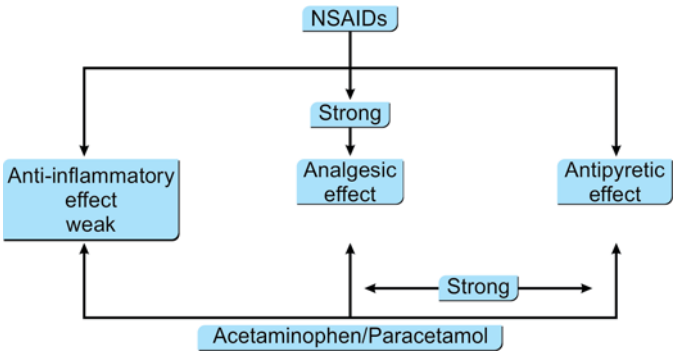
It is very much essential to know the above pathway for clear understnading of analgesic action of NSAIDs



INFORMATIONS FROM A.A METABOLISM

- NSAIDs inhibit prostaglandin synthetase enzyme—Analgesic effect.
- Glucocorticoids inhibit phospholipase A_2—Anti-inflammatory effect.
- Low dose of Aspirin selectively inhibit the Thromboxane synthetase pathway keeping the prostacycline. Synthetase pathway unaffected –Antiplatelet effect.
- Glucocorticoids can also block the production of leukotrienes—Anti-esthetic effect.
- Zafirlukast can block the leukotriene receptors—Antiesthetic effect.
- NSAIDs by blocking—Cyclooxygenase pathway, can produce more leukotrienes and can aggravate bronchial asthma.

PHARMACOLOGICAL EFFECT OF ASPIRIN



1. **Analgesic effect**: NSAIDs are superior to Opioids for management of pain in which inflammation is involved.
2. **Antipyretic effect**: The salicylates lower body temperature in patients with fever by impeding PGE_2 synthesis and release. Aspirin resets the "thermostat" toward normal, and it rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating. Aspirin has no effect on normal body temperature.
3. **Anti-inflammatory effect**: Because aspirin inhibits cyclooxygenase activity, it diminishes the formation of prostaglandins and, thus, modulates those aspects of inflammation in which prostaglandins act as mediators.
4. **Antidysmenorrheic**: Excess PG synthesis, causing uterine contraction, is the factor behind dysmenorrhea which can be relieved by Aspirin.
5. **Antiplatelet effect** (by low dose of aspirin): It causes inhibition of TxA_2 keeping the effect of PGI_2 unaffected.
6. **Antigouty effect**: High dose of Aspirin can prevent the 93% of uric acid reabsorption from renal glomerulus and proximal convoluted tubule thereby enhancing their excretion and making the normal uric acid level in blood. On the other hand, low dose can only prevent 7% of uric acid reabsorption, from the rest of the nephrones, so produce no significant effect against gout (hyperuricemia).
7. **Use in PDA**: Ductus arteriosus remain patent in the fetal life, but closes immediately after birth normally. If the patency persists, it is called patent ductus arteriosus (PDA). PGs keep the ductus arteriosus patent. Aspirin has been successfully used in PDA.
8. **Antihypofertility effect**: By diminishing the PG contents in seminal fluid (by inhibition of PG synthetase) and making the fluid less viscus and increasing the speed of mature spermatozoa, so that proper fertilization can take place.
9. **In preeclamptic toxemia**: It has been advocated in PET. In PET, there is an excess of TXA_2 formation.

10. **Bartter's Syndrome** There is rise of PGE_2 production → Stimulation of renin-angiotensin-aldosterone axis → Loss of K^+ from the body. One expects BP will be high because of stimulation of angiotensin aldosterone axis. But PGE_2 also acts directly on blood vessels producing vasodilatation, this nullifies the possibility of rise of BP. NSAIDs could be effective against the syndrome.

ADVERSE EFFECTS

It can be acute or chronic; the signs and symptoms may be local or systemic.

On GIT

a. Vomiting : ← By stimulating CTZ.
b. Ulceration: ← i. By inhibiting the mucosal barrier, as it is formed mainly by PGE series.
   ii. By increasing the gastric HCl secretion.
c. Bleeding:
   i. By blocking the synthesis of TxA_2 as it has platelet aggregatory action.
   ii. By inhibiting the collagen glucosyltransferase enzyme in platelet membrane as the enzyme helps in platelet aggregation.
   iii. By antagonizing vitamin K → Hypoprothrombinemia → Prolonged PT → Increased bleeding.
   iv. By breaking down the mucosal barrier against back diffusion of it thereby injuries the submucosal capillaries and necrosis of capillaries and bleeding.

- **Other effects**—Salicylism includes tinnitus, headache dimness of vision, difficulty in hearing and nausea.
- **Respiration in toxic**—Doses salicylates cause respiratory depression.
- **Hypersensitivity**—15% of patients taking Aspirin experience hypersensitivity reaction.
- **Reye syndrome**—Aspirin given during viral infections has been associated with an increased incidence of Reye syndrome, which is an often fatal, fulminating hepatitis with cerebral edema.

CONTRAINDICATIONS

1. Peptic ulcer—It is due to inhibition of PGEs synthesis.
2. Bleeding tendency—See above
3. Viral fever (chickenpox, influenza URTI) in children—It may cause Reye's syndrome.
4. Pregnancy at term—It may cause prolonged labor.
5. Where surgical interference is to be done within a week—Chance of bleeding.

SECTION-III (D) SEDATIVE-HYPNOTICS

OVERVIEW

Anxiety is an unpleasant state of tension, apprehension or uneasiness a fear that seems to arise from an unknown source. Disorders involving anxiety are the most common mental disturbances. The symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes called anxiolytic or minor tranquilizers) and/or some form of behavioral or psychotherapy.

Anxiety may be adaptive and beneficial, e.g. anxiety before and examination. Anxiety may also develop before a surgical operation (situational anxiety). Two forms of pathological anxiety are i. panic disorder and ii. generalized anxiety state.

PANIC DISORDER

The subject, without sufficient reason, develops an episode of panic which lasts for few minutes and is characterized by palpitation, fear of unknown, sweating, dyspnea and so on. Note: i. Symptoms of panic disorder resemble sympathetic overactivity. ii. Symptoms of panic disorder may be due to serious organic disease and before a diagnosis of panic disorder is made such organic diseases (e.g. mitral valve prolapse/thyrotoxicosis/others) must be eliminated.

The patient without sufficient reason remains in a state of chronic anxiety. A short course of a suitable BDZ may be helpful.

Definition

- **Sedatives** are agents which reduces anxiety, and calms the recipients without inducing sleep, but they can induce drowsiness, i.e. Benzodiazepines.
- **Hypnotics** are drugs which produce sleep that resembles to normal sleep. Hypnotic effect involves more pronounced depression of CNS than sedation, and this can be achieved by simply increasing the dose of sedatives.

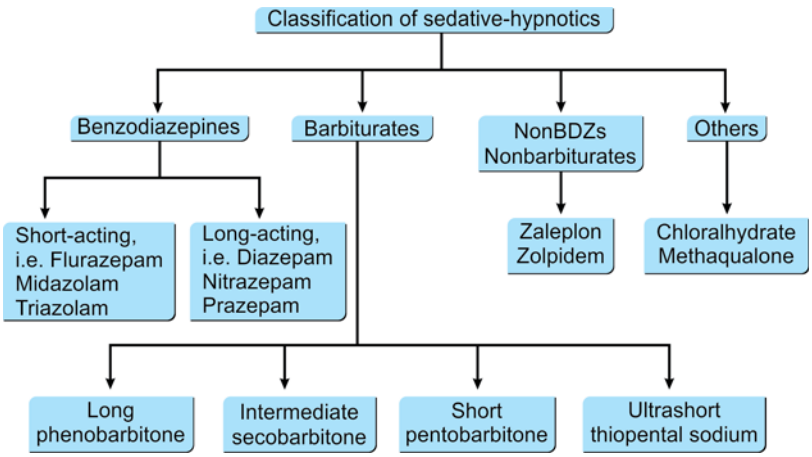
– History
– Classification
– Chemistry
– Pharmacokinetics
– Mechanism of action
– Pharmacological effect

– Clinical uses
– Adverse action
– Contraindications
– Differences between BDZ and BARBT.

History

Chlordiazepoxide was the first marketed drug of the family of BDZ, discovered accidentally in 1961 by a group, working in the Hoffman La Roche Laboratory. This is because of their relative safety, they (BDZ) have virtually completely replaced the barbiturate from the market.

Classification



Chemistry

BDZs contain a benzene ring and a 7 membered ring (ring C). In addition they also contain a substituent ring (ring C).

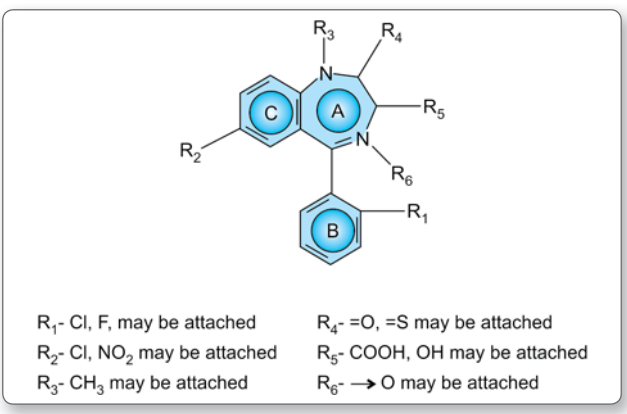


Fig. 6.14: BDZ skeleton

Various groups are attached to R_1 to R_5, Figure 6.11 BDZ skeleton examples are O_2, H_2, Cl, NO_2, H, C, etc.

Pharmacokinetics

Most, BDZs are absorbed from the GIT completely. After absorption, they traverse the body as follows: Available in blood → entry into brain, then again back to blood and an equilibrium is established. Then they reaches in the muscle and adipose tissue, biodegradation start and the effects begin to disappear. During biotransformation some members of BDZs form—

a. Active metabolites
b. Some are directly oxidized and then conjugated with glucuronic acid to form glucuronides
c. Some produce intermediary metabolites, e.g. hydroxylated compounds and extremely rapidly metabolized and excreted out.

Mechanism of action

1. GABA receptors → BDZs (sites distinct from GABA receptor) → 2. Increase GABA activity → 3. Opening of chloride channels → 4. Chloride entry (from ECF to ICF) → 5. Hyperpolarization of neuron → 6. Hypoexcitability → 7. CNS depression.

Pharmacological effects

Receptors for Benzodiazepines, the primary agents used today to reduce anxiety and alleviate insomnia, are found within a complex that contains a Cl channel, $GABA_A$ receptors for the inhibitory amino acid Y-aminobutyric acid (GABA), and receptors that bind barbiturates and the convulsant picrotoxin. A characteristic of the $GABA_A$ receptor is that the convulsant agent bicuculline is a competitive antagonist. GABA increases the affinity of Benzodiazepine receptors for Benzodiazepines and electrophysiologic effects of GABA are enhanced in the presence of Benzodiazepines.

Clinical uses

They can be used as—

1. Anxiolytic—It is often helpful in primary anxieties e.g. panic disorder and generalized anxiety.
2. Hypnotic—As hypnotics Flurazepam, Temazepam and Triazolam are specially popular.
3. Anticonvulsant—In emergency control of status epilepticus IV Diazepam may be given.
4. As muscle relaxant—In muscle spasm due to muscle strain, Diazepam can be used.
5. In alcohol withdrawal—Diazepam can be used.

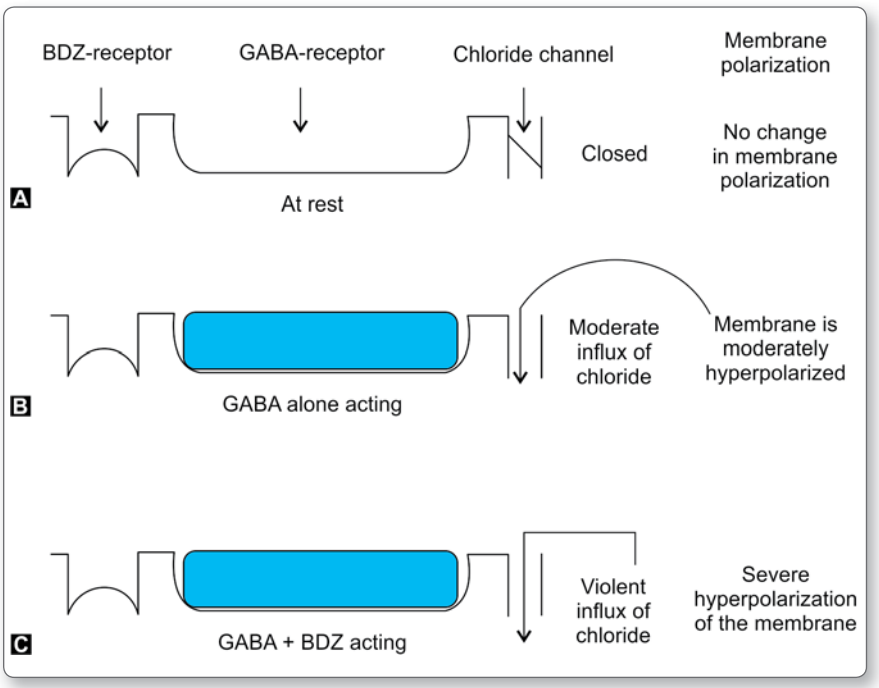


Fig. 6.15: Mechanism of action of BDZ

Adverse actions

1. Drowsiness – Particularly in day time drowsiness is seen with confusion.
2. Impairment of cognitive faculty (availability to learn new things plus availability to recollect events of past).
3. Ataxia—This may cause dangers in motor driving.
4. Day time anxiety—Particularly seen with BDZ having very low half- life.
5. Dependence—2 types of dependence.
   i. Pharmacokinetic is seen by barbiturates.
   ii. Tissue dependence by Benzodiazepines.

Contraindications

Severe hepatic or renal impairment, pregnancy and breastfeeding.

Differences between BDZ and BARBT

Points	BDZ	BARBT
Discovery year	1961	1903
Chemistry	Possess BDZ nucleus	Barbituric acid derivatives

Contd...

Contd...

Points	BDZ	BARBT
Classifications	Two groups	Four groups
Mechanism of action	By combining with receptor	Nonreceptor-mediated action
Clinical uses	Recent and more	Old and less
Therapeutic index	More	Less
Drug interaction	Less	More—Because of enzyme induction
Antagonist	Have (that is Flumazenil)	Have not
Dependents	Less	More

BARBITURATES (BARBT)

- Definition
- Chemistry
- Classification with basis
- Biotransformation
- Mode of action
- Pharmacological effects
- Clinical uses
- Adverse effects
- Contraindications with explanations

Definition

Barbiturates are the derivatives of barbituric acid.

Chemistry

Barbituric acid is formed by the condensation of urea and malonic acid.

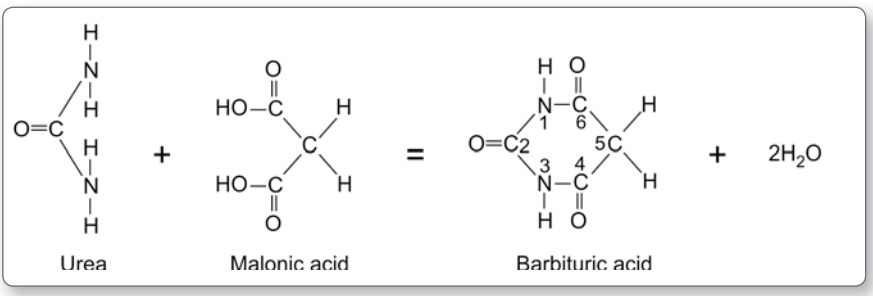


Fig. 6.16: Formation of barbituric acid skeleton

Barbituric acid itself is inactive, in consideration with different level of CNS depression. It becomes active when there is substitution of H at C_5 by ethyl or aryl radical or phenyl radical at C, increases the anticonvulsant action, e.g. phenobarbitone. if 'O_2' at C_2 is replaced by 'S' group. the derivative is called thiobarbitone. Which is highly lipid-soluble, is used as intravenous anesthetic.

Classification with Basis

On the basis of duration of action

a. Long-acting—For example, **Phenobarbitone, Mephobarbitone**
b. Intermediate acting—For example, **Amylobarbitone, Butobarbitone**
c. Short-acting—For example, **Pentobarbitone, Quinalbarbitone**
d. Ultrashort-acting—For example, **Thiopental sodium, Methohexital**.

On the basis of clinical use

a. Long-acting barbiturates are used as anticonvulsants, e.g. phenobarbitone.
b. Intermediate and short-acting ones are hypnotic, e.g. secobarbitone.
c. Ultrashort acting groups are intravenous anesthetics, e.g. thiopental sodium.

Barbiturates depress the activity of all brain cells, they specially depress the reticular activating system and neural activity in the posterior hypothalamus, amygdaloid complex and limbic system. In small doses, they also enhance the effects of GABA (an inhibitory neurotransmitter).

Biotransformation

They are biotransformed by the opening of barbiturate ring through the process of—
a. Oxidation
b. N- dealkylation
c. Desulfuration.

Mode of Action

Nonspecific action—Nonreceptor mediated, so that there is no specific antidotes in the management of barbiturate poisoning.

Pharmacological Effects

a. **CNS**— i. Sedation and hypnosis
   ii. Anticonvulsion
   iii. Anesthesia.
b. **CVS**—Lowering of BP—By reducing CO

c. **GIT**—Prolonged use may cause constipation
d. **Kidney**—Decreased urinary output, due to reduction of GFR and excess ADH release.

Clinical Uses

a. As sedative—Hypnotics
b. As anticonvulsants (in tetanus, eclampsia, hyperpyrexia, drug poisoing)
c. As antiepileptic
d. To induce general anesthesia
e. To treat hyperbilirubinemia and kernicterus in neonates
f. Selected cases of cholestasis.

Adverse Effects

Depending on dose effects may vary—

Drowsiness to unconsciousness, hangover, nightmares, cold and clammy skin, rapid and shallow—respiration, thready pulse, fall of BP, allergic skin rash.

Contraindications with Explanations

1. Severe pulmonary insufficiency in COPD
2. Hepatic failure
3. Attacks of porphyria.

Barbiturates can increase delta-aminolevulinic acid synthetase, which ultimately causes increase in porphyria synthesis incidentally porphyrin is required for the synthesis of heme of hemoglobin, leading to the dangerous exacerbation of the condition, of the subject, suffering from intermittent porphyria.

SECTION-III (E) GENERAL ANESTHETICS

- Introduction
  - Definition
  - Adjunct to anesthesia
  - Preanesthetic medication, basal and balanced anesthesia
- Types
- Three divisions of G/As
- Mechanism of action
- Stages of anesthesia
- Protocol of anesthesia
- Procedure of classical protocol

- Reasons of combination of N_2O, halothane and oxygen
- Individual agents
- Disadvantage of inhalation anesthetics
- Complications
- Toxicities

INTRODUCTION

Definition

General anesthetics are drugs which produce—(1) Analgesia. (2) Amnesia (3) Reversible loss of consciousness. (4) Adequate muscle relaxation and (5) Loss of reflexes in subject. Their therapeutic indices are low, that is slight overdose is potentially fatal. They have got no receptors, they are all nonspecific drugs and hence they have no antagonist.

No single drug is capable of achieving these effects both rapidly and safely. Rather, several different categories of drugs are utilized to produce optimal anesthesia. Some functions of adjuncts to anesthesia are given below.

IV anesthetics may be used as adjuncts to gaseous anesthetics either to induce anesthesia or for maintenance of anesthesia throughout surgery.

Adjunct to Anesthesia

Agents used **Objectives**

1. **Benzodiazepines** – To relieve anxiety
2. **Barbiturates** – To produce sedation
3. **H_1-blockers** – To prevent bronchial secretion
4. **Antiemetics** – To prevent stomach contents into respiratory tract
5. **Opioids** – To produce analgesia
6. **Atropine** – To prevent bradycardia
7. **Muscle relaxant** – To facilitate intubation.

Preanesthetic medication, basal and balanced anesthesia

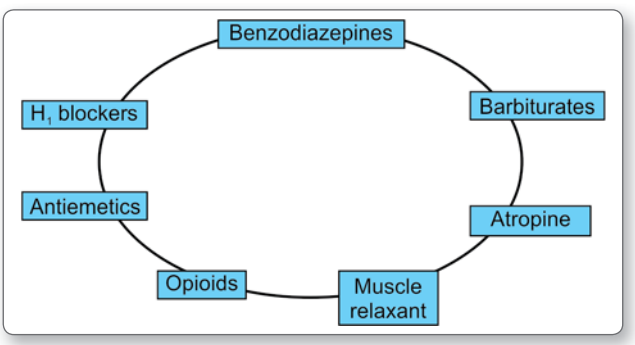


Fig. 6.17: Adjunct to anesthesia

Preanesthetic medication

These accessory drugs are given either to facilitate effect of the anesthetic drug or to combat adverse effects of the principal anesthetic agent.

These anesthetic adjuncts are used preoperatively, perioperatively, or postoperatively.

Basal anesthesia

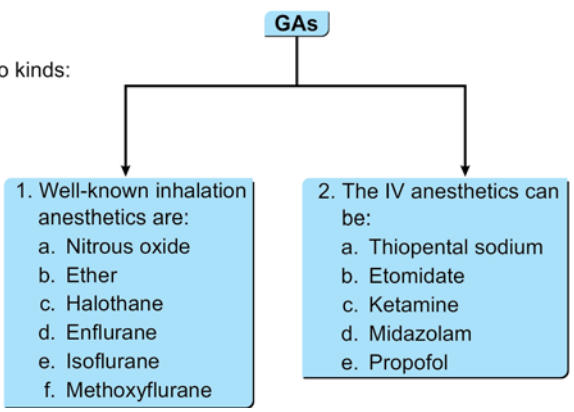
Parenteral administration of one or more sedative or hypnotics to produce a state of depressed level of consciousness and to form a base for surgical anesthesia is called basal anesthesia.

Balanced anesthesia

It is the procedure of anesthesia from which desirable quantities of unconsciousness, analgesia, and muscle relaxation is obtained by appropriate quantities of various drugs and technics. Here pulse, temperature BP are under the control of anesthetist. For example, unconsciousness is induced by Thiopental sodium, and maintained by nitrous oxide and Opioid drug, e.g. Morphine, Pethidine while analgesia is also maintained by Opioids, muscle relaxation is regulated by dose of neuromuscular agents.

TYPES

General anesthetics are of two kinds:
1. Inhalation anesthetics
2. Intravenous anesthetics



THREE DIVISIONS OF GAs

1. Induction
2. Maintenance
3. Recovery.

1. **Induction**—It is defined as the period of kind from the onset of administration of the anesthetic to the development of effective surgical anesthesia in the patient.

It is done with the followings—

a. Injection Thiopental sodium—3 mg/kg/IV rapidly.
b. O_2 by face mask @ 6–8 liter/min, simultaneously with Thiopental.
c. N_2O, by face mask—@ 5–6 liter/min, simultaneously with O_2. Which is diminished about 2.5–3 liter/min
d. Injection Gallamine 2–2.5 mg/kg/IV.
e. Halothane by face mask.
f. Endotracheal intubation is carried out after relaxation by direct laryngoscopy, and anesthesia is maintained with supply of a. O_2 b. N_2O c. Halothane.
g. Injection Gallamine is to be repeated at the interval of 30 minutes depending upon the length of operation and the patient relaxation.

2. **Maintenance** – It provides a sustained surgical anesthesia.
It is done with N_2O + halothane + O_2

3. **Recovery** – It is the time from discontinuation of administration of the anesthesia until consciousness and protective physiologic reflexes are regained.

a. Halothane supply gradually stopped and this results in starting of spontaneous respiration of the patient as the action of Gallamine is also expired.
b. As the operation is complete, N_2O supply is gradually stopped.
c. O_2 supply is increased to about 8–0 liters/min simultaneously with stoppage of CO_2 supply.
d. Injection Neostigmine 0.5 mg (1 ample) for each 40 mg of Gallamine + Injection Atropine 0.6 mg per mg Neostigmine is given IV as the patient respired normally.
e. Endotracheal tube is removed after the reflexes (cough and pain) return.

MECHANISM OF ACTION

At molecular level, mechanism of action of the general anesthetics is not clear, several theories have been developed. One popular theory is—

Mayer-Overton Principle

According to this theory, any substance can act as a narcotic anesthetic, provided it attained a sufficient molar concentration in the CNS neuronal membrane. Cell membrane being made up of mostly by phospholipid, is

oily in nature: Substances which are lipid-soluble (no matter what are their other chemical characteristics) therefore, can enter the (oily) cell membrane from ECF and attains the sufficient molar cone, and produce anesthesia. It is known that more a substance is lipid-soluble more is its potency as anesthetic and the anesthetic property of a substances does not depend upon its chemical structure. No receptors exists to catch the anesthetic molecules in the cells and what happens next is uncertain. It is known than all anesthetics decrease the responsiveness of neurons and makes the development of AP difficult.

Anesthetic molecules after appearing with the cell membrane they exert a pressure which tends to obliterate the Na^+ channels of the cell membrane therefore, these Na^+ channels fail to open properly, so insufficient flow of Na^+ ion from ECF to ICE → nondevelopment of AP, this will block the neuronal transmission.

STAGES OF ANESTHESIA

When G/A is produced by using ether as the sole agent, the following four stages are seen which appears one after another, as if in a procession.

- **Stage I—Stage of analgesia**—Due to decreased activity of the cells of SGR (substantia gelatinosa of Rolando) in the dorsal horn of spinal cord. So there is, interruptions of sensory transmission in spinothalamic tract, including nociceptive stimuli.

- **Stage II—Stage of delirium**—Due to blockade of many small inhibitory neurons, e.g. Golgi type II cells, together with a paradoxic facilitation of excitatory neurotransmitters.

- **Stage III—Stage of surgical anesthesia**—Due to progressive depression of ascending pathway in the reticular activating system, together with suppression of spinal reflex activity that contributes to muscle relaxation.

- **Stage IV—Stage of medullary depression**—Due to depression of neurons of respiratory and vasomotor center of the medulla that is cardiorespiratory center.

PROTOCOL OF ANESTHESIA

The protocol of general anesthesia varies from patient to patient, depending upon—

i. The nature of operation
ii. The state of health of the patient
iii. Whether the patient is strongly alcoholic, drug abuser.

PROCEDURE OF CLASSICAL PROTOCOL

For a surgical procedure of reasonably long duration the usual protocol is often as follows:

Use preanesthetic medication

↓

Induce by IV Thiopental or suitable alternative

↓

Use a muscle relaxant

↓

Intubate

↓

Use a mixture of nitrous oxide, O_2 and a halogenated hydrocarbon—maintain and monitor

↓

Withdraw the drugs—recovery

This above protocol is merely one of the many that are practised.

REASONS OF COMBINATION OF N_2O, HALOTHANE AND OXYGEN

Nitrous Oxide – Oxygen – Halothane mixture is often used in maintenance of GA.

When N_2O is used, during recovery the following can happen:
Because of its low solubility in blood nitrous oxide, during recovery from anesthesia, massively leaves the blood and escapes, via lung alveoli to exterior. During this, it can so overcrowded the lung alveoli that room for O_2 can shrink and a hypoxia called diffusion hypoxia can result during postoperative phase. Therefore, O_2 inhalation is a must (to prevent diffusion hypoxia) in postoperative phase where nitrous oxide is being used.
N_2O however, has remarkable ability to reduce dose of other potent anesthetics like Halothane. Note, Halothane, although a very powerful anesthetic, has many toxicities. Concomitant use of N_2O, by reducing the dose of Halothane, reduces the possible toxicity due to Halothane.

Halothane is a potent anesthetic but weak analgesic and hepatotoxic, whereas N_2O is a potent analgesic but weak anesthetic and least hepatotoxic among inhalation anesthetic. That is why, it (N_2O) is usually coadministered with halothane.

INDIVIDUAL AGENTS

Nitrous Oxide (N_2O)

It is a potent analgesic but a weak general anesthetic. For example, nitrous oxide is frequently employed at concentrations of 30% in combination

with oxygen for analgesia, particularly in dental surgery. However, nitrous oxide at 80% (without adjunct agents) cannot produced surgical anesthesia. It is, therefore, frequently combined with other, more potent agents to attain pain-free anesthesia. Nitrous oxide is poorly soluble in blood and other tissues, allowing it to move very rapidly in and out of the body. [Note: Nitrous oxide can concentrate the halogenated anesthetics in the alveoli when they are concomitantly administered because of its fast uptake from the alveolar gas, this phenomenon is known as the "second gas effect"] within closed body compartments, nitrous oxide can increase the volume (for example, causing a pneumothorax) or increase the pressure (for example, causing a pneumothorax) or increase the pressure (for example, in the sinuses), because it replaces nitrogen in the various air spaces faster than the nitrogen leaves. Furthermore, its speed of movement allows nitrous oxide to retard oxygen uptake during recovery, thus causing diffusion hypoxia. This anesthetic does not depress respiration, nor does it produce muscle relaxation. Under the usual circumstances of coadministration with other anesthetics, it also has moderate to no effect on the cardiovascular system or on increasing cerebral blood flow, and it is the least hepatotoxic of the inhalation anesthetics. It is, therefore, probably the safest of these anesthetics, provided that at least 20% oxygen is always administered simultaneously.

Thiopental Sodium

Introduction

Thiopental is a potent anesthetic but a weak analgesic. It is an ultra-short-acting barbiturate and has a high lipid solubility.

Route of administration IV anesthesia

Onset of action: It is on being given IV, produced unconsciousness in one circulation time (within 15 secs, or so) it is used chiefly as inducing agents.

Duration of action: 15 minutes to half an hour. The short duration of anesthetic action is due to the decrease of its concentration in the brain to a level below that necessary to produce anesthesia.

Metabolism: Metabolism of Thiopental is much slower than its tissue redistribution.

Effects: It has minor effects on cardiovascular system but it may contribute to severe hypotension in hypovolemic or shock patients. All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm and bronchospasm.

Advantages

a. Rapid induction
b. Good anesthesia.

Disadvantages

a. Laryngospasm
b. Poor analgesia
c. Poor muscle relaxant property.

Contraindication

In patients with acute intermittent or variegate porphyria.

Ketamine

1. History – In there 1960 phencyclidine was introduced in the USA as an IV anesthetic but soon abandoned. Today, PCP is used as an abusing drug.
2. Chemistry – Ketamine is a derivative of phencyclidine (PCP).
3. Properties – Ketamine causes dissociative anesthesia that is after (an IV) administration of Ketamine the patient becomes (i) immobile (ii) amnesic and (iii) analgesic and he retains his conscious state of mind and he feels as if he separated from his own body and environment.
4. Duration – The anesthesia last for about 10 minutes. It causes routine elevation of BP, cardiac output and produces tachycardia. Therefore, Ketamine anesthesia is popular in hypovolemic shock, in hypotension but not in hypertensives.
5. Popularity – Ketamine is the only IV anesthetic that causes routine elevation of BP, cardiac output and produces tachycardia. This is because (i) it stimulates the central sympathetic outflow and also (ii) inhibits the reuptake of catecholamines by the adrenergic neurons. Therefore, Ketamine anesthesia is popular in hypovolemic shock, in hypotension.
6. Risk in patient with IHD – IV Ketamine injection within about 2 minutes raises the plasma catecholamine levels → this returns to normal within about 15 minutes. Ketamine injection, therefore, is risky in patients with IHD.
7. Emergence phenomenon—Ketamine produce "emergence phenomenon", i.e. during anesthesia the patient may develop sensory/perceptual illusions (e.g. snakes swarming the body). After recovery Ketamine can produce (postoperative) psychic phenomenon, including nightmares for this reason although Ketamine has many advantages (good analgesia and bronchodilatation/no loss of consciousness), Ketamine is not very popular.

8. Indication—Ketamine is chiefly used in (a) poor risk geriatric patients (provided no IHD, no hypertension exists, (b) in surface surgical procedure like "burn dressing" particularly in children. Recall, burn dressing is very painful producer, (c) in patients with cardiovascular shock. It can (d) also be used in OPD surgical procedures (which are of short duration).

DISADVANTAGES OF INHALATION ANESTHETICS

1. **Toxic decomposition products**—Volatile liquid anesthetics are readily oxidized on exposure to air, light or moisture with the production of toxic and sometimes explosive decomposition products, such as phosgene from the halogen containing agents.
2. **Flammability and explosive properties**—These are serious disadvantages, even electrocautery cannot be done to stop small bleeding point in such situations.
3. **Prolonged induction**—Slow with ether due to its relatively high water solubility. Anesthesia is, therefore, usually induced with rapidly acting intravenous anesthetic, Thiopental sodium.
4. **Irritant action**—Ether is particularly be mentioned, because of producing bronchoconstriction and increased secretion of mucus and saliva, both of which may obstruct the airways and cause laryngospasm.
5. **Sympathetic stimulation**—Anxiety and fear in a patient before the operation increases the level circulating Adrenaline and this is raised further, when induction is slow and strongly occurs. Ether itself however, stimulates the sympathoadrenal mechanism during induction, therefore temporary rising the H/R and BP. Ether does not sensitize the myocardium to the action of circulating catecholamines.
6. **Other CNS effects**—Ether depresses myocardium, on the other hand, chloroform depresses the heart and blood vessels from the start of induction and this effect coupled with the sensitization to Adrenaline makes Cyclopropane particularly liable to precipitate ventricular fibrillation during induction.
7. **Inadequate muscle relaxation**—None of the members of nitrous oxide, ethylene and cyclopropane by themselves in subtoxic dose produce adequate muscle relaxation for major surgery. That is why muscle relaxation is achieved either by the use of neuromuscular blocking, drugs or by nerve blocking, produced by local anesthetics.
8. **Postoperative complications**.

a. **Renal failure**—Methoxyflurane through metabolism, releases fluoride, which by inhibiting the enzyme system responsible for reabsorption of sodium in the ascending limb of loop of Henle produce polyurea.

In addition, oxalate excretion is increased about four fold after methoxyflurane anesthesia, the oxalate probably being derived from metabolism of the anesthetic.

b. **Jaundice**—There is an increased risk, if a patient is exposed to Halothane more than once.
c. **Malignant hyperpyrexia**—This is rare but may be a fatal complication. It occurs in patients suffering from myopathy. These main manifestation of syndrome are a rapid rise in body temperature generally muscular rigidity and severe metabolic acidosis.

COMPLICATIONS

They vary depending upon
1. The drug used
2. State and general health of the patient
3. Whether or not the premedication was used and also to what extent
4. On the skill and experience of anesthetist.

A short list includes
1. Cardiac arrhythmias
2. Fall of BP
3. Aspiration of gastric contents
4. Respiratory failure and laryngospasm.

TOXICITIES

1. Malignant hyperthermia – See earlier
2. Carcinogenicity—Persons having chronic exposure in GA have a higher rate of cancer.
3. Miscarriages have a correlation between prolonged exposure and miscarriages.
4. Anemia—Chronic exposure can cause megaloblastic anemia.

SECTION-III (F) ANTIPSYCHOTICS

OVERVIEW

All the neuroleptic drugs reduce the hallucinations and delusions associated with schizophrenia (the so-called 'positive' symptoms). By blocking D_2 receptors in the mesolimbic system of the brain. The negative symptoms such as blunted affect, anhedonia (not getting pleasure from normally pleasurable stimule) apathy and impaired attention as well as cognitive impairment are not as responsive to therapy, particularly with the typical neuroleptics. Some atypical agents such as Clonazepine ameliorate the negative symptoms to some extent.

The antipsychotic effects usually take several weeks to occur suggesting that therapeutic effects are related to secondary changes in the corticostriatal pathway.

- Definition of schizophrenia
- Dopamine hypothesis
- Antischizophrenics
- Chlorpromazine
  - Pharmacokinetics
  - Pharmacodynamics
- Pharmacological effects of antipsychotics
- Adverse actions
- Contraindication and cautions
- Drug interaction.

DEFINITION OF SCHIZOPHRENIA

Schizophrenia is a psychosis characterized by a clear consciousness but a marked thinking disturbance (delusion and hallucination) and associated with aggressiveness, agitated behavior (positive schizophrenics) or with emotional blunting, poor socialization, and cognitive deficit (negative schizophrenics).

DOPAMINE HYPOTHESIS

Pharmacotherapy for schizophrenia and delusional disorders rests on the administration of agents that are commonly known as antipsychotic or neuroleptic drugs.

In general, they mostly act by blocking dopaminergic D_2-receptors in the mesocortical-mesolimbic area of the brain and as such the disorders of schizophrenia and delusion are explained as hyperactivity of dopamine neurotransmitter in the said area (dopamine hypothesis of psychosis).

However, the hypothesis is far from complete or unequivocal and involvement of other neurotransmitters like serotonin and aspartic acid are gaining emphasis.

Besides their predominant effect on dopamine receptors, most of the useful antipsychotics, particularly the old typical ones, also block cholinergic muscarinic, histaminergic H_1 and alpha-adrenergic receptors and can produce wide range of pharmacological effects.

ANTISCHIZOPHRENICS

Depending on extrapyramidal adverse effects—

Depending on the propensity to cause extrapyramidal adverse effects the commonly used antipsychotic drugs can be classed.

- **Category 1**—It includes Chlorpromazine, Methotrimeprazine, Promethazine, Thiothixene, Risperidone, Chlorprothixene, Molindone, and Perphenazine and is characterized by moderate extrapyramidal adverse effects.

- **Category 2**—Drugs are Thioridazine, Mesoridazine, Olanzapine, Clozapine, Sertindole, Ziprasidone, and Quetiapine and have fewer extrapyramidal adverse effects than category 1 and 3 drugs.
- **Category 3**—Drugs are characterized by more pronounced extrapyramidal adverse effects than category 1 and 2 drugs. This category includes Fluphenazine, Prochlorperazine, Trifluoperazine, Haloperidol, Pimozide, Flupenthixol, Sulpiride, Loxapine. In general, antipsychotic drugs are more effective in cases of positive schizophrenics than in patients with negative symptoms. The antipsychotics can also be used to Quieten disturbed patients with brain damage, mania, toxic delirium or agitated depression.

Chemical Classification

1. Phenothiazines → Aliphatic → Chlorpromazine
   Piperazine → Fluphenazine
   Piperidine → Thioridazine
2. Thioxanthenes → Thiothixene
3. Butyrophenones → Haloperidol
4. Others → Molindone.

CHLORPROMAZINE

Pharmacokinetics

Absorption after oral administration is irregular, bioavailability is around 30% but if given IM bioavailability increases sharply. It remains bound with plasma protein. The peak plasma conc. is reached between 2–4 hours and then begins to fall. The fall is due to two reasons—(i) Part of the drug is metabolized and eliminated. (ii) Rest finds its way into the adipose tissue, because of excessive lipid solubility it has a great volume of distribution. Metabolized by oxidation in hepatic microsomes. It yields 60 different metabolites, among these the 7 hydroxy derivatives are active metabolites. After metabolic degradation, some products then conjugated with glucuronic acid. The products are ultimately removed by urine.

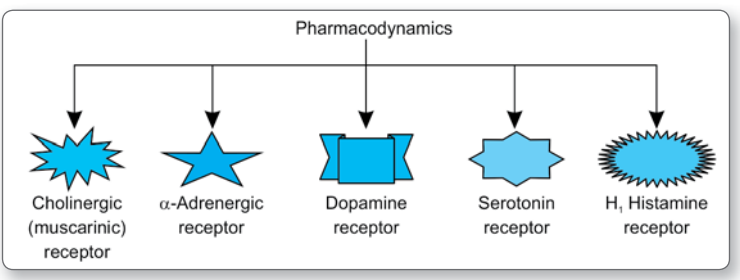


Fig. 6.18: Different receptors of chlorpromazine action

Chlorpromazine block D_2-receptors: Schizophrenia occurs, when there is overactivity of the Dopaminergic receptors in the **mesolimbic-mesocortical pathway**. Therefore, Chlorpromazine acts as an antipsychotic agent. It also produces drug-induced parkinsonism by blocking of Dopaminergic activity in the **nigrostriatal pathway** and this effect can be reversed by applying Levodopa or Bromocriptine. By blocking the Dopaminergic activity on **tuberoinfundibular pathway**, it can cause hyperprolactinemia (because DA inhibits prolactin release). It increases appetite, probably by involving the **medullary periventricular pathway**, which has got some role in eating behavior. The function of **incertohypothalamic pathway** is yet unknown.

PHARMACOLOGICAL EFFECTS OF ANTIPSYCHOTICS

1. Antipsychotic—By suppression of D_2-receptors produce relief of schizophrenia. It is the fundamental weapon against schizophrenia.
2. Antiadrenergic effects—Some antipsychotics can block α_1-receptors and can produce orthostatic hypotension.
3. Antiserotoninergic action—Particularly Clonazepine has strong 5-HT_2 blocking effect.
4. Antihistaminic action.
5. Antimuscarinic action—It is produced by blocking the muscarinic receptors.
6. Antiemetic action—It is due to DA blocking effect chiefly in CTZ.
7. Quinidine like action—Thioridazine can cause ECG abnormalities ventricular arrhythmias or heart block even sudden cardiac death.
8. Arrhythmic action—Sertindole causes prolongation of QT wave in ECG and thus can cause dangerous cardiac arrhythmia.
9. Local anesthetic action.
10. Diuretic effects.
11. Antihiccough—It benefits in hiccough.
12. Antipruritic effects—Promethazine HCl is used chiefly against allergic conditions – Antipruritic effect.
13. Anticonvulsant effects is seen in eclampsia.
14. Preanesthetic medication—It is due to antimuscarinic + antiemetic + antihistaminic effects.

ADVERSE ACTIONS

A. Neurological
   i. CNS

Parkinsonism	→	DA blockade in the nigrostriatal pathway
Akathisia	→	It is an uncomfortable motor restlessness like parkinsonism It occurs due to conventional drugs.

Dystonia
Tardive dyskinesia → Result symptoms as lateral jaw movements and sudden protrusion of the tongue as if the patient is trying to catch a fly in the air and so on. Some speculations is due to DA supersensitivity.

ii. ANS

Urinary retention ← Antimuscarinic action

Failure to ejaculation
Othostatic hypotension ← Due to alpha blockade

B. CVS—Orthostatic hypotension and fall of BP ← alpha blocking action
ECG—changes ← Quinidine like effects

C. Endocrine and metabolic

amenorrhea → Due to DA blockade by neuroleptics leads to
Galactorrhea → Hyperprolactinemia. Hyperprolactinemia in the male can
Loss of libido in males → cause decrease of sex appetite (libido) and gynecomastia while in female it causes galactorrhea and amenorrhea

D. Others
Neuroleptic malignant syndrome
Retinal and corneal deposits
Cholestatic jaundice ← Due to hypersensitivity reaction

CONTRAINDICATIONS AND CAUTIONS

Chlorpromazine should be used with caution in patients with—

1. Hepatic disease
2. Cardiovascular disorder
3. Glaucoma
4. Brain damage
5. History of seizure
6. Elderly patients
7. Pregnant women
8. Lactating mother. It is contraindicated in children with CNS infection, chickenpox, gastroenteritis and dehydration.

DRUG INTERACTION

1. Chlorpromazine + Riboflavin ← increased urinary excretion of riboflavin due to metabolic inhibition of riboflavin.
2. It (Chlorpromazine) reverses the Amphetamine-induced psychosis.
3. Chlorpromazine + ACE inhibitor—Severe postural hypotension.
4. It potentiates the CNS depression by alcohol and sedative hypnotic.

5. Anticholinergic action is potentiated if it is coadministered with Atropine.
6. Decrease the hypoglycemic effect of antidiabetics.

SECTION-III (G) MANAGEMENT OF NEURO–DEGENERATIVE DISEASES

- Overview
- Parkinsonism
  - Definition
  - Treatment strategy
  - Drugs effective in parkinsonism
  - Levodopa + Carbidopa
- Alzheimer disease
  - Drugs used

OVERVIEW

Neurodegenerative diseases of the CNS include

i. Alzheimer disease
ii. Parkinson disease
iii. Huntington disease
iv. Amyotrophic lateral sclerosis.

These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition or both. For example, Alzheimer disease is characterized by the loss of cholinergic neurons in the nucleus basalis of Maynert, whereas Parkinson disease is associated with a loss of dopaminergic neurons in the substantia nigra.

PARKINSONISM

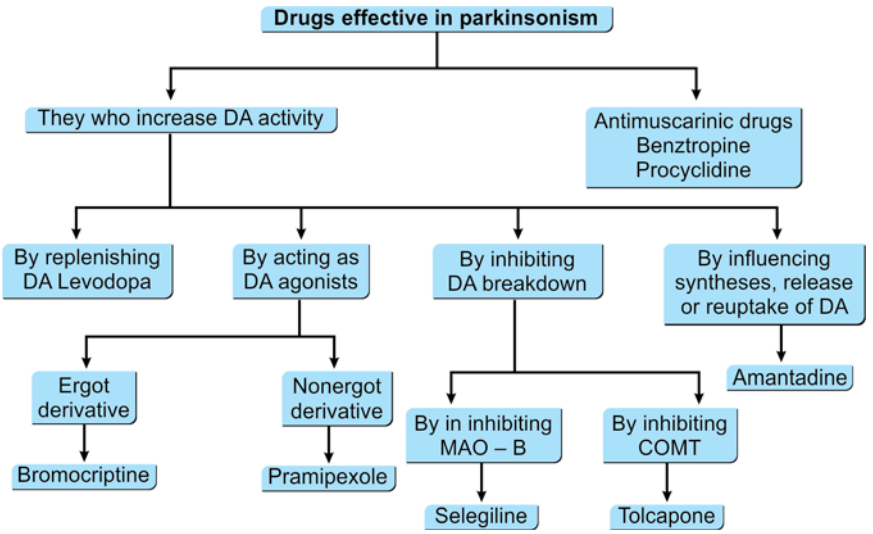
Definition

Parkinsonism is a disease of basal ganglia of brain, characterized by tremor, rigidity and akinesia which includes—

1. Paralysis agitans
2. Postencaphalitic parkinsonism
3. Wilson's disease
4. Shy-Drager syndrome
5. Mn- intoxication
6. Drug-induced parkinsonism.

Treatment Strategy

Among others, two NTs, DA and ACh deserve special attention so for as parkinsonism is concerned. In the striatum, the DAergic and cholinergic activities are balanced. In parkinsonism, the DAergic activity is remarkably low, so that cholinergic activity takes the upper hand. The rational drug therapy therefore, will be—(i) Either to increase the local availability of DA by (Levodopa, Selegiline), or to increase DAergic receptor activity by bromocriptine. (ii) Lower the cholinergic activity by anticholinergic rather than antimuscarinic drug, e.g by trihexylphenidyl. Very often these two types may be combined to treat the same individual.



Levodopa

(DOPA—dihydroxy phenylalanine)

- Chemistry
- Pharmacokinetics
- Pharmacodynamics
- Adverse actions
- Drug interaction
- Cautions

Chemistry

Levodopa on decarboxylation, becomes dopamine

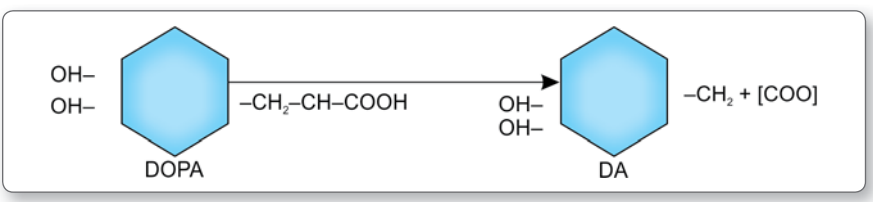


Fig. 6.19: Structure of DA

Pharmacokinetic

During absorption, a major portion of the drug is converted to DA by the intestinal amino acid decarboxylase, DA cannot penetrate the blood brain barrier but levodopa can. Therefore, conversion of Levodopa to DA represents a loss of the drug for its availability in the basal ganglia, where it is required. Even after reaching the blood, the surviving Levodopa is partly again decarboxylated by the same decarboxylase, present in different peripheral tissues. Ultimately, only about 2% of unchanged Levodopa, thus can reach the basal ganglia.

If a proper therapeutic action is desired, and if Levodopa alone be administered huge amount must be orally taken. Moreover, in this way, a huge excess of DA appears in the peripheral tissue, which is undesirable. Levodopa, therefore, is usually given with other drugs, i.e. Carbidopa, which prevents such conversion.

Pharmacodynamics

There is a deficiency of DA in basal ganglia and loss of DAergic fibers of substantia nigra, There are 5 subtypes of DA receptors. The DAergic fibers are destroyed in parkinsonism but their receptors survive. It is believed that the improvement seen in parkinsonism after Levodopa therapy is due to binding of DA with DA_2-receptor and its subsequent effects. However, paralysis agitans is a progressive disease and Levodopa cannot inhibit the progression.

Carbidopa

Levodopa is converted to DA by the enzyme amino acid decarboxylase (DC). Carbidopa inhibits DC, so that DA is not formed. However, carbidopa cannot cross the BBB, but levodopa can. Therefore, Carbidopa is concurrently given with Levodopa. DA formation from Levodopa does not occur anywhere in the periphery, but DA formation occurs in the brain.

Adverse actions

GIT—Nausea and vomiting ← central action. DA acts on medullary vomiting center.
CVS—Various arrhythmias-tachycardia extrasystole flutter, fibrillation, some of which are alarming hypotension as DA causes vasodilatation)
CNS—Involuntary movements

1. Choreiform movements.
2. Psychiatric problems—Schizophrenia-like symptoms.

Drug interaction

Pyrodoxine acts like Carbidopa.
Selegiline a MAO -B inhibitor prolongs the effects of Levodopa.

Cautions

Levodopa should be used with greater caution or the best avoided in—
1. Psychotic disorders
2. Ischemic heart disease
3. Peptic ulcer cases.

ALZHEIMER DISEASE

Drugs Used

Pharmacologic intervention for Alzheimer disease is only palliative and provides modest short-term benefit. None of the current therapeutic agents alter the underlying neurodegenerative process. Alzheimer dementia has three distinguishing features: (i) accumulation of senile plaques (β-amyloid accumulations), (ii) formation of numerous neurofibrillary tangles, and (iii) loss of cortical neurons—particularly cholinergic neurons. Current therapies are aimed at either improving cholinergic transmission within the CNS or preventing the excitotoxicity actions of NMDA glutamate receptors in selected brain areas.

Currently, four reversible AChE inhibitors are approved for the treatment of mild to moderate Alzheimer disease. They are Donepezil, Galantamine, Rivastigmine and Tacrine. Except for Galantamine, which is competitive, all are uncompetitive inhibitors of AChE and appear to have some selectivity for AChE in the CNS as compared to the periphery.

Overstimulation of glutamate receptors, particularly of the NMDA type, has been shown to result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative processes. Antagonists of the NMDA glutamate receptor are often neuroprotective, preventing the loss of neurons following ischemic and other injuries. Memantine is a dimethyl adamantine derivative related to Amantadine. It is an uncompetitive inhibitor of NMDA receptors and has been shown to prevent or slow the rate of memory loss in both vascular-associated and Alzheimer dementia.

SECTION-III (H) ANTIDEPRESSANTS

- Introduction
- Hypothesis
- Pictures of untreated endogenous depression
- Drugs – classification
- Individual groups of drugs
  a. Tri and Tetracyclics
  b. MAOIs
  c. SSRI.

INTRODUCTION

Mental depression is a form of affective disorder, where mood is changed, i.e. depressed.

The symptoms of depression are intense feelings of sadness, hopelessness and despair, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy and suicidal thoughts. Mania is characterized by the opposite behavior that is, enthusiasm, rapid thought and speech pattern, extreme self-confidence and impaired judgment. [Note: Depression and mania are different from schizophrenia, which produces disturbances in thought].

Depression itself can be subdivided into—(i) endogenous depression and (ii) reactive depression. In reactive depression, there is an external cause for depression, e.g. failure in a critical examination or death of a beloved one and so forth. In endogenous depression, there is no external cause, the patient is mentally depressed for nothing and such cases are the most important cases, from our point of view.

The antidepressant drugs are very effective against endogenous depression but not so effective against reactive depression.

HYPOTHESIS

The balance of opinion, favors that there is some abnormal functioning of monoaminergic neurons in the brain. In depression, there is deficiency of the NA or 5-HT or both; alternatively, there may be deficiency of NAergic or serotonergic receptors.

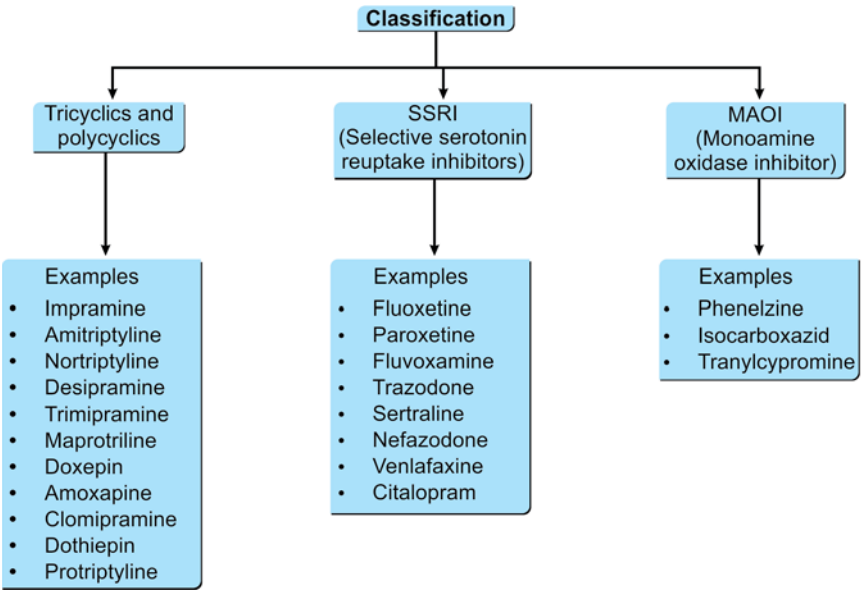
Apart from simple deficiency or excess of monoamines, others, i.e. environmental and genetic factors are also involved in depression.

PICTURES OF UNTREATED ENDOGENOUS DEPRESSION

a. Signs and symptoms appear—Patient suffers for a couple of months → signs and symptoms disappear → After a variable period the depression again recurs → and so on; the diagnosis of endogenous depression can now be made.
b. Depression is a chronic disease and its duration often exceeds the average duration of many nonpsychiatric medical diseases perceived as chronic. This is because the illness appears early in life and persists lifelong.
c. Depressives often develop suicidal tendency so, when the clinician first sees the case and the patient is already spoiling for suicide, as 'stopgap' arrangement ECT must be done.
d. Most cases of depression are idiopathic in origin. Nevertheless, secondary depressions are common. Thus depression due to—(i) drugs, (ii) alcohol, (iii) diseases, and (iv) vitamin deficiency are well-known.

e. Treatment of depression includes many measures other than the drugs, i.e. counseling, supportive treatment and psychotherapy.

DRUGS–CLASSIFICATION



INDIVIDUAL GROUP OF DRUGS

Tri and Tetracyclics

Pharmacokinetics

Tri and tetracyclics are incompletely absorbed, suffer a good deal of first pass effect, peak level in blood is reached between 2–8 hours. The lipid solubility is excellent and, therefore their volume of distribution (Vd) is very high.

The tertiary amines are broken down to secondary amines in the body. All tri and tetracyclics are metabolized in the liver → conjugated with glucuronic acid and rendered water-soluble → excreted via liver. Hepatic insufficiency thus can cause signs of toxicity.

Pharmacodynamics

1. They inhibit reuptake of NA and serotonin (5-HT)—The MARl action.
2. Block the muscarinic and histaminic receptors.

It is agreed that the MARl action is responsible for antidepressant effect while the antimuscarinic and antihistaminic actions produce side effects.

The tri and tetracyclics cause MARl effect → increase in the local availability of NA as well as 5-HT → relief from depression. However, this can cause the overactivity of α/β-receptors → on CVS. Also antimuscarinic effects in the periphery can produce an atropine like effect. They should, as a rule have some antihistaminic effects also.

Clinical benefit needs 2–4 weeks from the time of initiation of treatment, but why?

There are some speculations regarding this delay of benefits are—

1. Down-regulation of receptors—Excess NA in the synaptic gap in the local region due to use of TCA leads to down regulation of β-adrenoreceptors.
2. Increased sensitivity for 5-HT receptors ultimately relieves depression.

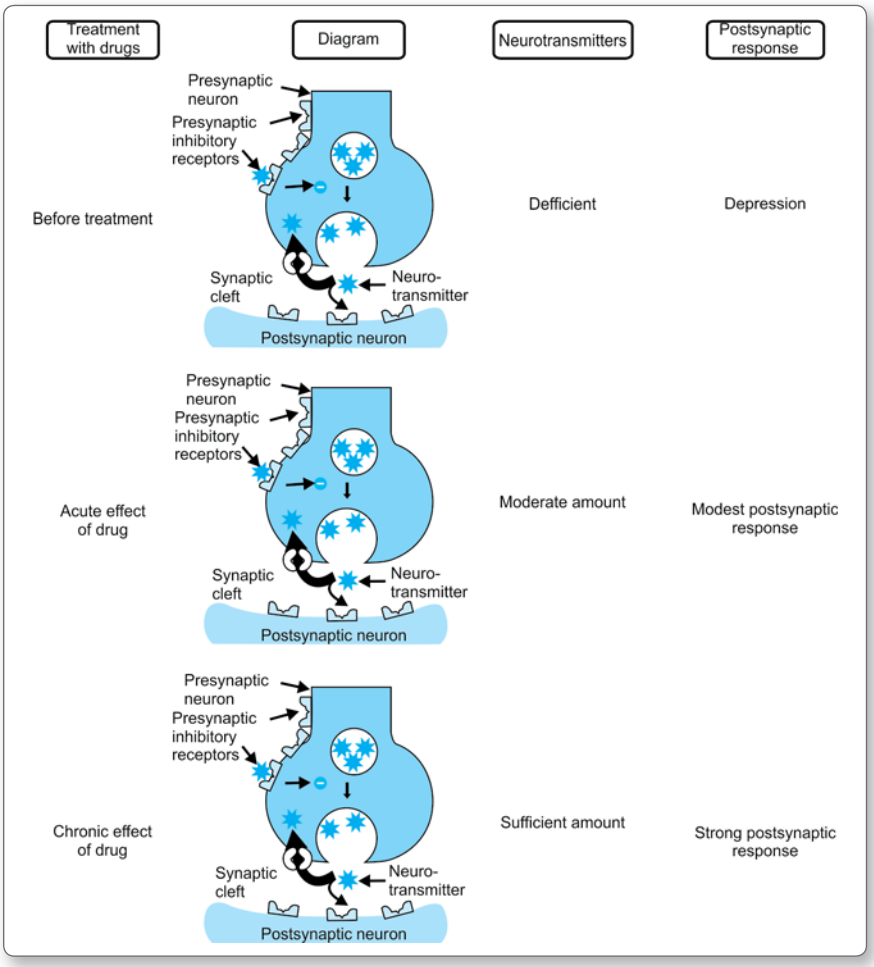


Fig. 6.20: The mechanism of action of TCA

3. Neurotrophic factors—There occurs some beneficial effects on neurotrophic factors.
4. Blocker of some receptors, like adrenergic, histaminic and muscarinic receptors.

When there is excessive activity of a hormone, or a chemical neurotransmitter, the receptor population diminishes in the target cell—the phenomenon being called down-regulation. When MARI or MAOIs act there is excessive availability of the concerned monoamines leading to fall of receptor population in the postsynaptic membrane.

Clinical benefits correlate excellently with the fall of receptor population, following antidepressant therapy.

Pharmacological effects

CNS: i. Mood—In normal persons tri or tetracyclics do not produce mental elation. However, in depressives, mood is elevated.
ii. Sleep—Many tri or tetracyclics are also sedative.

ANS: They have complex effects on ANS. Many of the members have antimuscarinic and alpha receptor blocking effects.

CVS: i. Tachycardia → Due to alpha blocking and antimuscarinic effects.
ii. Postural hypotension → Due to alpha blocking action.
iii. Direct toxic effect → On the myocardium.
iv. ECG changes → Delayed cardiac conductivity.

Clinical uses

They are primarily used in—
1. Depression mainly in major depression
2. Depressive episodes of bipolar disorders
3. Panic disorders, i.e. agoraphobia
4. General anxiety disorders
5. Obsessive compulsive disorder
6. Chronic pain, including headache
7. Childhood enuresis
8. Some forms of peptic ulcer
9. In attention hypersensitive deficit syndrome.

Adverse effects

1. Antimuscarinic actions—Dry mouth, constipation, blurring of vision, mental confusion, tachycardia, urinary retention
2. Sedation
3. Orthostatic hypotension, ECG abnormality, heart block
4. Epileptiform seizures
5. Allergy
6. Weight gain.

MAOIs

The enzyme MAO has two subtypes—MAO-A and MAO-B. Both the types of MAO cause degradation of monoamines. However, MAO-A is found in the gut, liver, CNS and sympathetic terminals whereas MAO-B is restricted to CNS and blood vessels.

Clorgyline selectively inhibits MAO-A whereas Selegline selectively inhibits MAO-B.

Drawbacks

Cheese Reaction: There are some foods and drinks, i.e. aged cheese, animal liver, fava or broad beans, meat, alcoholic drinks which are reach in tyramine. If these are ingested, there should be a threat that of rise of plasma tyramine concentration. However, normally this does not occur because gut wall contains heavy concentration. of MAO-A leading to degradation of tyramine.

Hypertension: In presence of MAOI, MAO-A is inhibited → excess tyramine in the body → as tyramine can behave as NA → signs of sympathetic overactivity → hypertension.

There is another reason so as to how a MAOI can elevate BP; MAOI → less degradation of NA in the sympathetic nerve terminal → NA accumulation → hypertension.

Selective Serotonin Reuptake Inhibitors (SSRI)

- Mechanism of action
- Advantages of SSRI
- Clinical uses
- Adverse effects
- Drug interaction.

Mechanism of action

1. Selectively and reversibly inhibits serotonin reuptake in serotonergic nerve
2. No antimuscarinic or antihistaminies effect.

Advantages of SSRI

1. Greater efficacy than older drug
2. Lack of antimuscarinic effect (main), so can be given in patient with BPH in old age, where TCA cannot be given
3. Less cardiovascular effect
4. Less or no sedation
5. Safe in a relatively overdose

6. Less sexual dysfunction
7. No problem with weight gain
8. No food reaction.

Clinical uses

1. SSRIs are primarily used in endogenous depression
2. They (=SSRIs) can be used in obsessive-compulsive disorders
3. In bulimia, Fluoxetine is effective.

Adverse effects

1. Anorexia
2. Sexual hypofunction
3. Loss of libido
4. Anxiety
5. Tremor.

Drug interaction

1. Fluoxetine reduces the hepatic degradation of TCS – TCA toxicity can develop.
2. Combination of SSRI and MAOI can be dangerous.
3. Serotonin syndrome – MAOI increases the store of monoamine in the neurons. SSRI prevents removal of serotonin from the synaptic gap. Combination of these two can lead to dangerously high level of serotonin in the synaptic gap—Leading to what is known as serotonin syndrome. There is hyperthermia, muscle rigidity and mental deterioration.

SECTION-III (I) ANTIEPILEPTICS

- Definition
- Preliminary notes
- Hypothesis
- Causes
- Types of seizures
- Drugs used in epilepsy
- Common mechanism of action—
  a. Blockage of NMDA receptors
  b. Enhancement of GABA mediated inhibition
  c. Modification of low threshold Ca^{++}
  d. Inactivation of ion channel

- Individual drugs
  1. Phenytoin
     a. History
     b. Mechanism of action
     c. Pharmacokinetics
     d. Indication
     e. Contraindication
     f. Adverse effects.
  2. Carbamazepine
     a. Mechanism of action
     b. Clinical uses
     c. Adverse effects.

DEFINITION

Group of disorders in which there are recurrent episodes of altered cerebral function associated with paroxysmal excessive and hypersynchronus discharge of cerebral neurons, which may or may not be associated with loss of consciousness.

PRELIMINARY NOTES

a. Incidence—Between 0.5%–2% of the population suffers from epilepsy.
b. Prognosis—With proper treatment about 70% of the epilepsy patients remain symptom-free.
c. Drugs—Epilepsy can be controlled by a single drug (monotherapy).
d. Character—Epilepsy is characterized by recurrent episodes of seizures.
e. Febrile convulsion—In the children and convulsions due to hypoglycemia should not be called epilepsy.

HYPOTHESIS

At molecular level, cause of the development of epileptic focus in the brain is one of the followings:
(1) Deficiency of GABA activity or excess NMDA activity in the local neurons of the focus. GABA activity leads to opening of the Cl^- channel in the cell membrane of the neuron → influx of Cl^- from ECF to ICF → Hyperpolarization.

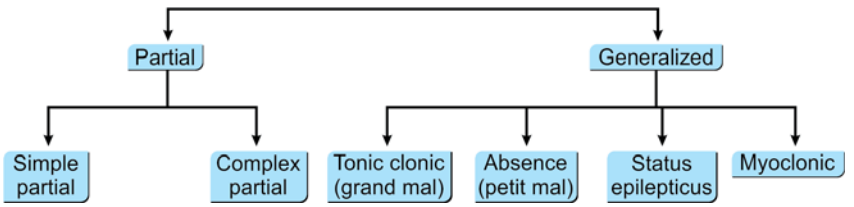
On the other hand, NMDA receptors are a variety of glutamic acid receptors. Glutamic acid is an excitatory neurotransmitter. Therefore, excess NMDA activity → hyperirritability.

CAUSES

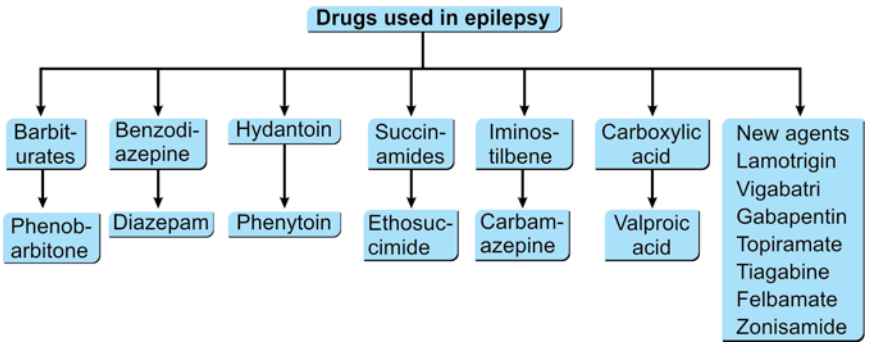
1. Primary of idiopathic
2. Secondary
   a. Tumor

b. Head injury
c. Hypoglycemia
d. Meningeal infection
e. Rapid withdrawal of alcohol from an alcoholic.

TYPES OF SEIZURES



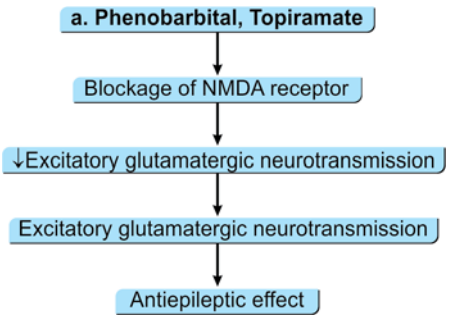
DRUGS USED IN EPILEPSY



COMMON MECHANISM OF ACTION

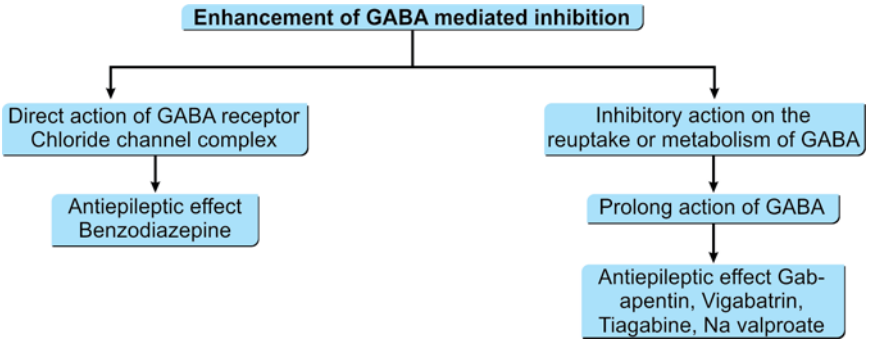
Blockage of NMDA Receptors

Glutamic acid causes increased synaptic transmission. A variety of glutamic acid receptor is NMDA receptors. Reduction of NMDA receptor activity can reduce seizure development.



Enhancement of GABA Mediated Inhibition

Some drugs, Benzodiazepine, Phenobarbital, Vigabatrine can increase GABA activity in the synapse causing neuronal inhibition–Antiseizure effect.

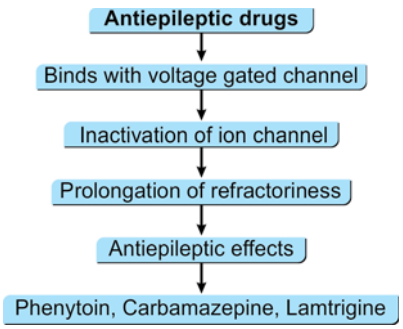


Modification of Low Threshold Ca^{++}

A low threshold Ca^{++} current (influx) helps to produce petit mal or absent seizure. Drugs which reduces this low threshold Ca current abolish petitmal seizure.

Inactivation of Ion Channel

Entry of Na^{+} via Na^{+} ion channel cause depolarization of neuron in the brain. After such a depolarization, the ion channel enters an inactive state. Some drugs can prolong this inactive state of Na^{+} ion channel which leads to refractoriness of the neuron to any stimulus.



INDIVIDUAL DRUGS

Phenytoin

History

Phenytoin (Diphenylhydantoin): It was synthesized in 1908 as a barbiturate analogue but shelved due to its poor sedative property. Its

anticonvulsant activity was specially tested in 1938 and since then it is a primary antiepileptic drug.

Mechanism of action —See above.

Pharmacokinetics

Absorption of phenytoin by oral route is slow, mainly because of its poor aqueous solubility. Bioavailability of different market preparations may differ. It is widely distributed in the body and is 80% to 90% bound to plasma proteins.

Phenytoin is metabolized in liver by hydroxylation and glucuronide conjugation. The kinetics of metabolism is capacity united; changes from first order to zero order over the therapeutic range—small increments in dose produce disproportionately high plasma concentration.

Indications

1. Epilepsy
2. Dysrrhythmias
3. Trigeminal neuralgias.

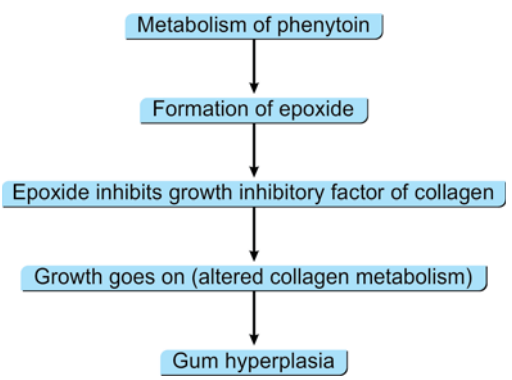
Contraindications

1. Hepatitis
2. Pregnancy
3. History of hypersensitivity.

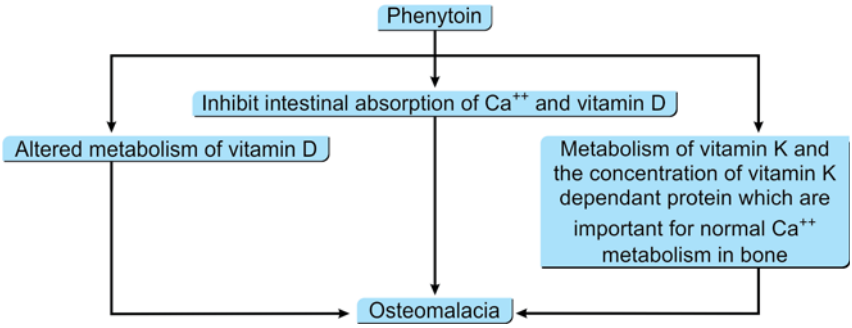
Adverse effects

These are numerous; some occur at therapeutic plasma concentration after prolonged use, while others are a manifestation of toxicity due to overdose.

1. **Gum hyperplasia**—Mechanism

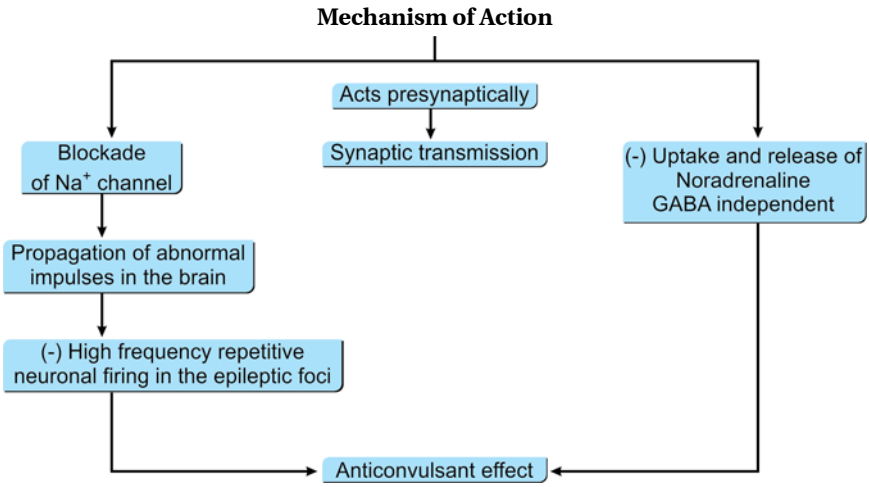


2. **Osteomalacia** – Mechanism



3. **CNS**—Nystigmus, ataxia, diplopia, confusion, vertigo, dystonia.
4. **Hematological—**Megaloblastic anemia, blood dyscrasias, lymphadenopathy.
5. **Bone marrow**—Depression.
6. **Teratogenicity**—Cleft palate, spina bifida.

Carbamzepine



Clinical uses

1. Epilepsy
2. Trigeminal neuralgia.

Adverse effects

1. Diplopia
2. Ataxia
3. Enzyme induction
4. Teratogenicity.

CHAPTER

7

Cardiovascular System

SECTION-I ANTIHYPERTENSIVES

- Physiological background
  - Definition of BP
  - Types
  - How it is expressed?
  - Control mechanism
- Antihypertensive drugs
  - Hypertension
  - Definition
  - Types
  - Causes
  - Drugs
- Clinical selection of antihypertensives.

PHYSIOLOGICAL BACKGROUND

Definition of BP

It is the lateral pressure exerted by the blood on the vessel wall perpendicularly while flowing through it.

Types

1. Systolic pressure: Pressure exerted during contraction (systole) of the heart.
2. Diastolic pressure: Pressure exerted during relaxation (diastole) of the heart.
3. Pulse pressure: It is the difference between systolic and diastolic pressure.
4. Mean pressure: It is the diastolic pressure + one-third of pulse pressure.

How it is Expressed

Blood pressure is directly equal or proportional to the product of cardiac output and the peripheral vascular resistance.

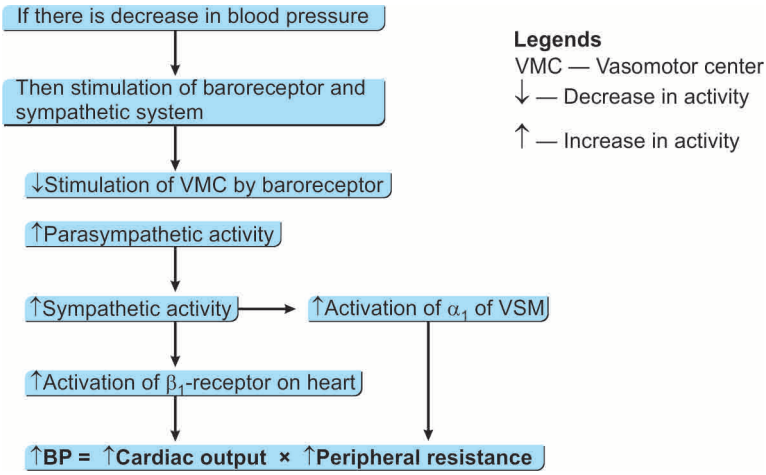
Blood pressure = Cardiac output × Peripheral resistance.

Control Mechanism

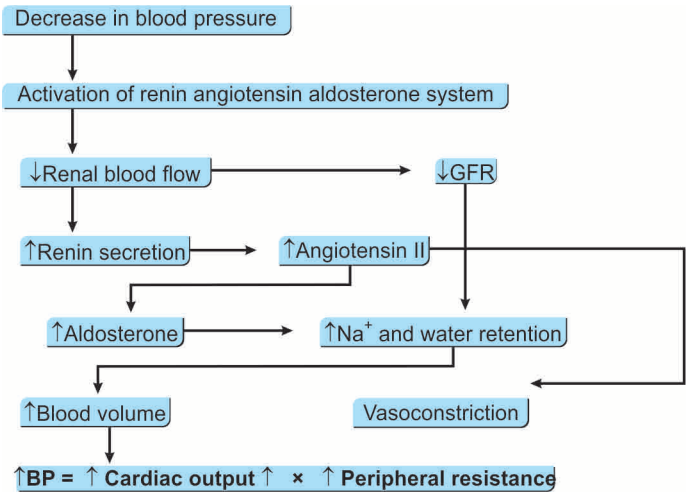
There are two ways of blood pressure control. These are—

1. Baroreceptor mechanism
2. Renin angiotensin aldosterone system.

Baroreceptor mechanism



Renin angiotensin aldosterone system



ANTIHYPERTENSIVE DRUGS (FIG. 7.1)

Hypertension

Definition

It is a condition where BP values are over 140/90 mm Hg.

Types

- Primary or essential —Where cause is unknown (Incidence 95%)
- Secondary — Where cause is known (Incidence 5%).

Causes

1. Renal cause – Renal artery stenosis, glomerulonephritis, polycystic kidney, diabetic nephropathy.
2. CVS cause – Coarctation of aorta.
3. Endocrine cause–Pheochromocytoma, Cushing syndrome, thyrotoxicosis.
4. Pregnancy – Preeclampsia, eclampsia.

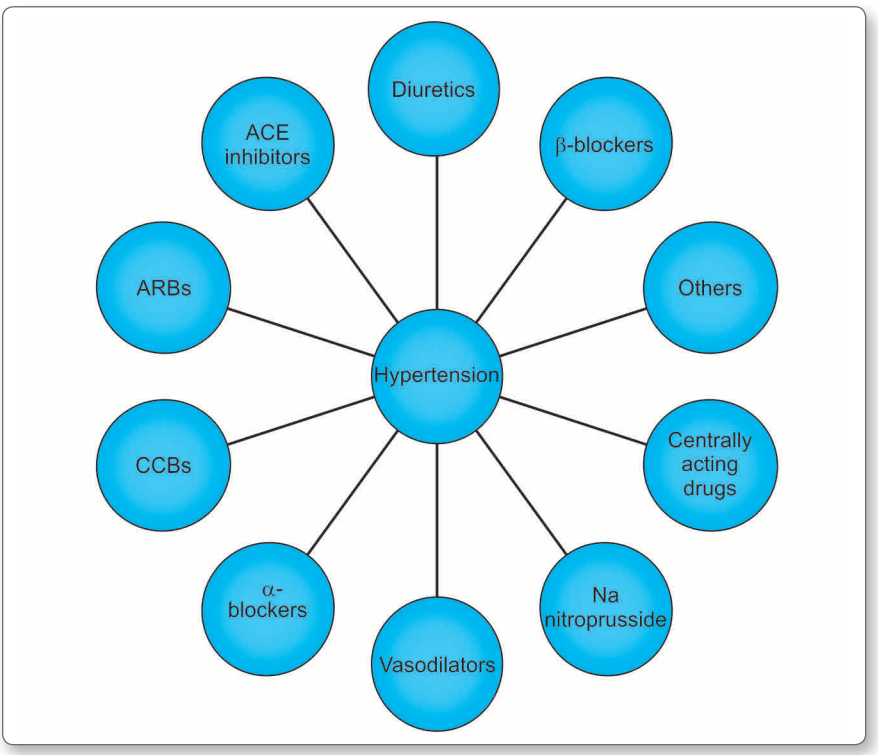
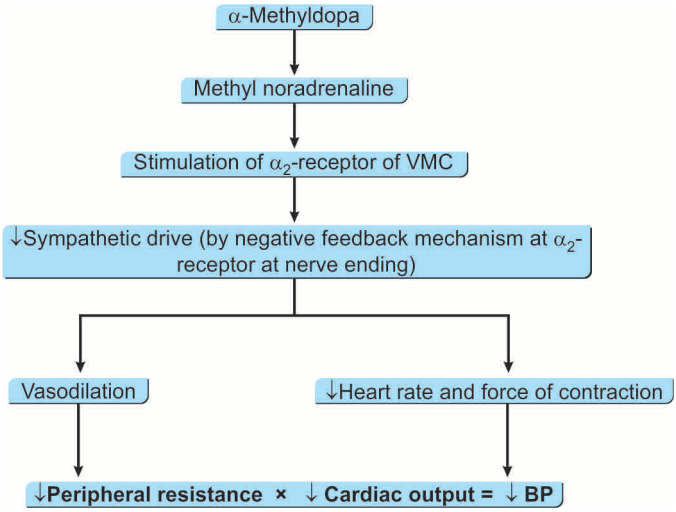


Fig. 7.1: Antihypertensive drugs

CENTRALLY ACTING ANTIHYPERTENSIVES, THAT IS METHYLDOPA, CLONIDINE

Mechanism of Action of Methyldopa



Properties

1. α-methyldopa is chemically related to dopa.
2. It is a prodrug.
3. It is converted to methyl noradrenaline.
4. Its acts as agonist of α_2-adrenergic receptors in the brainstem.
5. Methyldopa is a moderate efficacy antihypertensive.
6. Methyldopa had been a widely used antihypertensive for mild to moderate cases, specially in combination with a diuretic.
7. Antihypertensive effect develops over 4–6 hours and lasts 12–24 hours.
8. Circulating levels of NA and renin tend to fall due to reduction in sympathetic tone.
9. Inhibition of postural reflexes is mild.

Adverse actions

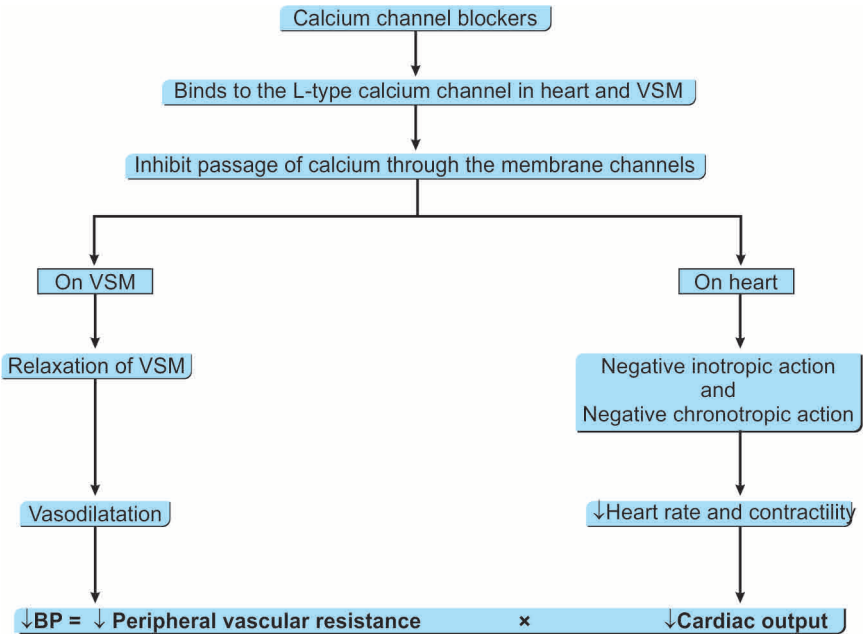
1. Drowsiness, sedation
2. Fatigue, nightmares
3. Fever, GIT upset, dry mouth
4. Parkinsonism, nasal congestion
5. Failure of ejaculation, hemolytic anemia
6. Gynecomastia, impaired lactation
7. Thrombocytopenia and rarely lupus
8. Fluid retention and weight gain.

Indication

It is popular in pregnancy with hypertension.

CALCIUM CHANNEL BLOCKERS (CCBs)

Mechanism of Action



Current Status

1. According to JNCV1 CCBs are not 1st line drugs but WHO recommend them as 1st line drugs.
2. They are very effective in elderly and also in black in USA.
3. They are also effective in low renin hypertension.

Outcome

(reduction of mortality in long-term study) and
Hard end point: Reduction of incidence of stroke/AMI.

1. Study are still going on and are awaited also.
2. It is dangerous to use short acting immediate release capsule formulation of Nifedipine for hypertension. Because they reduce blood pressure sharply as a compensatory mechanism CAs secretion occurs → injury of heart and coronary vessels can occur.
3. However Verapamil and Diltiazem lower blood CAs levels modestly.
4. Nifedipine raise CAs and angiotensin II level in blood modestly.

5. It is encouraging to know that long-term Nifedipine are (a) well-tolerated (b) effective in the old and diabetic (c) reduce stroke remarkably (d) preserve renal function.

Adverse Actions

1. Dizziness
2. Fatigue

– both are due to hypotension

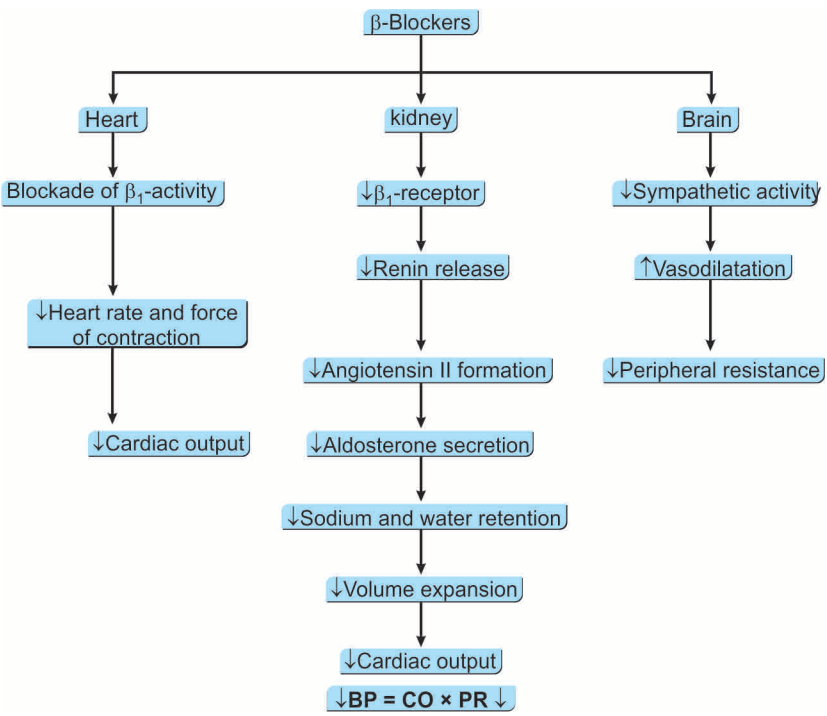
3. Some persons complain of headache
4. Verapamil can worsen CHF due to inhibition of myocardial contractility.

Contraindications

They include:
1. Unstable angina
2. Heart failure
3. Hypotension
4. Postinfarct cases
5. Severe aortic stenosis.

β-BLOCKERS

Mechanism of Action



Current Status

According to JNC:

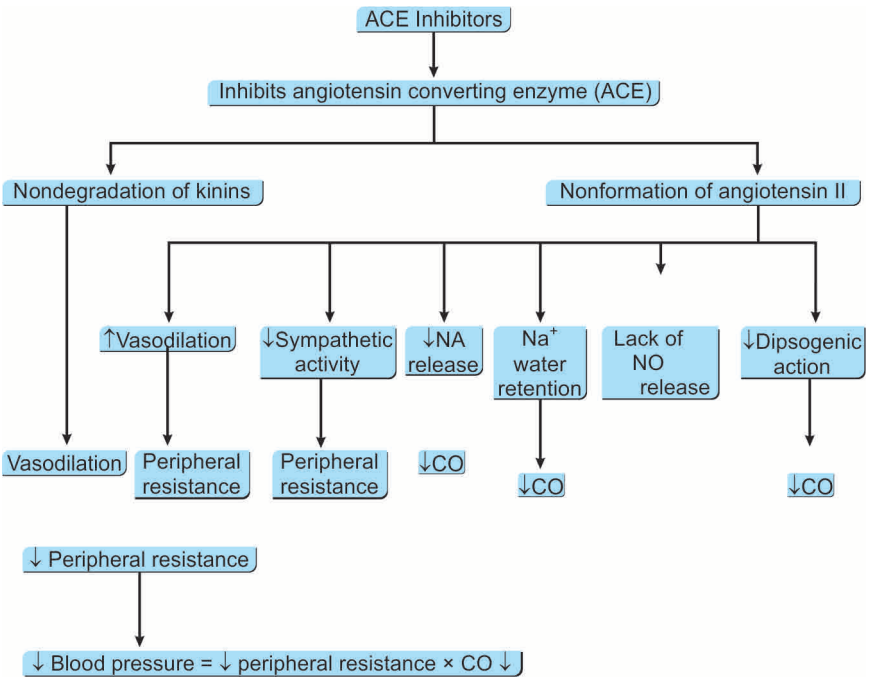
1. They are 1st line drugs in hypertension
2. They are very popular in subjects of hypertension with angina
3. In dyslipidemias with hypertension cardioselective β-blockers should be used.

Adverse Actions

1. Fatigue
2. Lethargy
3. Hypotension and impotence
4. Worsening of blood lipid profile
5. Some patients complain of nightmares
6. Sudden stoppage of β-blockers is dangerous. Because of they can precipitate sharp rise of BP and cardiac arrhythmia
7. Nonselective β-blockers can produce bronchospasm
8. β-blockers can adversely affect the CHF.

ANTIHYPERTENSIVE ACTION : ACE INHIBITORS

Mechanism of Action

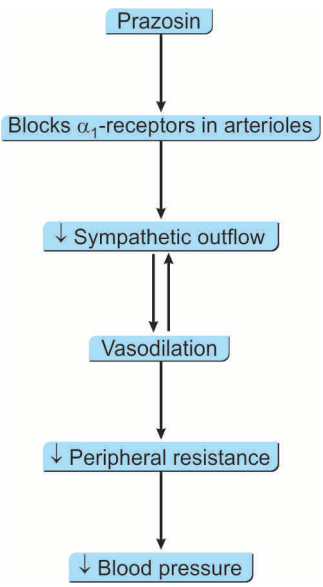


Current Status

1. According to JNC diuretics and β-blockers are 1st line of drugs in hypertension yet ACE inhibitors are becoming very popular.
2. They are particularly useful in hypertension complicated by diabetes, hyperuricemia, diabetic and hypertensive nephropathy and in postinfarct state.
3. Contraindications of ACE inhibitors are very rare.
4. They are however less effective in blacks in USA and elderly.
5. They can be used as monotherapy in mild or moderate hypertension.
6. They can be used where diuretic and β-blockers are proving insufficient.
7. When used as monotherapy, for full blown action salt restriction in the diet is important.

α-RECEPTOR BLOCKER

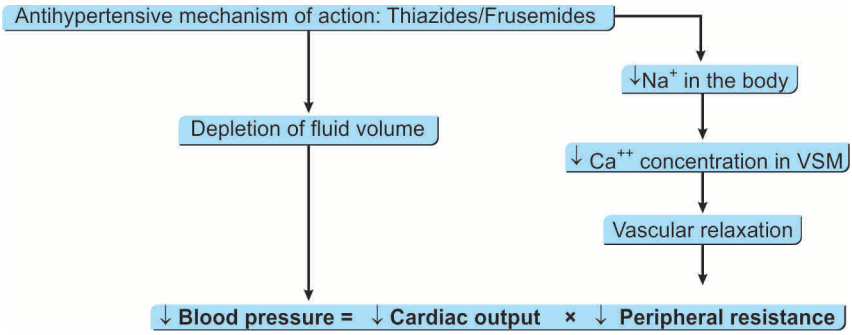
Mechanism of Action



Advantages

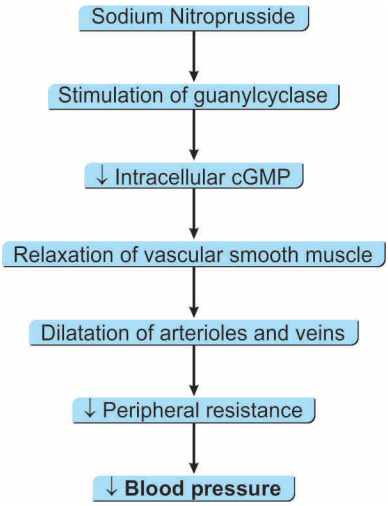
1. They improve the bad serum lipid profile.
2. They do not have adverse effects on blood glucose or serum potassium levels.
3. They are also helpful in BPH.

DIURETICS (SEE DETAILS IN SECTION : VI)



VASODILATORS

Mechanism of Action



Adverse Effects

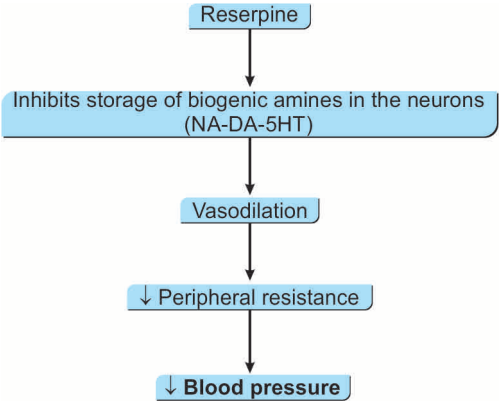
Includes—
1. Headache
2. Palpitation
3. Tachycardia
4. Cardiac arrhythmia
5. Lupus (rarely).

Indication (Minoxidil)

1. As an antihypertensive
2. As a promoter of growth of hair in baldness.

NONRECEPTOR ADRENERGIC INHIBITORS

Mechanism of Action



Side Effects

1. Depression/parkinsonism—Due to depletion of biogenic amines from brain neurons.
2. Peptic ulcer/nasal stuffiness—Due to parasympathetic overactivity.
3. Some fluid retention is common.
4. It also causes sedation.

CLINICAL SELECTION OF ANTIHYPERTENSIVES

- **Elderly patients**: Diuretics are the first choice of drugs. CCBs are very popular. ACE inhibitors are also very popular. As monotherapy β-blockers are not very useful. Very frequently, combination of more than one drug is needed.
- **For blacks**: Elderly blacks are somewhat resistant to ACE inhibitors. Blacks respond to diuretics, CCBs.
- **Patients with hyperlipidemia**: Minimum dose of diuretic+ α_1-blocker can improve lipid profile. CCBs + ACE inhibitors are lipid neutral. These group of patients needs simultaneous treatment of hyperlipidemia by diet – exercise – drug is mandatory.
- **Hypertension with angina**: β-blockers, CCBs as monotherapy or both together are agents of choice.
- **Diabetes with hypertension**: High dose diuretics or β-blockers are risky. CCBs has proved efficacy in diabetes with hypertension. ACE inhibitors appear to be very good drugs in this condition.
- **Pregnancy and hypertension**: Safe drugs for this condition are methyldopa or clonidine.
- **Hypertension with bronchial asthma**: CCBs as monotherapy or cardioselective β-blockers.

- **Hypertension with heart failure**: Diuretics or β-blockers or ACE inhibitors or ARBs.
- **Hypertension with previous myocardial infarction**: β-blockers or ACE inhibitors.
- **Hypertension with chronic renal disease**: β-blockers or ACE inhibitors or ARB or Ca channel blockers.
- **Hypertension with recurrent stroke**: ACE inhibitors or diuretics.

SECTION-II ANTIANGINAL DRUGS

- Overview
- Duration and characteristics of anginal pain
- Effects and dangers of angina
- Angina and diabetes
- Antianginal drugs.

OVERVIEW

Angina (pain) pectoris (chest) is a very common disease, mostly affecting middle-aged persons usually men.

Angina is caused by myocardial ischemia. Basically, there are two factors to be considered (i) the requirement (the demand) of the heart; and (ii) the O_2 supply, via the coronary blood flow. Obviously, fail of O_2 supply or rise of O_2 demand or combination of both the factors can precipitate an anginal attack. The whole phenomenon is often viewed as a balance of O_2 supply and O_2 demand.

DURATION AND CHARACTERISTICS OF ANGINAL PAIN

Usually anginal attacks occur occasionally and they are of short duration; but why?

Answer, may be like that; the balance of O_2 supply and demand is normally maintained but sudden spasm of the epicardial artery, (e.g. due to emotion) rise of O_2 demand due to physical demand hemorrhage in the atherosclerotic plaque and so forth can lead to unbalancing. However intense vasodilatation of coronary vessels produced by the resultant anoxia due to the angina relieves the attack, often without the necessity of using any drug.

EFFECTS AND DANGERS OF ANGINA

i. Ischemia can cause metabolic abnormalities of myocytes → K ions come out of the JdF to enter ECF → Whereas ECF Na^+ ions enter the myocytes → Disturbances of polarization of myocardium → Cardiac dysrhythmia.

Malignant ventricular arrhythmia can cause sudden cardiac death (SCD)

ii. Ischemia of myocardium → Small sized necrosis of myocardium → Scar formation → Many scars together can cause → Myocardial dyskinesia which may progress to → Ventricular insufficiency → Left ventricular hypertrophy.

iii. Ischemia can be prolonged → Acute myocardial infarction. Many other effects are possible.

ANGINA AND DIABETES

Why diabetics are more prone to develop coronary atherosclerosis?
Atherosclerosis occurs in bigger or medium sized (coronary) arteries. But microangiopathy develops in small vessels. Diabetic microangiopathy, paves the way, for such diseases like diabetic nephropathy, diabetic retinopathy and so on.

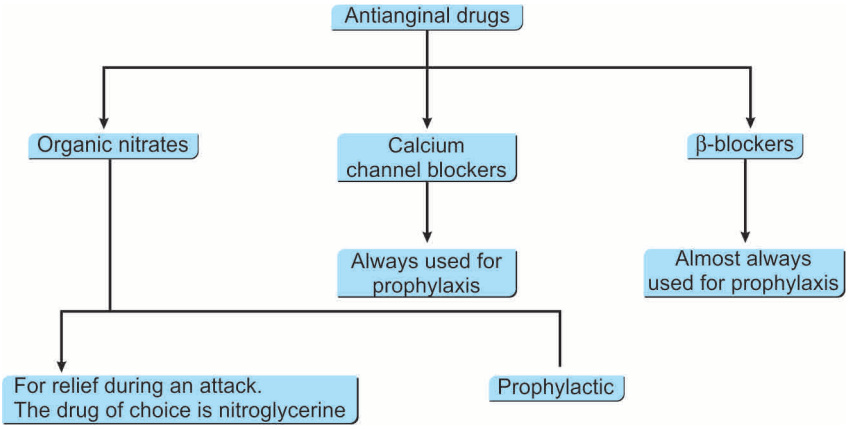
Glycation is a term which means the addition of sugar (glucose/fructose) to such agents/structures like proteins collagen.

It is a nonenzymatic process. In long standing DM or improperly treated ones are characterized by glycation of proteins (albumin Hb/collagen).

Ultimately, the glycated proteins become, advanced glycated end products AGE. These AGEs, can bind with some receptors → this leads to release of cytokines → initiation of coagulation → white thrombus (in atherosclerosis) formation. Glycated LDLs produce atherosclerosis.

Where there is, in tissues plenty of glucose (as in DM) some glucose molecules are converted into sorbitol which is a poison to tissues. Long continued stay of sorbitol, as stated above, may be the major cause of **retinopathy, nephropathy and neuropathy**.

ANTIANGINAL DRUGS

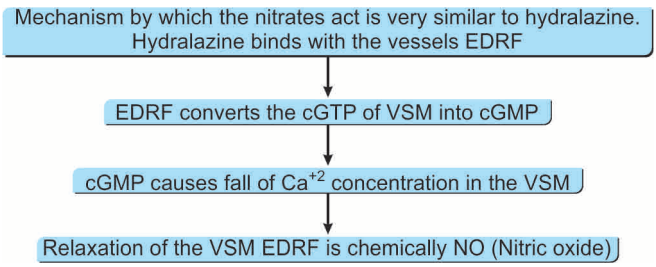


1. Nitrates reduce the O_2 demand by **venodilatation** (i.e. by reducing the preload of the heart).
2. The Ca^{+2} channel blockers by **reducing** BP **(i.e. the afterload, i.e. the systemic arteriolar dilation as well as epicardial ones)**.
3. The β-blockers by reducing the **tachycardia+contractility** (work done by the heart).

However, apart from drug therapy the patient should also undergo the nonpharmacological therapies, e.g.

i. Avoidance reduction of risk factors, i.e. Obesity, diabetes, smoking, hypertension.
ii. Rescheduling the lifestyle where necessary and so forth surgical intervention is indicated.

NITRATES—MECHANISM OF ACTION



Clinical Uses of Nitrates

1. Angina pectoris
2. Heart failure
3. Acute hypertension
4. Acute myocardial infarction.

CA^{+2} CHANNEL BLOCKER (SEE DETAILS IN SECTION)

Mechanism of Action in Angina

1. **They reduce arterial BP**
↓
They reduce after load
↓
Reduction of myocardial oxygen demand
↓
Reduction of chance of development of angina
↓
2. **They dilate coronary arteries**
↓
They reduce exercise induced coronary vasospasm

3. **They slow down the heart rate**
4. **They reduce myocardial contractility both (3 and 4) reduce the chance of development of angina**.

Side Effects

1. Bradycardia
2. CHF if present, may be aggravated
3. Edema, constipation, headache and dizziness.

β-BLOCKERS

Mechanism of Action in Angina

1. They reduce myocardial oxygen demand by reducing—
   a. Heart rate
   b. Myocardial contractility
   c. BP.
2. They also increase diastolic period.

Effects of β-Blockers in Angina

1. It prevents development of exertional angina
2. It increases the duration of exercise tolerance
3. By opposing the injurious effects of CA, it reduces the reach of angina during emotional outbursts (e.g. rage-panic)
4. It reduces the chance of mortality in IHD
5. In silent ischemia (where pain is absent but ECG signs of ischemia are present) β-blockers are helpful.

Side Effects

1. Extreme bradycardia
2. Bronchospasm
3. Precipitation of LVF
4. Depression.

SECTION-III ANTIARRHYTHMIC DRUGS

- Overview
- Shape of AP of cardiac muscles and conductive tissue—Cardiac electrophysiology
- Pathophysiology of arrhythmia—Reentry phenomenon
- Principles of selection of antiarrhythmic drugs
- Classification of antiarrhythmic drugs
- Site of action of drugs (with diagram) and mechanism of action

OVERVIEW

For the clear understanding of antiarrhythmic drugs, one has to understand—

1. Cardiac electrophysiology in health and diseases

2. Pathophysiologic process that lead to the development of arrhythmias—but both of them are difficult issues. In the text very simplified account has been presented.

In contrast to skeletal muscle which contracts only when it receives a stimulus, the heart contains specialized cells that exhibits automaticity; that is they can intrinsically generate rhythmic action potentials in the absence of external stimulus. These pacemaker cells differ from other myocardial cells in showing a slow spontaneous depolarization during diastole caused by an inward positive current carried by sodium and calcium ion flows. These depolarization is fastest in the sinoatrial (SA) node the normal initiation site of action potential and decreases throughout the normal conduction pathway through the AV node to the bundle of His-Purkinje fiber.

SHAPE OF AP OF CARDIAC MUSCLES AND CONDUCTIVE TISSUE – CARDIAC ELECTROPHYSIOLOGY (FIG. 7.2)

Action potential, AP, develops in nerve fiber, skeletal muscle fiber and myocardial cell. The mechanism of AP development in nerve fiber and skeletal muscle fiber was discovered in 1912 but that of myocardial cell only in the 1980s.

Shape of AP of myocardial cell differs, depending whether it is (1) fast response or (2) slow response, AP.

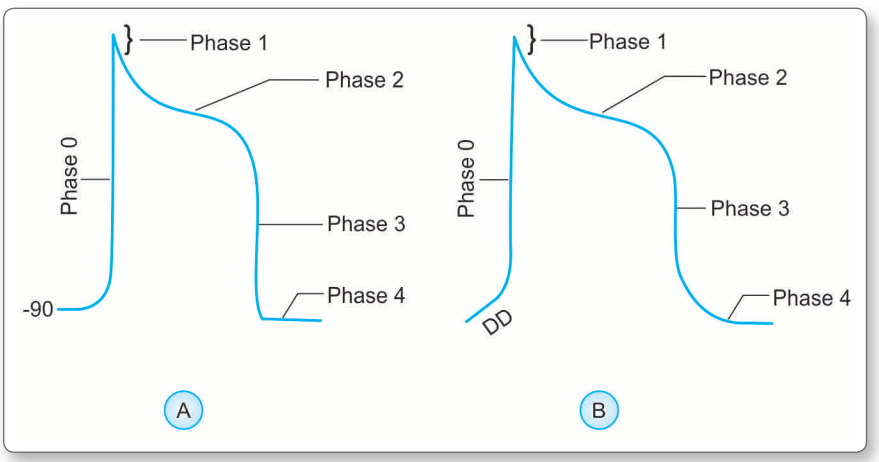


Fig. 7.2: Shape of action potential. A. Cardiac myocardial cells; B. His-Purkinje system

PATHOPHYSIOLOGY OF ARRHYTHMIA-REENTRY PHENOMENON

Arrhythmias are dysfunction in impulse formation and conduction in the myocardium. Cardiac arrhythmias may cause the heart—

1. To beat too slowly (sinus bradycardia).
2. To beat too rapidly (sinus or ventricular tachycardia, atrial or ventricular premature depolarization, or atrial flutter).
3. To respond to impulses originating from sites other than the SA node.
4. To respond to impulses traveling along accessory (extra) pathways that lead to deviant depolarizations (AV reentry, Wolff-Parkinson-White syndrome).

Reentry (Fig. 7.3)

Reentry can develop in one of the two following classical conditions—

1. An AV node + an accessory pathway (a congenital condition).
2. An area of normal tissue and an area of ischemic tissue this is explained below in detail.

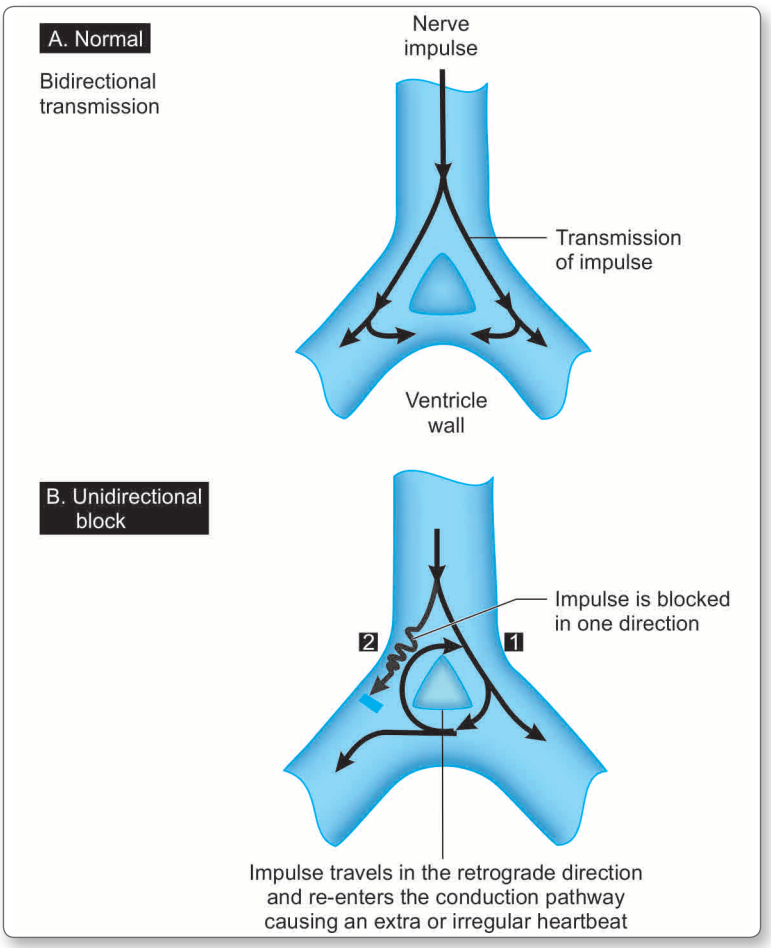
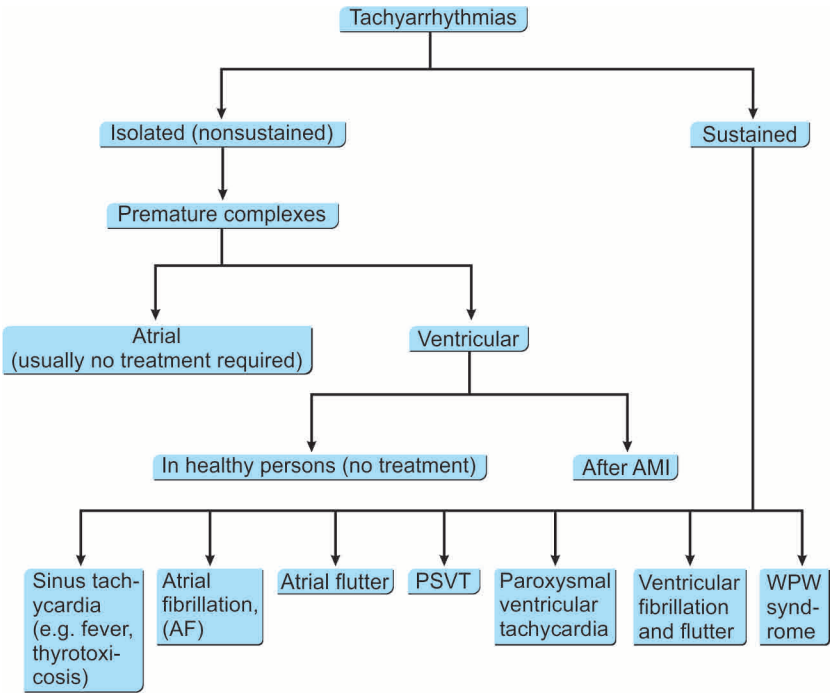


Fig. 7.3: Development of reentry by impulse block

Normally, when a stimulus passes via PF it divides and passes via both 1 and 2 pathways and to reach the ventricular muscles but suppose a portion of pathway 1 because of ischemia has develop delayed conductivity. In this pathological setting the likely scenario can be:

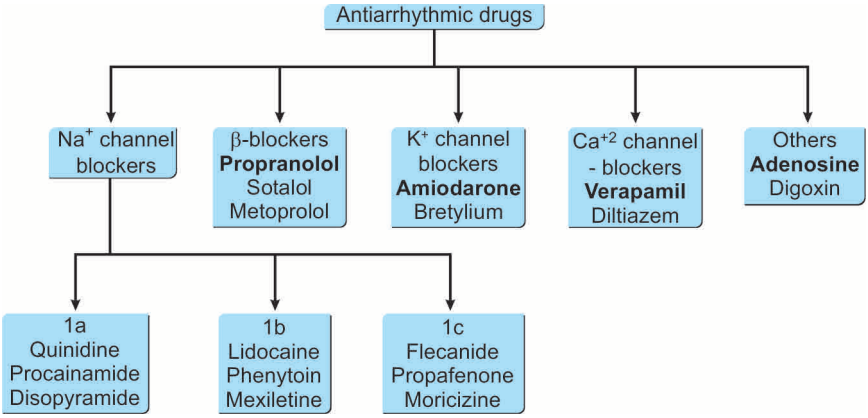
The stimulus proceeds via PF → bifurcates → passes, via both pathway 1 and 2 → but because of the block in pathway 1 the stimulus which was proceeding via pathway 1 becomes extinct whereas that which was proceeding via pathway 2 continues, and reaches ventricular muscle → this eventually bifurcates again and enters pathway 1 → proceeds as retrograde stimulus, via pathway 1 and eventually reaches the ischemic area. By now the area has become conductive again so that the retrograde stimulus passes through ischemic area and reenters in pathway two again to complete a loop → the circular movement goes on and on relentlessly so that this spot of cardiac muscle becomes a self-sustained ectopic spot and acts as an ectopic pacemaker.



PRINCIPLES OF SELECTION OF ANTIARRHYTHMIC DRUGS

1. Many arrhythmias do not require drug treatment at all
2. Most antiarrhythmic drugs can be dangerous
3. Most of the antiarrhythmic agents are proarrhythmogenic
4. Cardioversion (DC current shock) is more easier and safe.

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS



SITE OF ACTION OF DRUGS (WITH DIAGRAM) AND MECHANISM OF ACTION (FIG. 7.4)

- **Phase 0**: It is due to explosive Na^+ entry from ECF to ICF (Na^+ influx)
- **Phase 1**: It is due to stoppage of Na^+ and entry of Cl^- ions
- **Phase 2**: It continued entry of Na^+ stoppage + beginning of exit of K^+ + influx of Ca^+
- **Phase 3**: It is due to stoppage of Na^+ + exit of K^++ stoppage of Ca^{+2}
- **Phase 4**: Finally develops.

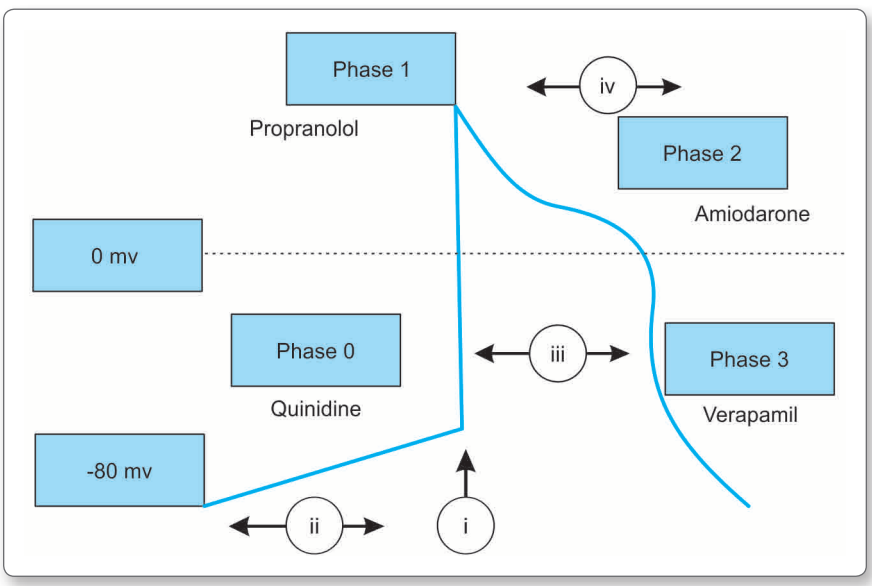
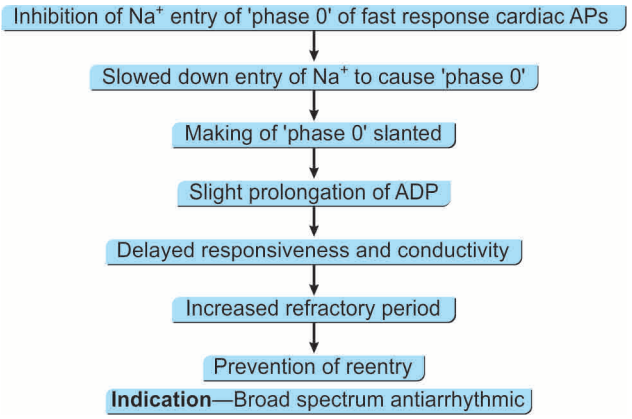


Fig. 7.4: Site of action of antiarrhythmic drugs

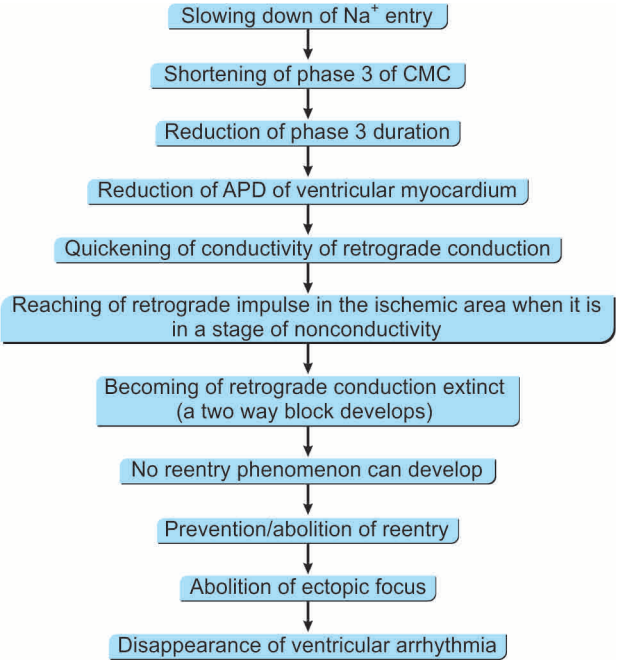
MECHANISM OF ACTION

- **Group 1**

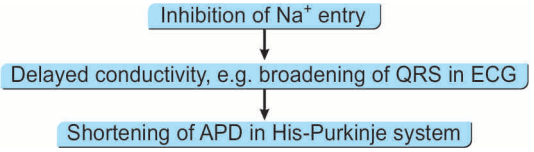
1a. Quinidine



1b. Lidocaine



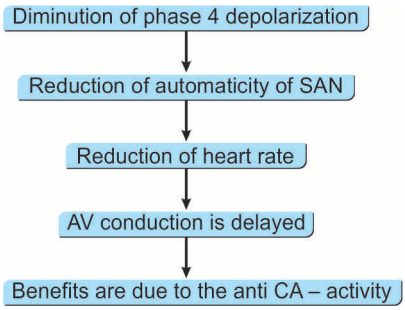
1c. Flecanide



They (group 1c) are not very popular as they are proarrhythmogenic. Both (CAST) cardiac arrhythmia suppression trial as well as CASH (cardiac arrest studies in Hamburg) studies show they are proarrhythmogenic.

- **Group 2**

Propranolol

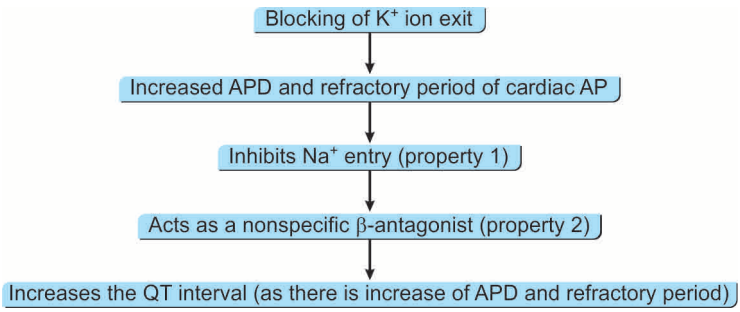


Advantages

1. They are relatively safe
2. They are wide spectrum.

- **Group 3**

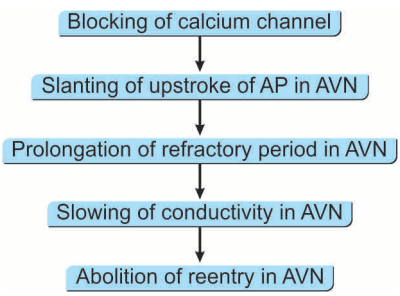
Amiodarone



It can precipitate torsades de pointes, if there is hypokalemia, bradycardia and hypomagnesemia.

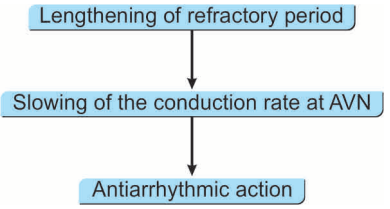
- **Group 4**

Verapamil



- **Others**

Adenosine



Indication It is the drug of choice for termination of PVST. Its duration of action is only few seconds.

SECTION-IV HYPERLIPOPROTEINEMIA; ITS PHARMACOTHERAPY

- Overview
- High incidence of coronary atherosclerosis – explanation
- Biochemical background
- Lipoprotein metabolism
- Cholesterol metabolism
- Antihyperlipidemic measures.

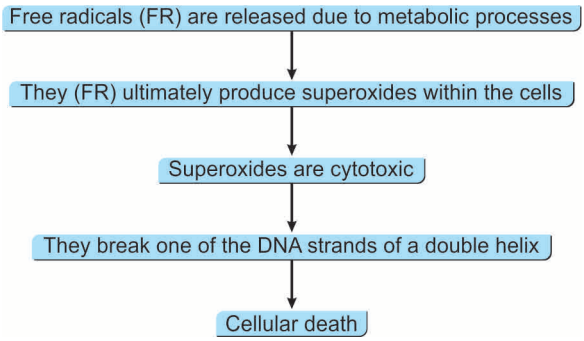
OVERVIEW

Coronary heart disease (CHD) is the cause of about half of all deaths in the United States. The incidence of CHD is correlated with elevated levels of low-density lipoprotein (LDL) cholesterol and triacylglycerols and with low levels of high-density lipoprotein (HDL) cholesterol. Other risk factors for CHD inculde cigarette smoking, hypertension, obesity, and diabetes. Cholesterol levels may be elevated as a result of an individual's lifestyle (for example, by lack of exercise and consumption of a diet containing excess saturated fatty acids). Hyperlipidemias can also result from a single inherited gene defect in lipoprotein metabolism or, more commonly, by a combination of genetic and lifestyle factors.

HIGH INCIDENCE OF CORONARY ATHEROSCLEROSIS—EXPLANATION

Within our body, there is a mechanism which terminates the free radicals. Well-known mechanism to terminate free radicals include—

i. Antioxidants (like vitamin- E, vitamin-C)
ii. Superoxide dismutase (SOD)
iii. Glutathione and so on.



SOD Induced Opposing Effect on DNA Breakage

Many cells have a high concentration of an enzyme, called superoxide dismutase (SOD). Presence of SOD in high concentration opposes the superoxide induced DNA breakage. Unfortunately, myocardial concentration of SOD is low; which **explains the etiology of higher incidence of coronary arteriosclerosis and myocardial infarction**.

Catalase Deficit

Side by side with the production of superoxides, **H_2O_2 is also produced which is also cytotoxic**. H_2O_2 is broken down by catalase enzymes. Adequate catalase thus protects cytotoxicity, and myocardium is deficient in catalase. Coronary heart disease (CHD), arteriosclerosis and some other diseases are strongly associated with disorder of lipid metabolism and hyperlipoproteinemia. Therefore, hyperlipoproteinemia should be corrected.

BIOCHEMICAL BACKGROUND (FIG. 7.5)

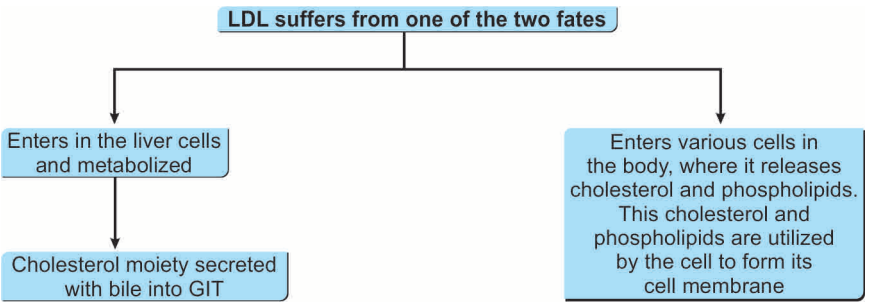
Important lipids of our plasma are—a. triglycerides, b. cholesterol, c. phospholipids, and d. free fatty acid. The lipids as such are insoluble in plasma but in combination with protein, they are soluble. In the plasma they combine with a kind of protein called apolipoprotein. The complex formed by this combination, i.e. apolipoprotein + lipid, is called lipoprotein. Lipoproteins are thus soluble in plasma. Apolipoproteins can be of several varieties, i.e. apolipoprotein B 100, B48 and E.

LIPOPROTEIN METABOLISM

Description

(1) Dietary fat → (2) Concentrated into micelles (in the human) → (3) Absorption follows → (4) Formation of chylomicron → (5) Transported

via lymph duct → (6) Entry into the blood vascular compartment → (7) Reaching of chylomicrons in the capillaries → (8) Secretion of lipoprotein lipase by the capillary endothelium → (9) Hydrolysis of triglycerides (TG) component of chylomicron into FFA and glycerol → (10) Removal of TG by lipoprotein lipase (LPL) → (11) Change of chylomicron into chylomicron remnant → (12) Entry of chylomicron remnant into hepatocytes→ (13) Further metabolism → (14) Formation of VLDL → (15) Ejection of VLDL from hepatocytes → (16) Entry of VLDL into systemic blood → (17) Reaching into the capillaries → (18) Action of lipoprotein lipase (LPL) → (19) Conversion into IDL → (20) Receiving cholesterol from HLD, DL is converted to LDL.



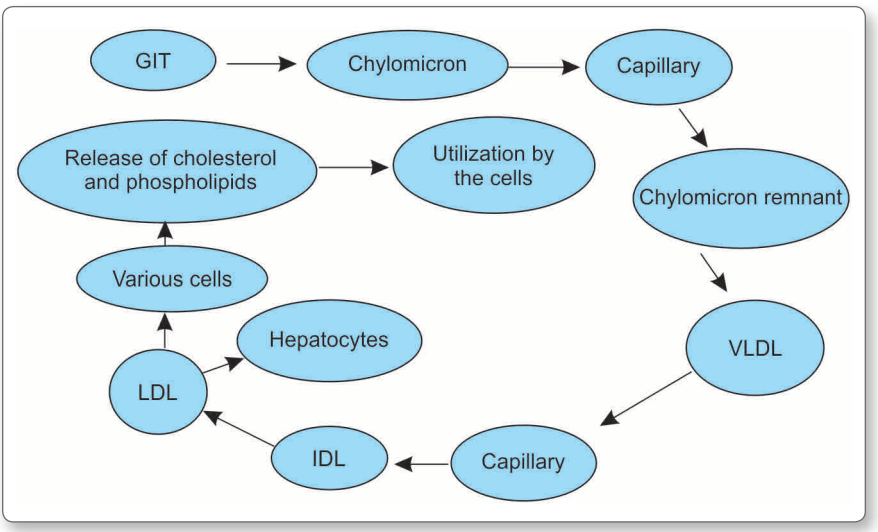


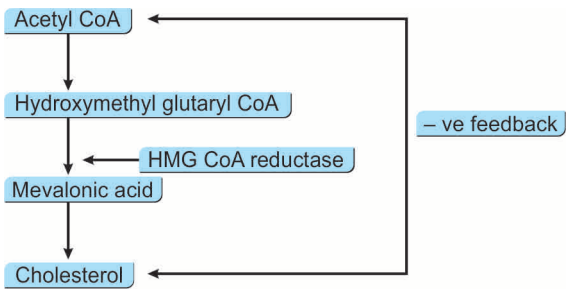
Fig. 7.5: Lipoprotein metabolism

CHOLESTEROL METABOLISM

Cholesterol is a C27 structure, containing a perhydrocyclopentanophenanthrene (CPP) ring. CPP ring can be synthesized in our body but once

formed cannot be destroyed. All that can be done is to shorten/remove the side chain so that cholesterol becomes converted to some other steroid compounds (e.g. bile salts, steroid hormones). Excretion of bile salts, via (GIT accounts for about 75% of the cholesterol removal from our body. Excessive loss of bile salts, thus removes cholesterol. In normal persons, a good deal of bile salts of (GIT) return back to the hepatocytes by enterohepatic circulation.

In our body, cholesterol certainly plays a vital roles. However rise of plasma cholesterol is strongly associated with atherosclerosis. The most major constituent of an atheromatous plaque is cholesterol. Our ability to remove cholesterol is unsatisfactory and grossly dependent on removal though bile, via GIT. One method of cholesterol lowering is reduction of cholesterol synthesis.



Cholesterol Synthesis

A negative (-ve) feedback operates in the steps of cholesterol synthesis. That is, if there is excessive cholesterol in the body, synthesis of cholesterol is inhibited and conversely if there is only little cholesterol in the body, the cholesterol synthesis is stepped up. This means, if dietary cholesterol intake be even drastically lowered, the plasma cholesterol concentration will not be seriously affected as the body synthesis will increase. Therefore, substantial reduction of serum cholesterol level of the body cannot be achieved by reducing cholesterol intake alone, side by side cholesterol synthesis must be stopped.

The association between high serum cholesterol and atherosclerosis is statistically well-proved; and a high value of HDL probably indicates that the mechanism of removal of cholesterol from the atherosclerotic plaques is satisfactory.

According to European Atherosclerotic Society [(1987) Cur Heart JB, 77–88.] serum cholesterol values should be less than 200 mg/100 ml. Where the values are between 200 to 250 mg/100 ml, treatment to lower cholesterol value should be started but the treatment should be by nondrug regimen (dietary restriction–exercise–removal of risk factors). Where the values are still higher; drugs should be included. HDL values below 35 mg/100 ml demand lipid-lowering therapy strongly.

ANTIHYPERLIPIDEMIC MEASURES

a. Nondrug measures, plus if needed
b. Drug measures.

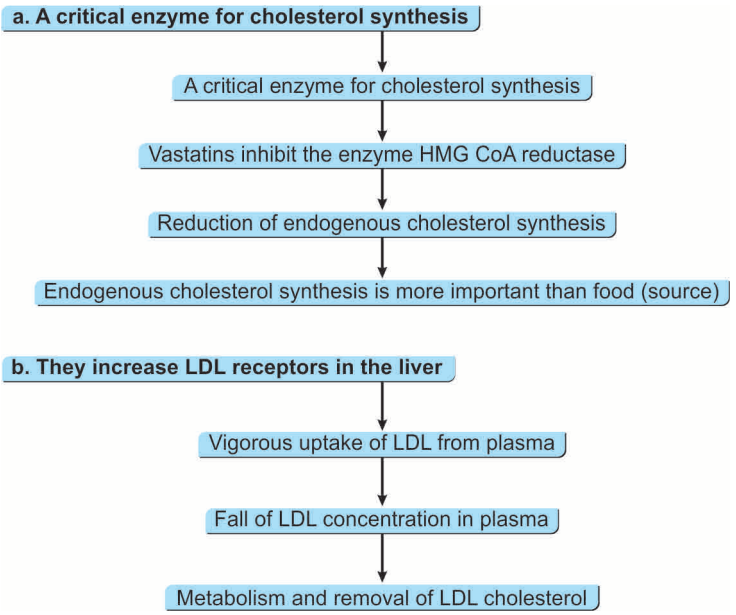
Nondrug Measures

i. Dietary fat restriction (not more than 25% of the calories should come from fat, 50% of this must be vegetable oil or unsaturated fat).
ii. Reduction of obesity.
iii. Increased fibers, vegetables in the diet, as well as glassful of fruit juice.
iv. Exercise (even 2 hours walking/week can improve serum cholesterol values).
v. No smoking; reduction of alcohol consumption.
vi. Low cholesterol intake (< 300 mg/ day).

Drug Measures

i. HMG CoA reductase inhibitors, i.e. Lovastatin, Atorvastatin, Rosuvastatin.
ii. Fibric acid derivatives, i.e. Gemfibrozil, Fenofibrate, Clofibrate.
iii. Inhibition of hepatic production of lipid—Niacin and others.
iv. Bile acid sequestering agents—Cholestyramine, Colestipol.
v. Increased cholesterol clearance—Probucol.

MECHANISM OF ACTION OF HMG CoA REDUCTASE INHIBITORS



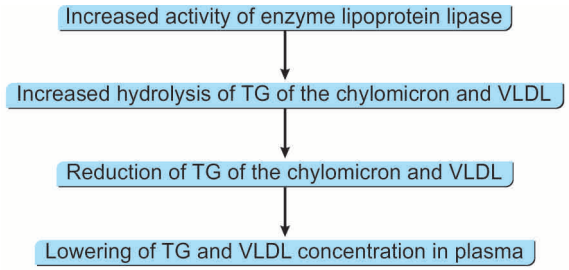
Adverse Action

Alteration of liver functions – so it requires to test SGOT and SGPT while taking the drugs. And very rarely myopathy can occur.

Contraindications

Pregnancy, lactating mothers, and children.

MECHANISM OF ACTION OF FIBRIC ACID DERIVATIVES, THAT IS GEMFIBROZIL



They can increase HDL cholesterol concentration in plasma.

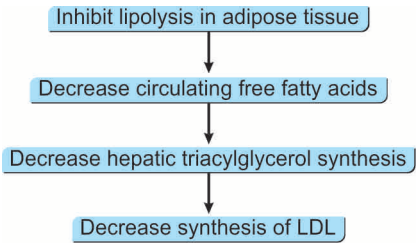
Indication

Primary hypertriglyceridemia and familial combined hyperlipidemia.

Adverse Effect

GI upset can occur. Some patients can develop gallstones. Renal failure, myopathy can occur.

MECHANISM OF ACTION OF INHIBITION OF HEPATIC PRODUCTION OF LIPID-NIACIN AND OTHERS



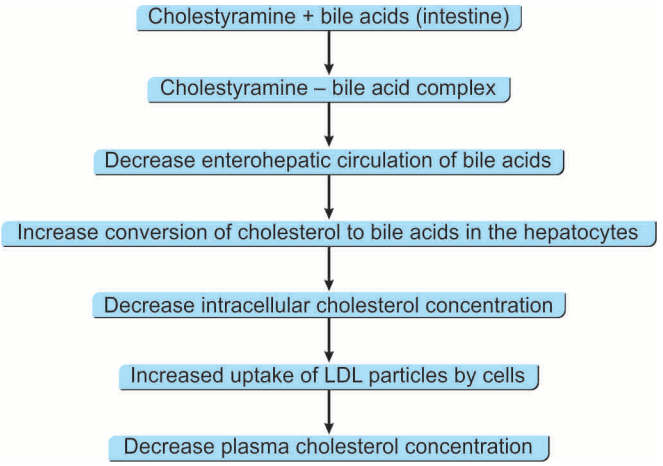
Indications

1. Type II b hyperlipoproteinemia
2. Severe hyperlipoproteinemia.

Adverse Effects

1. Intense cutaneous flush
2. Pruritus.

MECHANISM OF ACTION OF BILE ACID SEQUESTERING AGENTS—CHOLESTYRAMINE, COLISTIPOL



Indication

Type II (a) and II (b) hyperlipidemias.

Adverse Effects

1. GIT disturbances – Nausea, constipation
2. Impaired absorption of fat-soluble vitamines (A,D,E and K)
3. Impair intestinal absorption of Tetracycline, Phenobarbitone, Digoxin, Warfarin.

SECTION-V EDEMA AND ITS MANAGEMENT

- Nephrons—Structure and function
- Definition of edema
- Causes of generalized edema
- Pathogenesis of generalized edema
- Diuretics

NEPHRONS—STRUCTURE AND FUNCTION

Kidneys are the organs for urine formation and excretion of nitrogenous liquid end products from the body, via urine. Each kidney contains about

1.2 million nephrons in man, among them about 85% are cortical and 15% are juxtamedullary. The two types of nephrons have some structural and functional differences.

a. **In a cortical nephron**, there is—
   i. **Renal corpuscle** (means the glomerulus [the tuft of capillaries] surrounded by the Bowman's capsule. It (BC) has 2 layers visceral and parietal)
   ii. Proximal convoluted tubule
   iii. Loop of Henle
   iv. Distal convoluted tubule
   v. Collecting tubule.

Mesangial cells lie in between the afferent and efferent arterioles of the glomerulus. These cells are nongranular and can secrete renin when necessary.

b. **Juxtamedullary nephrons** are primarily concerned with sodium and water conservation plus concentration of urine.

Its anatomical features are—

i. Glomerulus (although in the cortex) is situated close to the medulla.
ii. The loop of Henle, are very long segmented (whereas in the cortical ones, they are short).
iii. In the loop of Henle, in the descending limb there is in addition, the beginning of the ascending limb is also thin.
iv. There is no peritubular capillaries surrounding the tubules instead there are vasa recta.

DEFINITION OF EDEMA

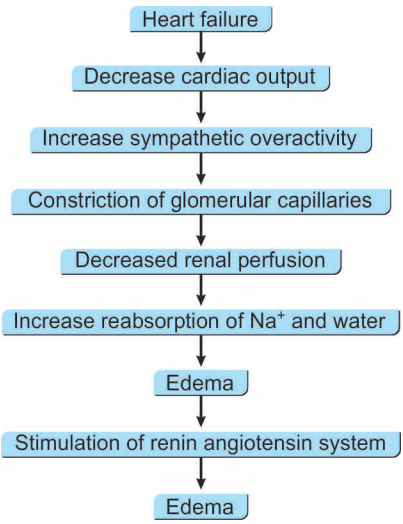
Abnormal accumulation of fluid in the intercellular tissue space or serous cavity is known as edema.

CAUSES GENERALIZED EDEMA

1. Edema due to heart failure
2. Edema due to nephritic syndrome
3. Edema due to hepatic ascites
4. Edema due to famine cause (nutritional).

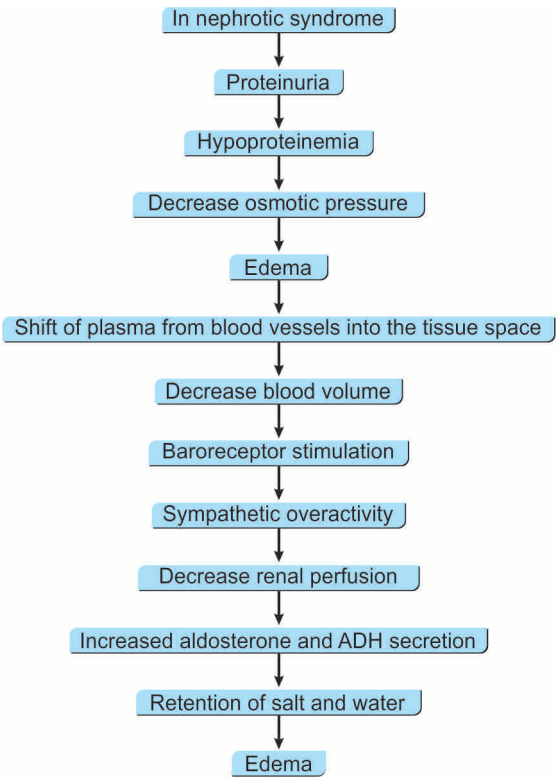
PATHOGENESIS OF GENERALIZED EDEMA

a. **Edema in heart failure**: Exact pathogenesis is unknown but there are several hypotheses. Possible mechanism is as follows:



Cardiac edema first appears in the dependent part because edema fluid can change its position by gravity.

b. **Edema in nephrotic syndrome**



Renal edema first appears in the face and eyelid due to less tissue tension in these areas.

c. **Hepatic edema**

1. Diseased liver → decrease synthesis of protein mainly albumin decreased → colloidal osmotic pressure.
2. Diseased liver → failure of aldosterone metabolism → secondary hyperaldosteronemia.
3. Increase hydrostatic pressure—Due to portal hypertension.
4. Lymphatic obstruction → accumulation of fluids (initially) in abdomen.

DIURETICS

- Overview
  - Definition
  - How acts
  - Efficacy
  - Uses.
- Classification
- Loop diuretics – frusemide
- Thiazides in brief
- Clinical uses of diuretics.

Overview

Definition

Diuretics are agents that increase the volume of urine as well as solutes dissolved in it, by decreasing the reabsorption of sodium at different sites in the nephron.

How acts

As a result sodium and other ions, e.g. chloride enter the urine in greater than normal amount along with water, which is carried passively to maintain osmotic equilibrium.

Efficacy

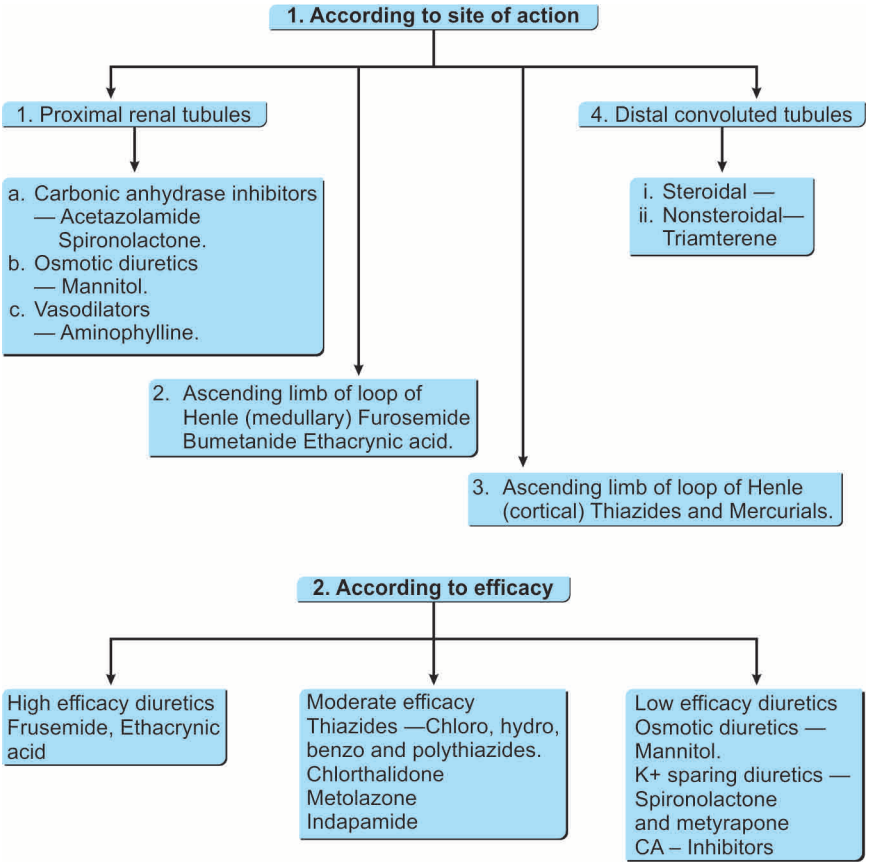
Diuretics thus increase the volume of both urine and often change its pH as well as the ionic composition of urine and blood. Their efficacy in sodium secretion varies from 2% to 20 % incase of potassium sparing diuretics and loop diuretics respectively.

Uses

Major clinical use of diuretics are in managing disorders involving abnormal fluid retention (edema) or treating hypertension and glaucoma.

Classifications

There are two basis of classification:
1. According to site of action
2. According to efficacy.



Loop Diuretics—Frusemide

- High ceiling diuretics
- Mechanism of action
- Symport system
- Therapeutic uses
- Adverse action.

High ceiling diuretics

It is a member of loop diuretics. Site of action is thick (medullary part) of ascending loop of Henle. The intensity of diuresis produced by maximum dose is high, hence they are called high ceiling diuretics.

Mechanism of action

At molecular level, loop diuretics bind with the site for Cl^- ions of uniport, symport or cotransport system and thus blocking the working of the symporter they produce diuresis.

Symport system

Symport system is present in the luminal border of the epithelium in the thick segment and is called, Na^+ K^+ $2Cl^-$ symporter. This symporter causes concomitant reabsorption of Na^+, plus K^+, plus $2Cl^-$ ions. So frusemide and other loop diuretics cause loss of Na^+ as well as Cl^- and K^+ ions, via urine. Mg^{+2} and Cl^2 reabsorption also prevented but Mg^{+2} ions are reabsorbed in the DCT so that hypomagnesemia (but not to a greater extent, hypocalcemia) can occur with chronic excessive loop diuretic therapy as they (loop diuretics) inhibit the cotransport proteins.

Therapeutic uses

1. Drugs of choice for reducing the acute pulmonary edema of heart failure. Because of their rapid onset of action, particularly when given intravenously.
2. They are useful in emergency situations such as acute pulmonary edema which calls for a rapid intense diuresis.
3. They are also useful in treating hypercalcemia because they stimulate tubular calcium excretion.
4. They also are useful in the treatment of hyperkalemia.

Adverse actions

1. **Ototoxicity**: Hearing can be affected adversely by the loop diuretics when used in conjunction with the aminoglycosides. Vestibular function is less likely to be disturbed.
2. **Hyperuricemia**: Frusemide compete with uric acid for the renal and biliary secretory systems, thus blocking its secretion and thereby, causing or exacerbating gouty attacks.
3. **Acute hypovolemia**: Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock and cardiac arrhythmias.
4. **Hypercalcemia**: May occur in above (3) condition.
5. **Potassium depletion**: The heavy load of sodium presented to the collecting tubule results in increased exchange of tubular sodium or potassium, with the possibility of inducing hypokalemia. Potassium depletion can be averted by use of potassium sparing diuretics or dietary supplementation with potassium.
6. **Hypomagnesemia**: A combination of chronic use of loop diuretics

and low dietary intake of magnesium can lead to hypomagnesemia, particularly in the elderly.

Thiazides in Brief

a. Why thiazides are only moderately effective diuretics compared to loop diuretics?

Thiazides act on the DCT. Bulk of Na^+ ions have already been absorbed by PCT and the ascending limbs; Na^+ availability on the DCT is low. So thiazides are considered as moderately potent diuretics.

b. Thiazides cause diuresis; but why they are used in nephrogenic diabetes insipidus?

In nephrogenic diabetes, there is no vasopressin (V2) receptors in the renal tubule. Usually it is congenital but may be lithium induced diabetes insipidus.

i. Thiazides cause Na^+ depletion → Fall of GFR → Decreased delivery of Na^+ to loop of Henle → Less need of ADH to concentrate the urine.
ii. Decrease glomerular filtrate reabsorption in the PCT → Decrease NaCl delivery and potential-free water to the DCT → Thus, a fluid smaller in volume and less dilute escape the distal tubule → Antidiuresis.

c. Why thiazides are the preferred diuretic in prolonged hypertension?
Use of thiazides in hypertension.

i. Thiazides cause decreased Na^+ reabsorption → Increased urinary output → Decreased plasma volume → Decreased CO → Fall of BP (as BP = CO × PR).
ii. Thiazides cause hypokalemia → Decreased sensitivity of vascular α-receptor to the action of adrenaline. → Vasodilatation fall of PR+ fall of BP.

Adverse actions

1. **Potassium depletion**: Thiazide diuretics cause more sodium to reach the sodium-potassium exchange site in the distal tubule and so there is increase amount of potassium excretion. The safe lower limit for serum potassium concentration is normally quoted as 3.5 mmol/l.
2. **Magnesium deficiency**: They cause significant amount of urinary loss of magnesium; but potassium retaining diuretics probably also cause magnesium retentions.
3. **Hypovolemia**: It can result from over treatment. Acute loss of excessive fluid leads to postural hypotension and dizziness.
4. **Hyponatremia**: It may result, if sodium loss occurs in patients who drink a large quantity of water. Other mechanisms are probably involved, including enhancement of antidiuretic hormone release.

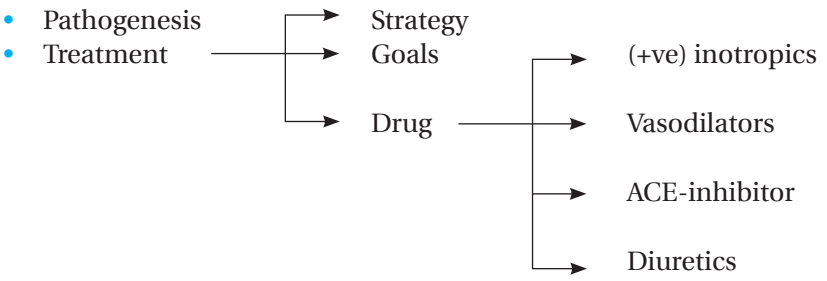
5. **Urate retension**: Occurs due to—(a) Volume depletion, reduction in glomerular filtration and increased absorption of almost all solutes in the proximal tubule including uric acids. (b) Diuretics and uric acids are organic acids and compete for the transport mechanism which carries such substances from the blood into the urine.
6. **Carbohydrate intolerance**: It is usually associated with thiazides and loop diuretics. It appears that intracellular potassium is necessary for the formation of insulin, and glucose intolerance is probably due to insulin deficiency.
7. **Calcium homeostasis**: Hypercalcemia is seen due to decrease in renal excretion of Ca^{+2}.

Clinical Uses of Diuretics

Clinical conditions	Diuretics used	Explanations
Glaucoma	CA inhibitor- Acetaz-olamide	CA is utilized in the formation of aqueous humor
Ascites	Aldosterone antagonist-Spironolactone	Aldosterone metabolism is inhibited in ascites
Nephrotic syndrome	Loop diuretic-Frusemide	Requires immediate relief from huge edema
Pulmonary edema	Loop diuretic-Frusemide	To get rid of respiratory embarrassment
Edema due to starvation	Loop diuretic-Frusemide	Severe form of edema is usually associated with
Long-standing hypertension	Thiazides	To produce vasodilatation
Hypertensive crisis	Loop diuretic-Frusemide	To get immediate effect
Head injury/increased intracranial pressure	Osmotic diuretic-Mannitol	To reduce intracranial pressure
Diabetes insipidus	Thiazides	To reduce serum potassium

SECTION-VI MANAGEMENT OF CONGESTIVE HEART FAILURE

- Definition
- Prognosis
- Causes
- Varieties



DEFINITION

CHF is a condition where the heart is—(i) Pumping insufficiently to meet the demands of the body or (ii) Pumping sufficiently only under greater preload.

PROGNOSIS

The prognosis of CHF is not good till recent past 50% of severe cases of CHF used to die within 2 years and 50% of all CHF used to die within 5 years.

CAUSES

i. AMI
ii. Hypertension
iii. Cardiomyopathies
iv. Rheumatic valvular disease.

VARIETIES

Backward Failure

Poor myocardial contractility in CHF results in accumulation of blood behind the failing ventricle—This is backward failure.

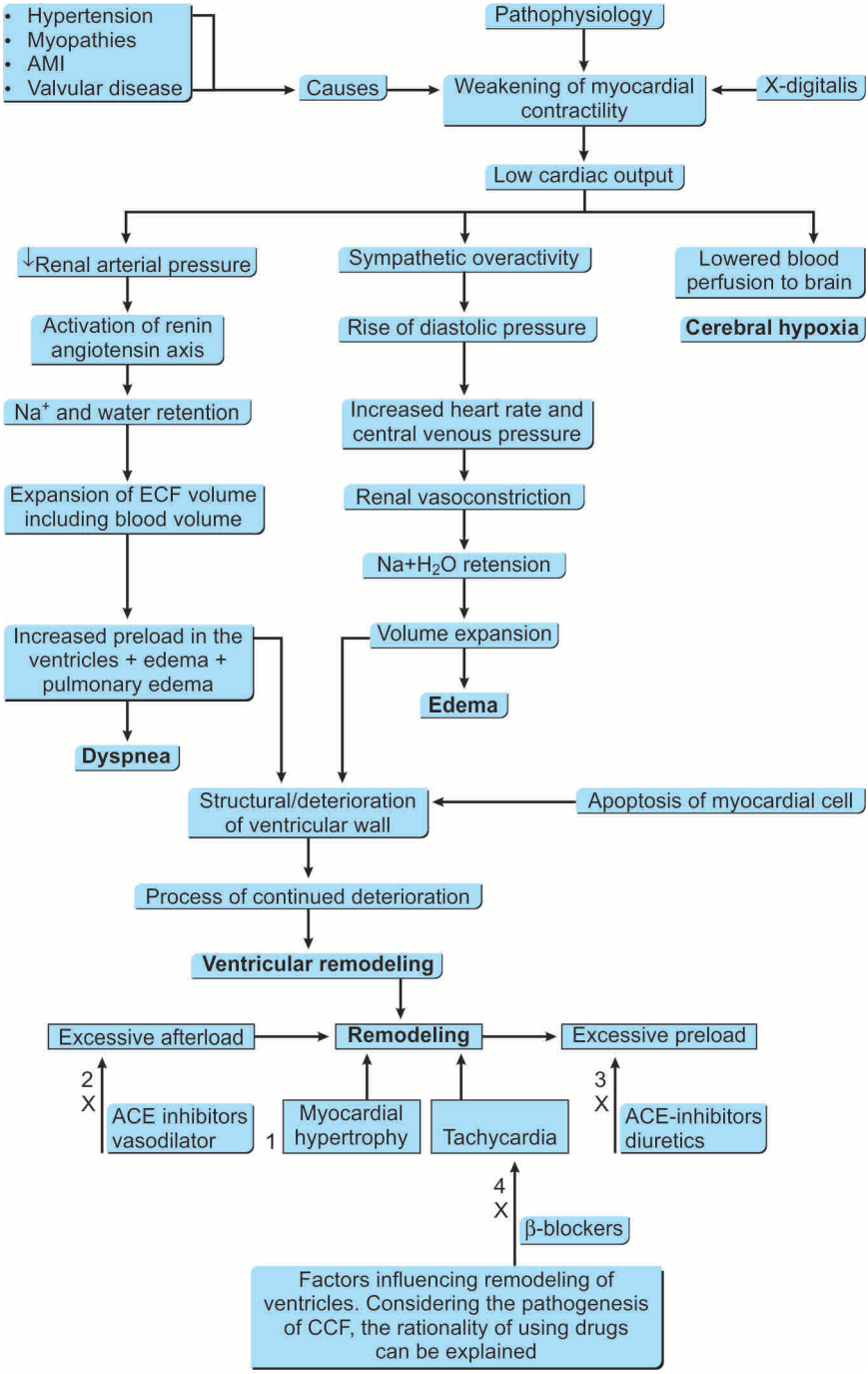
In LVF, there is thus pulmonary congestion, pulmonary edema leading to dyspnea.

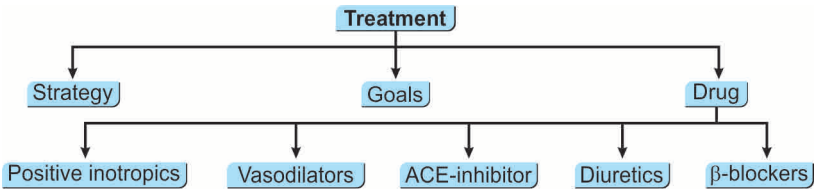
In RVF, there will be peripheral venous congestion, peripheral edema and hepatomegaly.

Forward Failure

Develops because of low cardiac output due to poor myocardial contractility producing cerebral hypoxia, so dizziness and sluggish renal circulation.

PATHOGENESIS





Strategies

There are of two types:

a. General measures, e.g.
   i. Bed rest
   ii. Low Na^+ diet
   iii. Avoidance of alcohol NSAIDs
b. Drug therapy–Drugs are used
   i. To relieve pulmonary congestion, hypervolemia of blood
   ii. To relieve preload and afterload on heart to increase cardiac contractility.

Goals

a. To relieve symptoms (e.g. those due to pulmonary congestion/ cerebral hypoxia)
b. Prevention of damage to the ventricles (e.g. those due to wall tension, apoptosis, etc.) and prolong the life and the attempt for an useful life.

Drugs

Positive inotropics

Digitalis

- Introduction
- Advantages
- Drawbacks
- Chemistry
- Sources
- Mechanism of action
- Pharmacological effects
- Pharmacokinetics
- Therapeutic indications
- Contraindications
- Adverse effects
- Predisposing factors for adversity.

Introduction

In 1875 William Withering wrote a treatise on digitalis. In the period between 1875 and today (2009) the popularity of digitalis has undergone

many ups and downs. In chronic CHF with chronic atrial fibrillation it is still an extremity favored drug.

Advantages

1. It has (+ve) inotropic and (-ve) chronographic effect
2. It can be administered orally.

Drawbacks

1. Low margin of safety
2. Correct dose, therapeutic ranges cannot be certained
3. It has many drug interactions.

Chemistry

Cardiac glycoside means a molecule consisting of 1. CPP ring 2. sugar and 3. lactone.

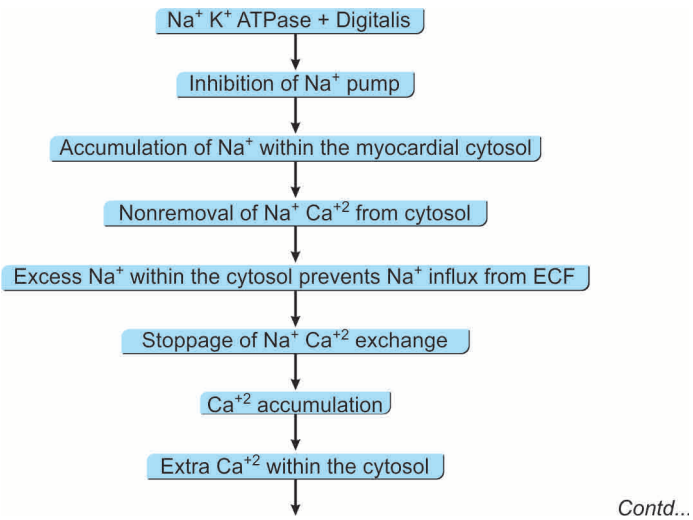
CPP + lactone, together called aglycone (genin).

Sources

Digitalis purpura—Digitoxin, gitalin
Digitalis lanata—Gitoxin, digoxin
Digitalis gratus—Ouabain
Digitalis kombe—Strophanthin K.

Mechanism of action

Effects on sodium pump



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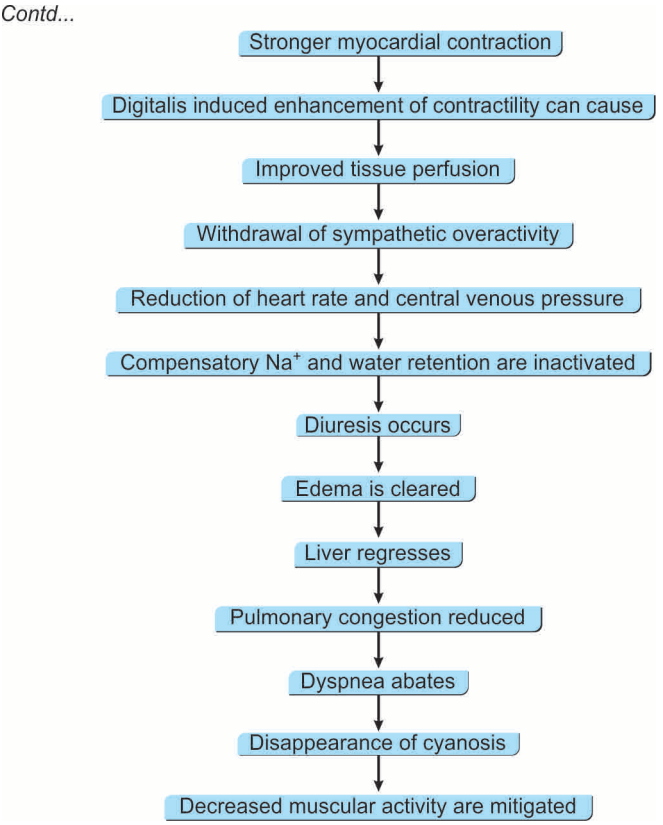
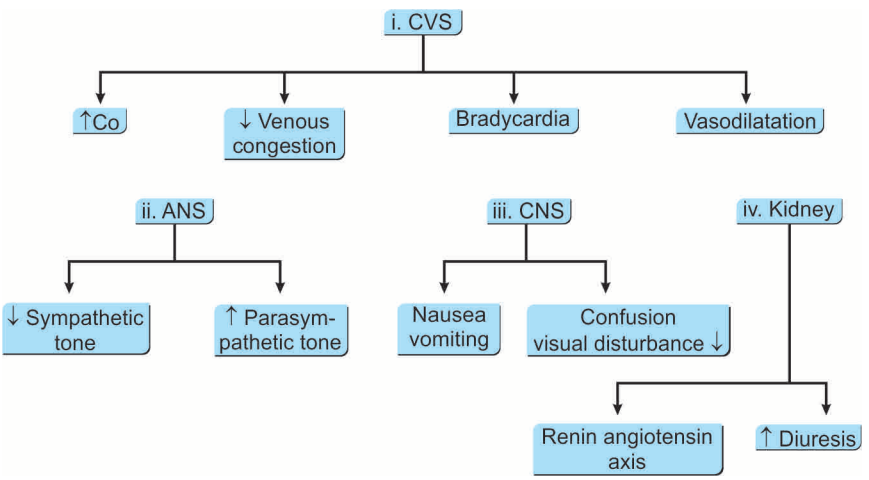


Pharmacological effect

Principally on



Pharmacokinetics

Digoxin is used clinically $t_{1/2}$ of digoxin is 1.5 days, while for digitoxin is 5 days.

Presuming same dose is repeated at proper interval, to reach steady state, 4 doses are required. Thus digitalization with digoxin requires 4 × 1.5 = 6 days while with digitoxin it requires 4 × 5 = 20 days. Thus, this is a major trouble with digitoxin.

Dialysis is of no help in digitalis intoxication because after absorption digitalis is distributed mainly within the cells.

Indications

1. In CHF with chronic atrial fibrillation
2. In CHF with sinus rhythm.

Contraindications

1. Obstructive cardiac myopathy
2. Diastolic dysfunction of heart
3. WPW syndrome
4. AV nodal block.

Adverse effects

Digitalis toxicities are often grouped as (1) cardiac (2) extracardiac as stated below—

1. **Cardiac**: Cardiac dysrhythmias like delayed AV conduction, PSVT, heart block ventricular tachycardia and ventricular fibrillation.
2. **Extracardiac**: GIT, nausea, vomiting, anorexia
3. **CNS**: Headache, blurring of vision, mental confusion.

Predisposing factors for adversity

Some factors facilitale the development of digitalis toxicity:

1. Depletion of serum K^+ level can occur if concomitantly used with Frusemide or Thiazides.
2. Concomitant use of drugs like quinidine.
3. Presence of renal failure and hypothyroidism.
4. Old age.

Vasodilators

It reduces afterload.

ACE Inhibitors in CHF

1. They are very effective in the treatment of CHF.
2. Their long-term use can increase the life expectancy and reduce mortality reduce the need to hospitalize the patient of CHF.
3. Combination of ACE inhibitors and diuretics are very effective in CHF.

Mechanism of Action

ACE inhibitors cancel the following harmful effect produced by angiotensin II—

a. Vasoconstriction → following increased afterload.
b. Increased aldosterone secretion leading to increase preload.
c. Sympathetic overactivity.
d. Myocardial hypertrophy and damage of coronary and renal cells.

Diuretics in CHF

Diuretics in general, causes natriuresis and water removal → removal of fluid from the body → reduction of volume of blood and other ECF components → reduction of pulmonary congestion (dyspnea) + peripheral congestion (peripheral edema) + preload. Diuretics promptly relieve pulmonary congestion. In acute LVF—acute pulmonary congestion—severe dyspnea—IV frusemide often produce dramatic relief. In chronic CHF diuretic relieve pulmonary congestion + peripheral edema + venous pressure. There is some fall of arterial BP too.

β-blockers (Carvedilol) in CHF

Mechanism of action of β-blockers in CHF is unclear but probabilities include—

1. CA induced injury to the heart are blocked by β-blockers
2. They prevent the ventricular remodeling
3. They prevent myocardial apoptosis
4. Carvedilol by α_1-blocking causes reduction of afterload
5. It (carvedilol) has some antioxidant effect.

CHAPTER

8

Introduction to Chemotherapy

SECTION-I INTRODUCTION TO CHEMOTHERAPY

- Definition of chemotherapy and short history
- Some terms related to chemotherapy
- Steps of protein synthesis
- Classification of antimicrobials and their mechanism of action
- Chemotherapeutic potentiation and antagonism
- Causes of chemotherapeutic failure and their management
- Mechanism of microbial resistance.

DEFINITION OF CHEMOTHERAPY AND SHORT HISTORY

Chemotherapy is the subdivision of pharmacology that, according to the definition proposed by Paul Ehrlich, deals with drugs that can destroy the invading organism without destroying the host. This term is used when referring to use of antimicrobial agents and also to drug treatment of malignancy.

"Destruction of Parasites without the Injury of Host is Possible"—How?
It is due to some structural, functional and behavioral differences between the parasites and the host.

1. **Presence of cell wall in bacteria (but lacks in humans)**: The specific site of action of some drug, i.e. Penicillins and Cephalosporins.
2. **Sensitivity of some enzymes**: Folic acid synthetase and folic acid reductase are required for the Synthesis of folic acid (an essential metabolite for microbes) is less sensitive in mammals and these enzymes are the targets of some drugs, i.e. Sulfonamide and Trimethoprim.
3. **Difference in ribosomal constituents**: The chemistry of human rRNA differs from that of the bacteria. Human rRNA (80s) has 2 subunits, 60s and 40s whereas the bacterial rRNA (70s) has 30s and

50s subunit respectively. Antimicrobials bind, block and inhibit the protein synthesis in case of bacterial ribosomes in 50s and 30s but not in 60s and 40s, i.e. why they are injurious to the microbe, but not the host.

4. **Difference in cytoskeletal structure and release of neurotransmitter**: There are differences between the human and helminthes regarding the neurotransmission and cytoskeletal system; is the target through which anthelmintics act.
5. **Presence of ergosterol**: Rather than cholesterol in the cell membrane of fungal cell. Antifungals bind with ergosterol but not with cholesterol.
6. **Presence of mycolic acid in mycobacterium**: INH inhibits the synthesis of mycolic acid, an important constituent of *Mycobacterium tuberculosis* only; this is why, INH has no other indications than tuberculosis.

Short History of Chemotherapy

The year 1935 was an important one in the chemotherapy of systemic bacterial infection. Fleming found that a mold of penicillium prevented multiplication of staphylococci and that filtrates of cultures of this mold had similar properties. Its remarkable antimicrobial activity and lack of toxicity were demonstrated by Florey and colleagues subsequently.

In the year 1944 Streptomycin was discovered by Waksnnn. In 1950s Tetracyclines, Chloramphenicol, Polymyxin, Bacitracin and Neomycin increased the range of effectiveness of antibacterial chemotherapy. In 1957, British virologist lssacs and Swiss scientist Lindermann discovered Interferon.

SOME TERMS RELATED TO CHEMOTHERAPY

Antimicrobials, antibiotics, chemotherapeutics, antiseptics, disinfectants, germicide, fungicide, sporocide, bacteriostatic, bacteriocidal, broad and narrow spectrum of activity, MIC and MBC.

- **Antimicrobials**: These are agents which are used against microorganism, either to inhibit their growth or multiplication, or to kill them. They include antibiotics and chemotherapeutics or chemotherapeutic agents.
- **Antibiotics**: These are the agents which are usually produced by nonpathogenic micro-organism (bacteria, fungi) and are used for either killing or inhibiting the growth of other pathogenic micro-organism, without affecting the host tissue. Penicillins, Aminoglycosides, Chloramphenicol and Tetracyclines.
- **Chemotherapeutics**: Synthetic drugs which are used in chemotherapy, i.e. Sulfonamides, Isonicotinic acid hydrazide and Trimethoprim.
- **Antiseptics**: These are drugs that are applied to living tissues to kill or inhibit the growth of bacteria, i.e. alcohol and iodine preparation.
- **Disinfectants**: These are able to kill bacteria when applied to non-living materials, i.e. surface acting compounds, DDT, $KMnO_4$.
- **Germicides**: Anything that destroys bacteria but not necessarily spores, i.e. 70% ethanol, 1% iodine.

- **Fungicides**: Anything that destroys fungi, i.e. acids such as benzoic, salicylic have been used for many years as fungistatic agents.
- **Sporocides**: Aything that destroys spores, i.e. 8% formaldehyde and 2% glutaraldehyde.
- **Bacteriostatic**: It refers to the idea, that agents which inhibit the growth or multiplication of micro-organism rather than direct killing effect. Chloramphenicol, Tetracycline, Sulfonamides and Erythromycin.
- **Bactericidal**: It refers to the ability to kill the microorganism, i.e. penicillins, cephalosporins, aminoglycosides, fluoroquinolones and Rifampin.
- **Antimicrobial spectrum**: It refers to the range of activity of a compound. A broad spectrum antimicrobial drugs can affect a wide variety of micro-organisms, usually including both gram +ve and gram –ve bacteria, i.e. Sulfonamide, Chloramphenicol, etc. Narrow spectrum antimicrobials are only effective either against gram +ve or gram –ve bacteria but not against both; Flucloxacillin and phenoxy methyl penicillin.
- **MIC**: Bacteriostatic activity of a chemotherapeutic agent is usually expressed as the lowest concentration (MIC) at which the drug inhibits multiplication of the susceptible micro-organism.
- **MBC**: Bacteriocidal activity refers to the ability to kill micro-organism expressed as the minimal bacteriocidal concentration MBC.

It is very much related with the understanding of mechanism of action of many antimicrobials. So it is described briefly here.

Description

Protein synthesis takes place in the following order—

1. Messenger RNA (mRNA) is formed on the template of DNA in the nucleus and thus has the same nucleotide sequence as that of the template of DNA.
2. mRNA migrates from nucleus to cytoplasm of bacterial cell.
3. A 70s ribosome rides on mRNA.
4. Amino acids of cytoplasm are enzymatically activated and quickly get attached to specific adaptor molecules of RNA designated as tRNA (transfer RNA).
5. Each tRNA has at it's one end triplet of bases (anticodon) complementary to triplet of bases on mRNA (codon) and an amino acid molecule at the other end.
6. tRNA anticodon finds it's complementary codon on mRNA on the surface of the ribosome which, moves along the mRNA. The amino acid carried by one tRNA is attached to that of the preceding one in peptide linkage and thus a polypeptide is sequentially built up as the ribosome moves from one end of mRNA to the other.
7. The nucleotide sequence giving rise to a complementary sequence of amino acids in a polypeptide chain leading to the formation of the

required protein molecule. The probable steps of protein synthesis have been shown in (Fig. 8.1).

STEPS OF PROTEIN SYNTHESIS

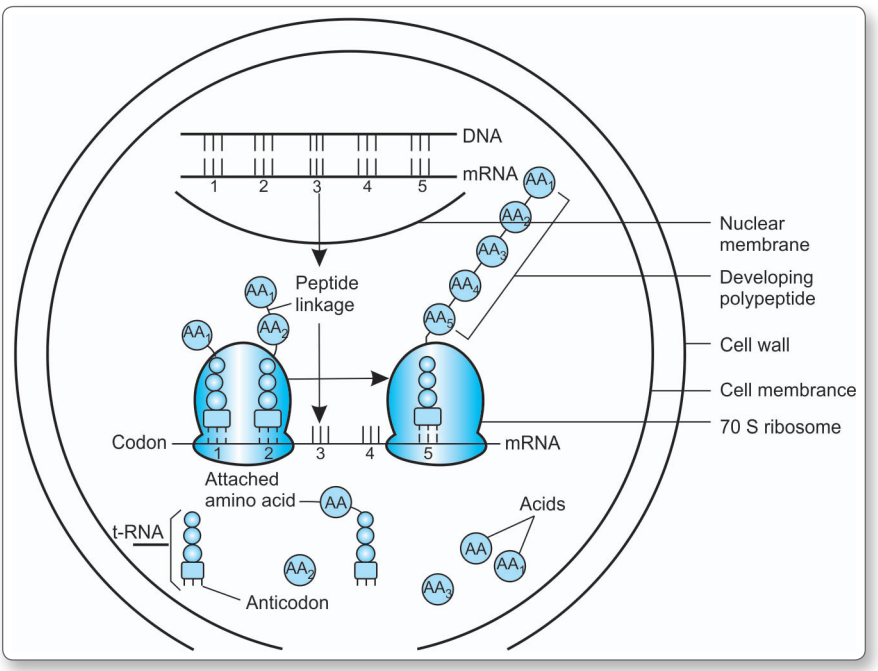


Fig. 8.1: Steps of protein synthesis

CLASSIFICATION OF ANTIMICROBIALS AND THEIR MECHANISM OF ACTION

Classification

There are several basis of classification of antimicrobials, i.e.

1. Site (target) of action, e.g. cell wall, cell membrane, 30s and 50s ribosome and DNA gyrase enzyme.
2. Spectrum of activity, e.g. broad or narrow spectrum.
3. Chemical nature-β, e.g. Lactum, Azoles, Aminoglycosides, Macrolides, Quinolones and Tetracyclines.
4. Type of organism against which they are effective, e.g. clinical classification—Antibacterial, antiviral, and antifungal.
5. Type of action, e.g. bacteriostatic or bacteriocidal.

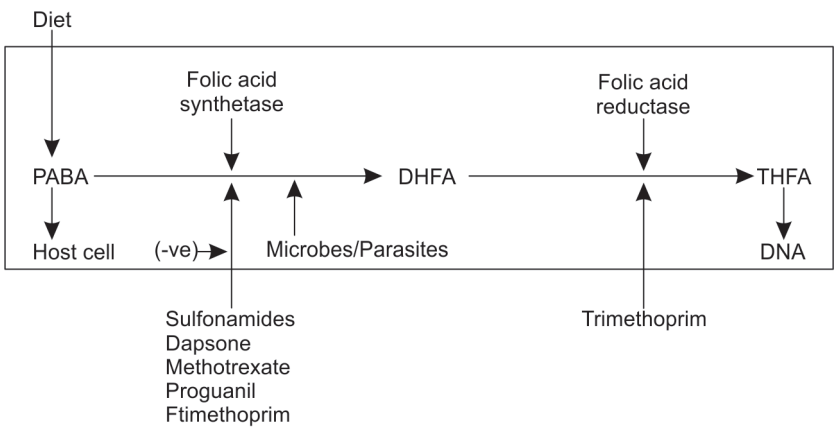
But no single basis is satisfactory. Therefore, they are presented here according to their mechanism of action:

Most of the commonly used antimicrobial compounds act by one of the following five basic mechanisms. (see the description below)

Action	Examples	Mechanism
Competitive antagonism	Sulfonamides	Competition with PABA interferes with synthesis of precursors of folic acid
Inhibition of cell wall synthesis	β-lactam (Penicillin's), Cephalosporins, Carbapenem, Monobactam, Vancomycin and Bacitracin	Binding to PBPs and inhibition of cross linking with subsequent autolysis
Alteration of cell membrane permeability	Amphotericin-B, Azoles, Polyenes, Polymyxin	Binding to ergosterol results in loss of cations from the fungal cell causing fungicidal effect
Inhibition of protein synthesis	Tetracyclines, Chloramphenicol, Erythromycin, Aminoglycosides	Inhibition of binding of tRNA to 30s and 50s ribosomal subunit
Inhibition of nucleic acid synthesis	Acyclovir, Rifampicin, Quinolones	Block5age of DNA replication by inhibiting the DNA supercoiling

Mechanism of Action

Competitive antagonism



- DHFA — Dihydrofolic acid
- THFA — Tetrahydrofolic acid

Fig. 8.2: Competitive antagonism by sulfonamide

For many micro-organism PABA is an essential metabolite. It is used by them as a precursor in the synthesis of folic acid in the pathway

leading to the synthesis of nucleic acids. The specific mode of action of PABA probably involves an ATP dependent concentration of pteridine with PABA to yield dihydropteroic acid, which is subsequently converted to folic acid. Sulfonamides are structural analogues of PABA and inhibit dihydropteroate synthetase (or folic acid synthetase in diagram).

- **Sulfonamides**: It can enter into the reaction in place of PABA in susceptible bacteria and complete for the active center of the enzyme. As a result nonfunctional analogues of folic acid are formed, preventing further growth of the bacterial cell. The inhibiting action of Sulfonamides on bacterial growth can be counteracted by an excess of PABA in the environment (competitive inhibition). Animals cell cannot synthesize folic acid and must depend upon exogenous sources, therefore they are resistant to the action of sulfonamides. Some bacteria like animal's cells are not inhibited by sulfonamides.
- **Trimethoprim**: It inhibits the dihydrofolic acid reductase of bacteria 50,000 times more efficiently than the same enzyme of mammalian cells. This enzyme reduces DHFA to THFA, a stage in the sequence leading to the synthesis of purines and ultimately of DNA. Sulfonamides and trimethoprim produce sequential blocking of these pathways resulting in marked enhancement (synergism) activity. Such mixtures (Sulfonamides five parts and Trimethoprim one part) have been used in the treatment.

Inhibition of bacterial cell wall synthesis

Composition of Bacterial Cell wall

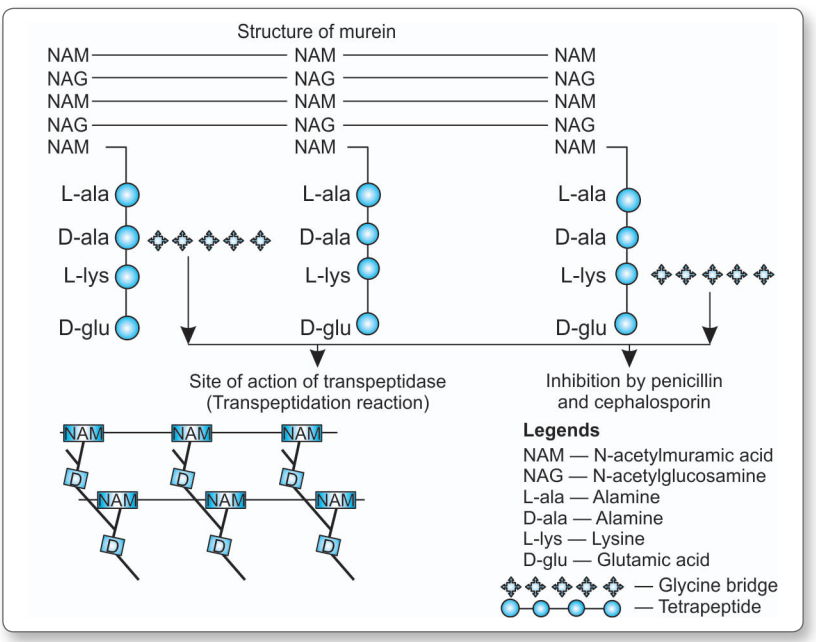


Fig. 8.3: Inhibition of bacterial cell wall synthesis

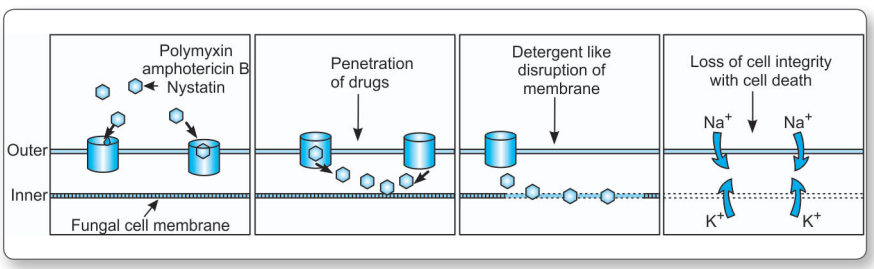
Cell Wall Synthesis Inhibition

The basic structure of bacterial cell wall is composed of a complex polymer, called mucopeptide (murein). The murein is a linear polymer composed of alternating units of two amino sugars N-acetylglucosamine and N-acetylmuramic acid. To each molecule of N-acetylmuramic acid, a tetrapeptide is attached. Tetrapeptides consists of L-alanine, D-alanine, L-lysine and D-glutamic acid. Finally these polymer strands are cross linked by amino acid bridges of glycine which connect the L-lysine of one tetrapeptide to D-alanine of another. This cross linking (tetrapeptide reaction) is carried by an enzyme called transpeptidase and gives rigidity of the cell wall.

Penicillin binds to D-alanine side of the enzyme transpeptidase in the bacterial cell wall and inhibits the enzyme transpeptides and suppress transpeptidation reaction (cross linking). So that there is defective formation of cell wall and lysis of bacterial cell wall due to higher internal osmotic pressure and there is extrusion of protoplasmic contents and death of the bacteria.

In addition, penicillin activates an autolytic enzyme which remains in inactive form. Activated autolytic enzyme causes lysis of the bacterial cell wall if the environment is isotonic and hence there is bactericidal effect.

Alteration of Cell Membrane Permeability



Figs 8.4 A to D: Alteration of cell membrane permeability. A. Bacterial cell. B. Penetration of polymyxin to inner cytoplasmic membrane. C. Detergent like disruption of cytoplasmic membrane, D. Loss of cell integrity with subsequent cell death

Some antibiotics, such as polymyxins and antifungal polyenes exert a detergent like action that alters the permeability of cell membrane.

Interactions of the polyenes antibiotics, i.e. Amphotericin B and Nystatin with ergosterol (a cell membrane lipid important for maintaining membrane integrity) causes loss of cation and, consequently, fungal cell death. Unfortunately, these polyenes also binds to mammalian cell

sterols and are quite toxic, particularly for red cells and kidney tubular membranes. The detergent-like activity is prevented if the antimicrobial agent is unable to penetrate through the outer cell wall to reach the inner cytoplasmic membrane.

Inhibition of Protein Synthesis

TCs enter micro-organisms in part by passive diffusion and in part by an energy dependent process of active transport. As a result susceptible cells concentrate the drug so that the intracellular drug concentration is much higher than the extracellular one. Once inside the cell, TCs hind reversibly to receptor on the '30s' subunit of the bacterial ribosome in a position that blocks the binding of aminoacyl tRNA to the acceptor site on the RNA ribosome complex. This effectively prevents the addition of new amino acids to the growing peptide chain, inhibiting protein synthesis. The selective inhibiton of protein synthesis in micro-organisms may be explained by largely the failure of mammalian cells to concentrate, Tetracycline.

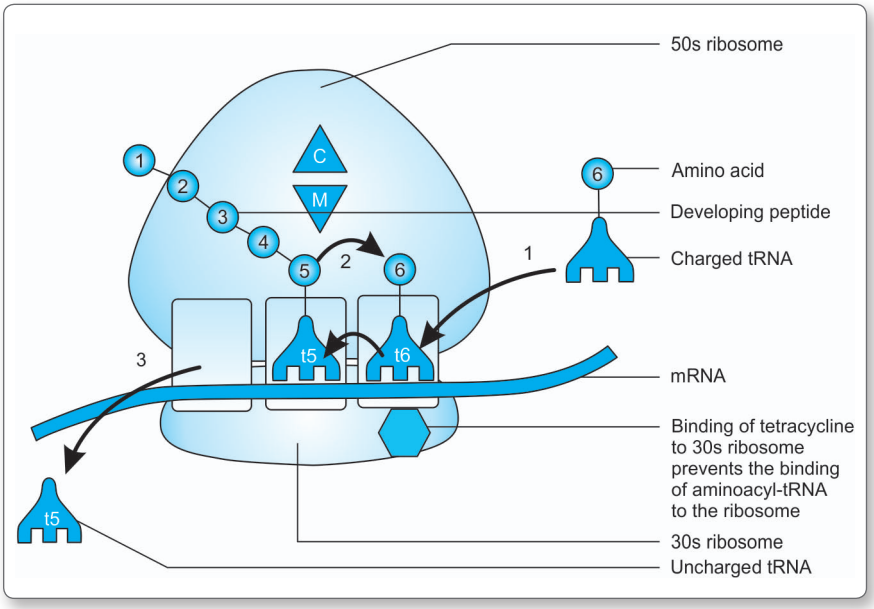


Fig. 8.5: Inhibition of protein synthesis by tetracycline

Inhibition of Nucleic Acid Synthesis

The virus comes in contact with the host cell and the following steps are covered prior to produce diseases.

1. **Adsorption**: The viruses occupies the specific receptor in the host cell, process is called adsorption.

2. **Penetration**: Following adsorption, the virus penetrates within the cell to reach inside the cell.
3. **Uncoating**: During penetration, the envelope merges with the cell membrane of the host cell and within the cell, the capsid is removed by a process called uncoating.
4. **Biosynthesis**: The DNA or RNA genome after being free, the host cell then begins to synthesize nucleotides, proteins, etc. required to synthesize viral DNA (or RNA) capsid and so on. The viral DNA transcripts and finally, a new genome capsid are formed. Finally, the newly formed capsid covered the newly formed genome, the process being called biosynthesis.
5. **Release**: The new virion is now released from the host cell. Acyclovir is a prodrug, it inhibits viral DNA synthesis only after phosphorylation by virus specific thymidine kinase, produced by virally infected cell. It is shown in diagram below.

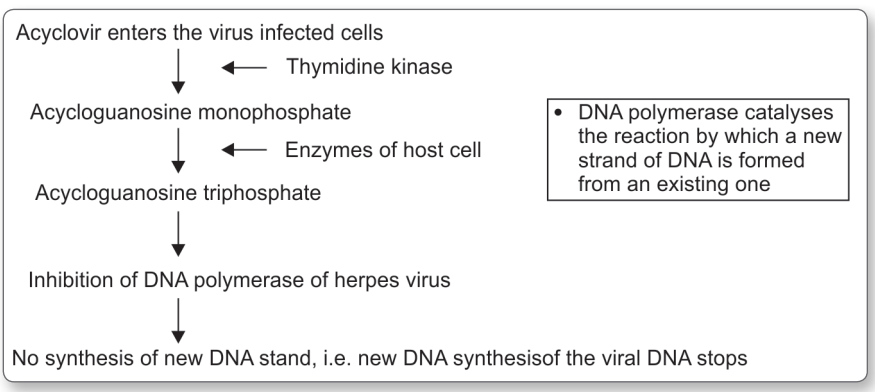


Fig. 8.6: Inhibition of nucleic acid synthesis by acyclovir

CHEMOTHERAPEUTIC POTENTIATION AND ANTAGONISM

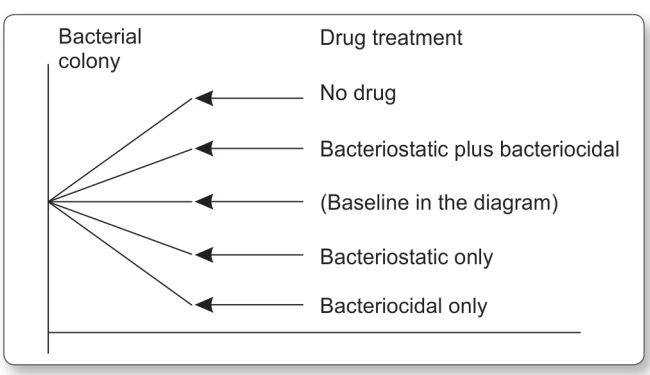


Fig. 8.7: Antimicrobial antagonism and synergism

If two or more antimicrobials are administered simultaneously or subsequently their combined effect may be—(1) Greater, (2) Same or (3) Smaller than the sum of the effect of individual drugs. These probable consequences are known as chemotherapeutic potentiation, summation or additive action and chemotherapeutic antagonism respectively.

1. Bacterial endocarditis caused by *Strep faecalis* responds well to a combination of Gentamicin + Penicillin (bacteriocidal+bacteriocidal combination)—Potentiation.
2. Sulfonamide+ Trimethoprim is a very popular combination. (It is a bacteriostatic + bacteriostatic combination) but combined effect is bacteriocidal—Potentiation.
3. Combination of bacteriostatic and bacteriocidal one is an example of bad combination, because bacteriocidal drugs act best when the bacteria are multiplying, whereas bacteriostatic drugs inhibit multiplication, e.g. Antagonism. The position has been illustrated above by a diagram.

CAUSES OF CHEMOTHERAPEUTIC FAILURE AND THEIR MANAGEMENT

1. Incorrect clinical or microbiological diagnosis
2. Improper drug administration or inadequate dosage
3. Poor patient compliance
4. Alteration in bacterial flora during drug administration and superinfection with a resistant organism
5. Infection in a location inaccessible to the drug
6. Failure to use indicated surgical drainage
7. Development of drug resistance by mutant forms of infecting organism
8. Deficiency in host defences
9. Drug toxicity and hypersensitivity
10. Incompatible chemotherapeutic combination.

MECHANISM OF MICROBIAL RESISTANCE

Microbial resistance to drugs may develop by two ways—

1. Natural way
2. Acquired way.

They are reviewed here briefly—

1. a. Micro-organisms produce enzymes, that destroy the active drugs. Staphylococci resistant to penicillin G produce a β-lactamase that destroy the drug (Cloxacillin is stable to the action of lactamase). Gram-negative bacteria may be resistant to Chloramphenicol if they produce a chloramphenicol acetyltransferase.

b. Micro-organisms change their permeability to the drug. Tetracyclines accumulate in susceptible bacteria, but not in resistant ones. Resistance to polymyxin is probably associated with a change in permeability to the drug.
c. Micro-organism can develop an altered structural target for the drug. Chromosomal resistance to Aminoglycosides is associated with the loss or (alteration) of a specific protein on the 30's subunit of the bacterial ribosome but serves as a receptor in susceptible organism. Resistance to some specific penicillin and cephalosporins may be a result of the loss or alteration of PBPs (Penicillin binding protein).
d. Micro-organisms may develop an altered metabolic pathway that by passes the reaction inhibited by the drug. Some sulfonamide resistant bacteria do not require extracellular PABA, but like mammalian cells, can utilize preformed folic acid.
e. Micro-organism may develop an altered enzyme that can still perform it's metabolic function but is much less affected by the drug than the enzyme in the susceptible organism. In some sulfonamide susceptible bacteria, dihydrofolate synthetase has much higher affinity for sulfonamide than for PABA. In sulfonamide resistant mutants, the opposite is the ease.

2. a. **Mutation**: Any large population of antibiotic susceptible bacteria is likely to contain some mutants that are relatively resistant to the drug.
b. **Conjugation**: The passage of resistant genes from cell to cell by direct contact through a sex pilus or bridge is termed conjugation.
c. **Transduction**: Passage of resistant genes from an insensitive organism to a sensitive organism by bacteriophase.
d. **Transformation**: DNA released by cell lyses is incorporatived directly into bacteria, i.e. contained in it's environment. This is essentially confined to gram-ve bacteria.

SECTION-II ANTIBIOTICS, PENICILLINS AND CEPHALOSPORINS A (PENICILLINS)

- History
- Source
- Chemistry
- Limitations of initial penicillins
- Classifications
- Pharmacokinetics
- Pharmacodynamics
- Potency/unit
- Ampicillin and amoxicillin—A comparison
- Indication of penicillin

- Contraindications
- Adverse actions and their management

HISTORY

Almost 70 years ago, Sir Alexander Fleming reported his discovery of Penicillin in 1929. Chain, Florey and their associates succeeded in producing significant quantities of the first Penicillin from cultures of Penicillium notatum in 1940.

SOURCE

Penicillin is an organic acid obtained from cultures of the mold Penicillium chrysogenum.

CHEMISTRY

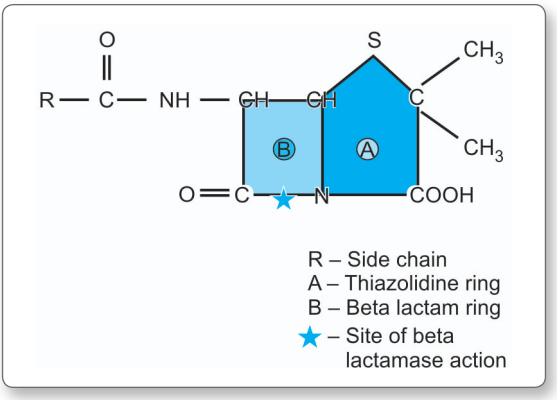


Fig. 8.8: Aminopenicillanic acid (6 APA)

The basic nucleus of Penicillin is (6-APA). 6-aminopenicillanic acid, consisting of Thiazolidine ring (a) fused with β-lactam ring (b) Thiazolidine ring is concerned with absorption, distribution and hypersensitivity reaction, while β-lactam ring is responsible for antimicrobial action of Penicillin. Nucleus contains side chain R and newer Penicillins are synthesized by alteration in side chain.

LIMITATIONS OF INITIAL PENICILLINS

The principal clinical limitation of Penicillin-G were

1. It's instability at acidic p^H
2. Susceptibility to destruction by β-lactamase (penicillinase)
3. It's relative inactivity against gram (–ve) bacilli.

CLASSIFICATIONS

Basis of classification of Penicillins are—
a. Source
b. Spectrum of activity
c. Duration of action
d. Route of administration.

According to Source

1. Natural Penicillins, i.e. Penicillin-G. Phenoxy methyl penicillin, i.e. Penicillin-V, (it is gastric hydrochloric acid resistant).
2. Semisynthetic penicillins are—Ampicillin, Amoxicillin, e.g. Cloxacillin, Flucloxacillin, Dicloxacillin, Oxacillin.

According to Spectrum of Activity

1. Narrow spectrum Penicillins, i.e. Benzyl penicillin, Phenoxy methyl penicillin.
2. Extended Spectrum
   a. Aminopenicillin—Ampicillin, Amoxicillin.
   b. Carboxypenicillin—Ticarcillin.
   c. Ureidopenicillin—Azlocillin, Mezlocillin.
3. Penicillinase resistant penicillin: Penicillinase or β-lactamase cannot degrade these Penicillins, hence, they are called penicillinase resistant Penicillins.
4. Penicillinase resistant Penicillins—Nafcillin, Mithecillin, Cloxacillin, Oxacillin.

According to Duration of Action

1. Short-acting(6–12 hours), i.e. Benzyl penicillin
2. Intermediate acting (12–24 hours), i.e. Procaine penicillin
3. Long-acting(3– 4 weeks), i.e. Benzathine penicillin.

According to Route of Administration

1. Oral Penicillin, i.e. Phenoxymethyl penicillin, Penicillin-V.
2. Parenteral Penicillin, i.e. Penicillin-G, Procaine Penicillin and Benzathine Penicillin.

PHARMACOKINETICS

Absorption of Penicillin-G from the GIT is incomplete and variable. Also Penicillin-G is inactivated by gastric juice, so that Penicillin-V which is

more resistant to acid, is the preferred oral form against streptococcal organisms.

Penicillin is considerably bound to plasma proteins and is not uniformly distributed to most regions of the body. It achieves adequate concentrations in pleural and synovial spaces but penetrates poorly into CSF and aqueous humor. However, inflammation increases meningeal permeability so that concentration, effective for treatment of meningitis can be achieved within 24 hours of treatment in patient of meningitis.

Repository preparations such as Penicillin-G procaine and Penicillin-G Benzathine can be used when sustained blood concentration in the range of 0.03 microgram /ml or so, are required for 10 days or longer.

Penicillin is eliminated from the body primarily by rapid renal clearance. With severe renal failure the half-life increases so that the dose interval is must be extended. Penicillin is actively secreted by renal tubules.

Probenecid, which blocks the tubular secretory mechanism, is occasionally used with Penicillin to prolong it's action after IM or oral administration.

PHARMACODYNAMICS

See Figure 8.3 with description.

POTENCY/ UNIT

1 mg of Penicillin-G potassium equal 1600 units conversely 1 unit is equivalent to 0.625 gm of Penicillin-G. 1 mg Penicillin-G potassium is equal to 1600 unit conversely.

1 Unit = 1/1600 mg
= 0.000625 mg = 0.625 gm
= 0.625 gm

1.0000 = 0.000625 mg
1600 =0.625 gm

AMPICILLIN AND AMOXICILLIN—A COMPARISON

Points of difference	Ampicillin	Amoxicillin
Bioavailability	Less absorbed from GIT (>65%)	Rapid and more absorption(>85%)
Sensitivity to shigella	More	Less (insignificant)
Duration of action	6 hours	8 hours
Chance of diarrhea	More	Less
Absorption and relation with food	It should be given in empty stomach	It has no relation with food

INDICATIONS OF PENICILLIN

Therapeutic

a. Pneumococcal infection, i.e. Pneumococcal pneumonia. Pneumococcal empyema, Pneumococcal meningitis.
   Others include: Supportive arthritis, osteomyelitis, acute supportive mastoiditis, endocarditis, peritonitis, pericarditis, otitis media.
b. Streptococcal infection, i.e. Streptococcal pharyngitis, streptococcal other infections.
c. Meningococcal infection, i.e. Meningitis.
d. Gonococcal infection, i.e. Gonorrhea, gonococcal arthritis, gonococcal urethritis.
e. Syphilis.
f. Actinomycosis.
g. Diphtheria.
h. Anthrax.
i. Rheumatic fever.
j. Tetanus.

Prophylactic

a. Streptococcal infection
b. Rheumatic fever
c. History or chance of contamination with gonorrhea
d. Surgical procedures in patients with vulvular heart diseases and also extraction of teeth.

CONTRAINDICATION

Patients hypersensitive to Penicillin.

ADVERSE ACTIONS AND THEIR MANAGEMENT

Type of reaction	Frequency of reaction	Examples
Hypersensitivity anaphylaxis serum sickness skin rash	>0.1% rare common	Penicillin-G Penicillin-G All
Idiopathic skin rash enterocolitis	Common rare	Ampicillin All
Gastrointestinal diarrhea enterocolitis	Common infrequent	Ampicillin All

Contd...

Contd...

Type of reaction	Frequency of reaction	Examples
Hematological neutropenia platelet dysfunction hemolytic anemia	Infrequent rare	Nafcillin Carbenicillin Penicillin-G
Electrolyte hypokalemia	Infrequent	Carbenicillin
Liver function elevated enzyme	Infrequent	Cloxacillin
Renal function interstitial nephritis	Infrequent	Methicillin
Neurologic seizures	Rare	Penicillin-G

Management

Anaphylactic shock

Step 1: Drug (Hapten) Combines with→Body protein→Forming→Antigen
Step 2: Antigen → P stimulates → Reticuloendothelial system producing → Antibody
Step 3: Subsequent re-exposure to drug (Antigen) → Combines with antibody → Allergic reaction
Antigen-antibody reaction
Change of permeability of mast cell membrane

Cause

Release of

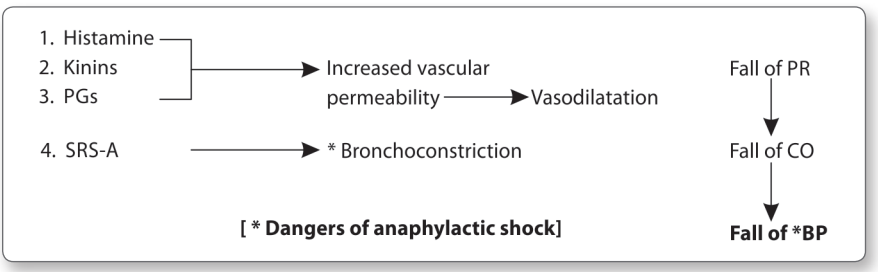


Fig. 8.9: Pathogenesis of anaphylactic shock

Treatment

General measure

- Precipitating cause (drug) is to be stopped
- Patient is to be kept in supine position
- Airway is to be cleared and ensured by endotracheal tube.

Specific measure

Injection of 1 ml adrenaline IM and it may be repeated after 3 minutes interval depending on, to relieve the patient from hypotension, bronchospasm and laryngeal edema.

Mechanism

1. Adrenaline stimulates both
   a. α-receptor → Cause vasoconstriction → Increased PR ↘
      BP ↗ CO↑
   b. β_1-receptor → Increased force of contraction of heart Rise of CO
   c. β_2-vreceptor → Activation of AC → increased CAMP → bronchodilatation
      Injection Hydrocortison hemisuccinate 100 mg IV slowly is given to sensitize the blood vessels to the action of Adrenaline.
2. Infusion of fluid to restoration of fluid volume.

SUPERINFECTION, SUPRAINFECTION OR OPPORTUNISTIC INFECTION

- Definition
- Organisms responsible
- Pathogenesis
- Common sufferer
- Clinical features
- Treatment.

Definition

It may be defined as the appearance of bacteriological and clinical evidence of a new infection, during the treatment of primary infection.

Organisms Responsible

Candida albicans, proteus pseudomonas true fungi.

Pathogenesis

In the intestine nonpathogenic and pathogenic bacterial flora always remain in balance. Antibiotics suppress the nonpathogenic flora and helps the growth and multiplication of pathogenic bacteria, and they take the upper hand, and clinical manifestations occur, condition is known as superinfection.

Common Sufferer

1. Patients less than 3 years and above 65 years of age having acute or chronic pulmonary infection other than tuberculosis or middle ear infection.
2. Those treated with broad spectrum antibiotics like Penicillin, Tetracyclines and Sulfonamides.
3. Others drugs, i.e. steroid and immunosuppressive drugs.

Clinical Features

1. Diarrhea that may contain blood, mucus and large number of polymorphonuclear leukocytes.
2. Stomatitis, glossitis, cheilosis—Due to suppression of nonpathogenic bacteria producing B vitamins.

Treatment

1. Cessation of the offending drug
2. Culture of the stool and then using proper antibiotics sensitive to organism responsible for superinfection
3. Supplementation of B vitamins.

β-lactamase inhibitors, e.g. Clavulanic Acid, Sulbactam

Coamoxiclav—It is a mixture of Amoxicillin and Clavulanic acid as potassium clavulanate.

Indication—Infections is due to Penicillinases producing strains including—

i. Respiratory tract infections
ii. Genitourinary infections
iii. Abdominal infections
iv. Cellulitis
v. Animal bites
vi. Severe dental infections.

MOA—In a situation where both lactam-antibiotic and β-lactamase inhibitors are available, the β-lactamase enzyme bind with β-lactamase inhibitor irreversibly; so the β-lactam antibiotic become harmless. In these way all β-lactamase enzymes are exhausted. So that the β-lactam antibiotic remaining intact, that is why β-lactamase inhibitors are known as suicide inhibitors.

CEPHALOSPORINS

1. Definition
2. Source

3. Chemistry
4. Classification
5. Mechanism of action (3rd generation)
6. Antimicrobial activity (3rd generation)
7. Superiority of Cephalosporins to Penicillin
8. Clinical uses of Cephalosporins
9. Resistance
10. Adverse action
11. Other β-lactam antibiotics.

Definition

Cephalosporins are a group of semisynthetic antibiotics, derived from cephalosporin-C which is obtained from a fungus cephalosporium. They are chemically related to Penicillins.

Source

Cephalosporium fungi yielded several antibiotics that resembled penicillin, but were resistant to β-lactamase and broader spectrum of activity.

Chemistry

The nucleus of the cephalosporins, 7 aminocephalosporanic acid bears a close resemblance to 6 aminopenicillanic acid consisting of a β -lactam ring fused to a dihydrothiazine ring. By addition of different side chains at position 7 of β-lactam ring affecting the spectrum of activity and position 3 of dihydrothiazine ring (affecting pharmacokinetic) a large number of cephalosporin have been produced.

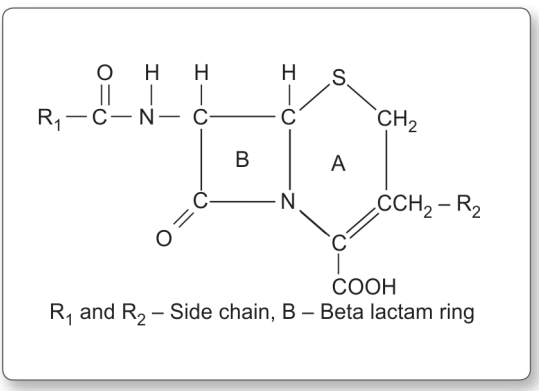


Fig. 8.10: Aminocephalosporanic acid (7 ACA)

Classification

Conventionally, it has been divided into three groups or generations depending mainly on the spectrum of activity, potency and chronological sequence of development. Recently, fourth generation have been introduced.

First generation	Second generation	Third generation	Fourth generation
Cefadroxil	Cefachlor	Ceftizoxime	Cefepime
Cefazolin	Cefamandole	Ceftazidime	
Cephalexin	Cefonicid	Ceftizoxime	
Cefalothin	Ceforanide	Ceftriaxone	
Cephapirin	Cefoxitin	Ceftariaxone	
Cephradine	Cefotetan	Cefixime	
	Cefuroxime	Moxalactam	
		Cefoperazone	

Mechanism of Action (3rd Generation)

Mechanism of action (3rd generation) of Cephalosporin is analogous to that of Penicillins, i.e.

1. Binding to specific Penicillin binding protein (PBP) that serves receptors on bacteria.
2. Inhibition of cell wall synthesis by blocking transpeptidation of Peptidoglycan.
3. Activation of autolytic enzymes in the cell wall, which results in lesions that cause bacterial death.

Antimicrobial Activity (3rd Generation)

1. Compared with second generation agents, these drugs have expanded gram-negative coverage and some are able to cross the blood brain barrier.
2. Third generation drugs are active against *citrobacter*, S marcescents and providencia (although resistance can emerge during treatment of infections caused by these species due to selection of mutants that constitutively produce Cephalosporinase.
3. They are also effective against β-lactamase—producing strains of Haemophilus and Neisseria. Ceftazidime and Cefoperazone are the only two drugs with useful activity against *P. aeruginosa*.
4. Like the second generation drugs, third generation Cephalosporins are hydrolyzable by constitutively produced by β-lactamase and they are not reliably active against enterobacter species, Serratia,

providencia and citrobacter also produce a chromosomally encoded cephalosporinase that, when constitutively expressed, can confer resistance to third generation cephalosporins.

5. Ceftrizoxime and Moxalactam are active against B fragilis. Cefixime, Cefdinir, Ceftibuten and Cefepodoxime proxetil are oral agents possessing similar activity except that Cefixime and Ceftibuten are much less active against pneumococci and completely inactive against Penicillin resistant strains and have poor activity against *S. aureus*.

Superiority of Cephalosporins to Penicillin

Cephalosporins are superior to Penicillins due to their following uses—Parenteral Cephalosporins are useful in the following clinical settings:

1. As therapy for persons allergic to Penicillin. However, one must proceed with caution in this situation.
2 For treatment of patients with gram-negative infection, such as the elderly with pneumonia or for hospital acquired bacteria caused by Klebsiella species (Cefotaxime or Ceftriaxone) or pseudomonas infection.
3. For therapy of mixed infection or initial treatment of certain infection of unknown causes (Cefotoxin or Cefotetan) for postoperative abdominal infections.
4. For prophylaxis before surgery, specially for GIT, pelvic or orthopedic surgery.
5. For meningitis potentially caused by either gram-positive or gram-negative organisms.
6. For treatment of gonococci infections, because the organisms frequently produce Penicillinase.

Clinical Uses of Cephalosporins

Cephalosporins are now widely used antibiotics. Their indications are—

1. **As an alternative to Penicillin** in patients developing rashes or other allergic reactions (but not in immediate type of hypersensitivity).
2. **Respiratory, urinary and soft tissue infections** caused by gram-negative organisms specially Klebsiella, proteus and enterobacter and serratia.
3. **Penicillinase producing staphylococcal infections** → Cephalothin is the preferred drug.
4. **Septicemias** caused by gram-negative organisms. An aminoglycoside may be combined with a cephalosporin.
5. **Surgical prophylaxis** in this cases 1st generation Cephalosporins are popular drugs, Cephazolin has been specially used in patients with surgical prosthesis such as artificial heart valves, artificial joints, etc.

6. **Meningitis** caused by *H. influenae*, enterobacteriaceae Cefuroxime, Cefotaxime and Ceftriaxone have been specially used.
7. **Gonorrhea** caused by penicillinase producing organisms ceftriaxone is a first line drug for single dose therapy of gonorrhea if the penicillinase producing status of the organism is not known.
8. **In typhoid**, as an alternative to fluoroquinolones (specially in children for *S. Typhi* strains resistant to Chloramphenicol, Ampicillin and Cotrimoxazole, Ceftriaxone is very valuable).
9. **Mixed aerobic** here anerobic infections seen in cancer patients, those undergoing colorectal surgery, obstetric complications, → cefuroxime or one of the third generation compound is used.
10. **Infection by odd organisms in hospital infections** resistant to commonly used antibiotics—Cefotaxime, Ceftizoxime or another third generation drug may work.
11. **Prophylaxis and treatment of infections in neutropenic patients**—Ceftazidime or in combination with an Aminoglycoside may be used.

Resistance

Can be attributed to—

1. Poor penetration of bacteria by the drug.
2. Lack of PBPs for a specific drug.
3. Degradation of drug by β-lactamase (Cephalosporinase, many such enzyme exists).
4. Appearance of special β-lactamase in course of treatment of certain gram-negative rods.

Adverse Actions

Cephalosporins are usually well-tolerated drugs but they may produce the following adverse actions:

1. Pain after IM injection occurs with many. This is so severe with Cephalothin and Cephapirin as to interdict this route. Thrombophlebitis may occur on IV injection.
2. Diarrhea due to alteration of gut ecology or irritative effect is more common with oral Cephradine and parenteral Cefoperazone.
3. Hypersensitivity reaction caused by Cephalosporins are similar to Penicillin.

   Rashes are the most frequent manifestation, but anaphylaxis, angioedema, asthma and urticaria have also occurred. About 10% patients allergic to Penicillin show cross reactivity with cephalosporins. Those with a history of immediate type of reactions to Penicillin should better not be given a Cephalosporin. Skin test for sensivity to cephalosporins are unreliable.

   positive (+ve) Coombs test occurs in many but hemolysis is rare.
4. Nephrotoxicity is highest with Cephaloridine which deserves to be withdrawn. Cephalothin and few others have low grade nephrotoxicity

which may be accentuated by preexisting renal disease, concurrent administration of an aminoglycoside or loop diruetic.

5. Bleeding occurs with Cephalosporins having a methyl thiotetrazole or similar substitution at position three (Cefamandole, Moxalactam, Cefoperazone, Ceftriaxone). This is due to hypoprothrombinemia caused by the same mechanism as Warfarin and is more common in patients with cancer, intra-abdominal infection or renal failure. Moxalactam has an carboxyl substitution in the side chain at position appears to cause perturbation of surface receptors on platelets prolongs bleeding time.
6. Neutropenia and thrombocytopenia are rare adverse effects reported with Ceftazidime and some others.
7. A Disulfiram like interaction with alcohol has been reported with Cefamandole, Moxalactam and Cefoperazone.

Other β-Lactam Antibiotics

Besides Penicillins and Cephalosporins, Carbapenems (Imipenem, Meropenem) and Monobactam (Aztreonam) are important therapeutic agents with a β-lactam structure. They are bactericidal and act by inhibiting cell wall synthesis of susceptible organisms.

The Carbapenems have wide spectrum of activity, being active against many aerobic and anaerobic gram-positive and gram-negative organisms, including listeria, pseudomonas and most enterobacteriaceae.

The Monobactam Aztreonam has different antibacterial activity in comparison to those of other β-lactam antibiotics and more closely resembles that of an aminoglycoside antibiotic. Its activity is limited to gram-negative aerobic bacteria, including *P. aeruginosa*, *N. meningitides*, *N. gonorrhoea* and *H. influenzae*. As Aztreonam is not effective against gram-positive organisms, it should not be used for 'blind treatment'. Both Carbapenems and Monobactams are resistant to wide spectrum of β-lactamases. Imipenem is rapidly inactivated to potentially nephrotoxic metabolite by dihydropeptidase in the brush border of proximal renal tubule and is therefore given in combination with Cilastatin, a specific inhibitor of this enzyme. Therefore use of Cilastatin has two effects:

1. It increases the conc. of imipenem in kidney
2. It prevents nephrotoxicity.

SECTION-III AMINOGLYCOSIDES AND ANTIMYCOBACTERIAL AGENTS

AMINOGLYCOCIDES

- Definition
- Names

- Source
- Chemistry
- Common properties
- Drawbacks
- Pharmacokinetics
- Pharmacodynamics
- Indication
- Toxicity

Definition

All the members contain two or more amino sugars joined through glycoside linkage to the central hexose nucleus, hence they are so called.

Names

Streptomycin, Tobramycin, Amikacin, Neomycin, Netilmicin, Kanamycin, Gentamicin and Spectinomycin.

Source

Aminoglycosides are a group of bactericidal drugs originally obtained from various streptomyces species, i.e. Streptomycin from *Streptomyces griseus*, Neomycin from *Streptomyces fradiae* and Kanamycin from *Streptomyces kanamyceticus*.

Chemistry

All aminoglycosides chemically contain—

1. One hexose unit
2. Amino sugar unit connected to hexose unit by glycoside linkages Streptomycin has a chemical structure with a molecular weight of 582. It is a triacidic base with three components, glycosidically linked together as follows.

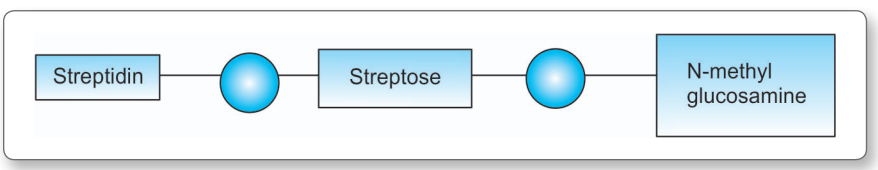


Fig. 8.11: Structure of aminoglycosides

Common Properties

1. They are very much polar or ionized, so that poorly absorbed from GIT and needs parenteral administration

2. They cannot cross the blood brain barrier (BBB) normally
3. They are very much effective against gram-negative organism
4. They are rapidly excreted by the kidneys
5. They possess some common toxicities, i.e. ototoxicity, nephrotoxicity and neuromuscular blockade.

Drawbacks

1. Toxicity, they commonly produce toxic symptoms, i.e. nephrotoxicity, ototoxicity and N/M blockade. Their TI (Therapeutic Index) is low.
2. Availability of better drugs aminoglycosides are mostly used against gram-negative bacterial infections. Currently many antibiotics, safer than AGs (broad spectrum penicillin, 3rd generation Cephalosporin, Fluoroquinolone and Aztrenonams and so on are available and some of them are not costly.
3. Emergence of registance in bacteria facing the AGs is often quick.

Pharmacokinetics

Aminoglycosides are water-soluble and don't readily cross cell membranes. Poor absorption from the intestine necessitates their administration IV or IM and they distribute mainly to the extracellular fluid, transfer into the cerebrospinal fluid is poor even when the meninges are inflamed. Their $t_{1/2}$ is 2 to 5 hours and they are eliminated unchanged mainly by glomerular filtration and attain high conc. in the urine. Significant accumulation occurs in the renal cortex unless there is severe renal parenchymal disease, dose reduction is necessary to compensate for varying degrees of renal impairment, including that of normal ageing, plasma conc. should be measured regularly and frequently in such patients and indeed, it is a good practice to monitor, even if renal function is normal.

Pharmacodynamics

1. AGs enter bacterium through porenpore.
2. AG is actively transported across cytoplasmic membrane.
3. AG binds to 30s ribosomal subunit, as a consequence of binding there occurs—
   a. Failure to initiate protein synthesis
   b. Failure of elongation of developing peptide chain
   c. Misreading of tRNA, leading to deformed proteins.

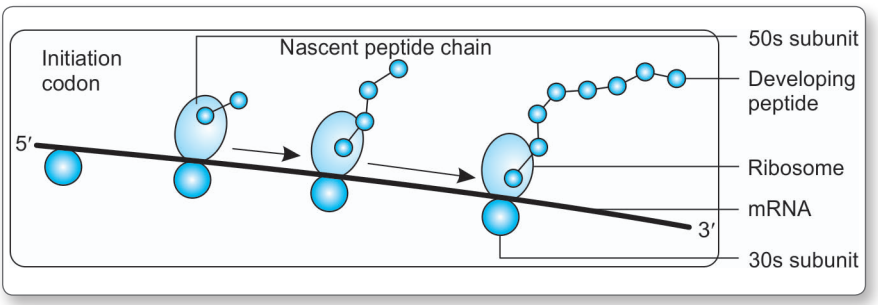


Fig.8.12: Normal bacterial cell

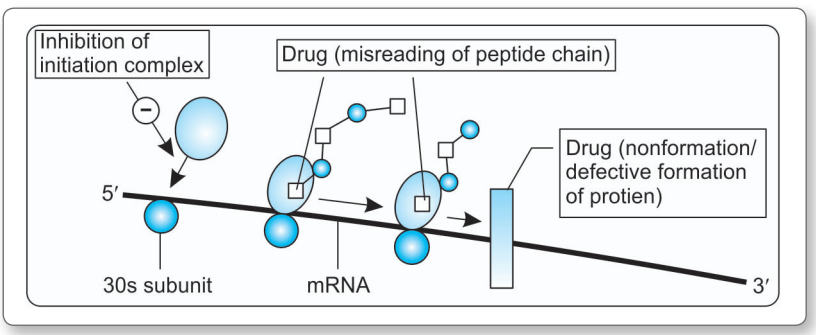


Fig. 8.13: AG treated bacterial cell

Toxicity

AGs can cause following types of toxicities—

1. **Ototoxicity**: Auditory impairment is usually associated with Amikacin, Neomycin and vestibular toxicity is with the Streptomycin. Endolymphatic fluid plays an important role in the generation and transportation of sound impulse to the auditory center. AOs, particularly Amikacin interferes the proper active transport of different ions to and away from endolymphatic fluids, so that milieu of environment is changed, leading to hair cell injury and auditory disturbance.
2. **Nephrotoxicity**: Normally, there is a balance between vasoconstrictor (angiotensins) and vasodilator (prostaglandins) in the kidneys. AGs after binding in renal cortex, in some unknown way inhibit the action of phospholipase group of enzymes (prostaglandin generating). Thereby angiotensin become unopposed and produce severe vasoconstriction and sequentially reduces renal perfusion resulting fall of GFR, renal tubular necrosis, albuminuria, increase serum creatinine, severe azotemia and uremia.
3. **Neurotoxicity**: AGs competitively block the nicotinic receptor, like that of curarin, so that there is no formation of transmitter-receptor complex.

4. **Other**: It includes rashes, drug fever, eosinophilia, marrow depression and hemolytic anemia, bleeding due to antagonism of factor V.

Indications

Clinically AGs can be used in—

1. Septicemia of undetermined but suspected to be of polymicrobial origin; here AG is given concurrently with other antibiotics. In fact, in many condition AG has to be given with another antibiotics.
2. In bacterial endocarditis due to enterococcus of *S. viridans* where Gentamicin+Penicillin is used.
3. In bacterial endocarditis due to *Strep. aureus*, where Ticarcillin + Penicillin used.
4. Complicated UTI is another disease; where AGs are effective.
5. AGs are often used in pelvic infection PID(pelvic inflammatory disease).
6. Followings are also the condition where AGs may be used.
   a. Plague
   b. Brucellosis
   c. Tularemia
   d. Tuberculosis.
7. In rare type of pneumonia or in meningitis due to pseudomonas the AGs can be used.
8. Tropical use of AGs very popular.

ANTIMYCOBACTERIAL AGENTS

- Tuberculosis in brief
- Pathogenesis of granuloma
- Classification of antitubercular drugs
- Regimen
- Principles of chemotherapy in TB
- Special problem
- Individual drugs:
  a. Streptomycin
  b. INH
  c. Pyrazinamide
  d. Rifampicin.

Tuberculosis in Brief

It is a worldwide chronic communicable disease caused by *Mycobacterium tuberculosis*, which usually affects the lungs but may cause lesion in any organ or tissue of human body. It evokes focal granulomatous inflammatory reactions that typically undergo central caseous necrosis.

Pathogenesis of Granuloma

During granuloma formation the following sequence of events occur.

1. Transient acute inflammatory reaction with an infiltration of polymorphs. These cells are rapidly destroyed by the causative agents.
2. A progressive infiltration of macrophages derived from the local histocytes and the monocytes of the blood.
3. The macrophages, phagocytose the agents. In a short period their character changes. Their cytoplasm becomes pale and eosinophilic and their nuclei elongated and vesicular. This appearance bears a resemblance to the epithelial cell.
4. Some macrophages instead of becoming epithelioid cells, fuse to form giant cells.
5. Surrounding the mass of altered macrophages, there is a wide zone of small round cells, mostly lymphocytes.
6. Surrounding the lymphocytes, proliferation of fibrovascular tissue occurs.
7. In case of tubercle, the central macrophages undergo characteristic necrosis, called caseation necrosis.

Classification of Antitubercular Drugs

- First-line drugs (More effective, less toxic) → Ethambutol, Isoniazid, Pyrazinamide, Rifampin, Streptomycin.
- Second-line drugs (Less effective but more toxic) → Amikacin, Capreomycin, Cycloserine, Rifabutin.

Regimen

Mycobacteria are slowly growing organisms, can remain dormant for long time and a substantial proportion reside within macrophages inaccessible to many drugs and can rapidly develop resistance to any single drug. As such, combinations of drugs are employed to overcome these obstacles and to prevent emergence of resistance. Another problem, to prevent disease relapse, required therapy is of long duration which most patients fail to comply. To overcome this problem, supervised short-course therapy with intermittent administration of drugs has been formulated and adopted by many national antituberculosis programes.

i. A large number of actively multiplying bacilli is killed; INH achieves this.
ii. Persister, i.e. semidormant bacilli that metabolize slowly or intermittently be killed: Rifampicin and Pyrazinamide are the most efficacious.
iii. The emergence of drug resistance be prevented by multiple therapy to suppress drug resistant mutant, by INH and Rifampicin are the best.

All short course regimens therefore, include the common drugs, i.e. INH, Rifampicin and Pyrazinamide.

Principles of Chemotherapy in TB

1. Use only the first-line drugs unless there is some special indications.
2. Typically *M. tuberculosis* has a remarkable tendency to develop resistance against antitubercular drugs. To prevent the development of this resistance, one must use at least two drugs of first-line concurrently, very often three and sometimes even four.
3. One major trouble is noncompliance of the patients. This is the global phenomenon, but more common in poorer countries.
4. Where compliance is good and the patient is immunocompetent, the cure rate is excellent near 100%.
5 Where compliance is defective, recurrence rate is high.
6. Considerations for exercising the option among first-line drugs are chiefly toxicity and the cost. Poor patients may be troubled because of cost involved.

Special Problem

1. **Resistant organisms**: Initial resistance occurs on about 4% of patients usually isoniazid but very rarely to Rifampicin or Ethambutol. By contrast atypical mycobacteria are usually resistant to most standard drugs. Their virulence is low but they can produce serious infections in immunocompromised patients which immunocompromised patients may respond, i.e. to erythromycin often in combination.
2. **Pregnancy**: Drug treatment should never be interrupted or postpond during pregnancy. On the general principle of limiting exposure of the fetus, the standard 3 drug, 6 months course is best. Streptomycin should be excluded from any regime.
3. **Nonrespiratory tuberculosis**: The principles of treatment multiple therapy and prolonged follow-up are the same as for respiratory tuberculosis. In only a few cases, surgery is now necessary. It should always be proceeded and followed by chemotherapy. Many chronic tuberculous lesions may be relatively in accessible to drugs as a result of avascularity of surrounding tissues and treatment frequently has to be prolonged and dose high, specially if damaged tissue cannot be removed by surgery, i.e. tuberculosis of bones.
4. **Meningeal tuberculosis**: It is essential to use Isoniazid and Pyrazinamide which penetrate well into the CSF. Rifampicin enters inflamed meninges well but noninflamed meninges so less. An effective regimen includes Isoniazid, Rifampicin, Pyrazinamide and streptomycin. Treatment may need to continue for much longer than modern short course chemotherapy for pulmonary tuberculosis.
5. **Tuberculosis of the skin**: Particularly lupus vulgares usually respond well. Some physicians have given Isoniazid alone but it is preferable to give two drugs.

Individual Drugs

Streptomycin

Uses of Streptomycin

i. Tuberculosis
ii. In endocarditis with Penicillin
iii. Plague
iv. Tularemia
v. Brucellosis
vi. Gut sterilization.

Dose and Administration

- **Route** Deep IM inj. or IV inj.
- **Dose tuberculosis** ADULT 1 gm daily for consecutive 2 months; CHILD 20–40 mg/kg/d, not to exceed 1–1.5 gm/d; for intermitten supervised therapy 1–1.5 gm twice or thrice weekly.
- **Bacterial endocarditis** 0.5 gm twice daily.
- **Tularemia** 1–2 gm/d in divided doses.
- **Plague** 1–4 gm/d in 2 to 4 divided doses.

Gut micro-organism produce ammonia which are transported to the liver through portal vein and utilized for urea synthesis in the liver and urea is excreted through kidneys. If ammonia is not utilized properly they enter into the CNS through systemic circulation and acts as an inhibitory neurotransmitter, leading to hepatic precoma and coma.

Streptomycin or Neomycin after oral administration suppresses gut micro-organisms from producing ammonia, thereby reducing urea production.

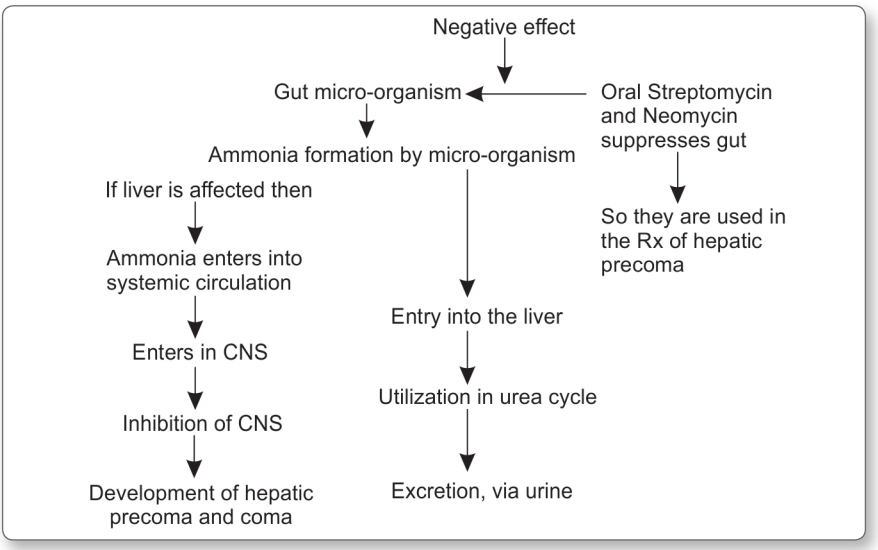


Fig. 8.14: Gut sterilization by AGs

INH

- **Pharmacodynamics**: It inhibits synthesis of myocolic acid, an essential component of mycobacterial cell wall and is effective selectively against *M. tuberculosis* and *M. kansasii*.
- **Pharmacokinetics**: After absorption diffuses readily into all body fluids and tissues including central nervous system and CSF (100% of simultaneous serum concentration). Hepatic clearance by genetically determined acetylation is the principal mode of elimination.
- **Dose and administration**: Oral or IM injection treatment and prophylaxis— ADULT 300 mg once daily; CHILD 10–20 mg/kg (max. 300 mg) once daily; for intermittent supervised therapy—10 mg/kg thrice or 15 mg twice weekly; pyridoxine, 15–50 mg/d particularly in high-risk patients for peripheral neuropathy.
- **Cautions**: Monthly evaluation of patients for symptoms of hepatitis has been advised, one-third to one-half of normal dose is recommended in moderate to severe hepatic insufficiency; other conditions that require cautious therapy with Isoniazid are epilepsy, history of psychosis, alcohol dependance, malnutrition, diabetes mellitus, slow acetylator status, porphyria, pregnancy, breastfeeding and HIV infection.
- **Indications**: Tuberculosis in combination with other drug
- **Contraindications**: Drug-induced liver disease.
- **Adverse effects**: Rash, fever, jaundice, peripheral neuritis leading to numbness, tingling of the feet particularly in slow acetylators, diabetic, HIV infected and malnourished or anemic patients; allergic reactions including hepatitis, skin eruptions and morbilliform eruptions, maculopapular, purpuric and urticarial rashes; hematological reactions like agranulocytosis, eosinophilia, thrombocytopenia, hemolytic anemia; convulsions, insomnia, muscle twitching, ataxia, paresthesia, stupor, toxic encephalopathy; optic neuritis and atrophy.

Pyrazinamide

An important frontline antituberculosis drug and is used in combination with Isoniazid and Rifampin in short-course, 6 months regimen as a **sterilizing agent** active against residual intracellular organisms responsible for relapse.

Adequately absorbed after oral ingestion and widely distributed into tissues and body fluids with excellent CSF penetration. The drug is taken up by macrophages and is converted to active pyrazinoic acid by mycobacterial Pyrazinamidase.

The drug eliminated principally by renal route. Pyrazinamide produces selective bactericidal effect against *M. tuberculosis*, but not effective against *M. bovis*.

Indications: Treatment of tuberculosis in combination with other drug. In combination with Ciprofloxacin or Ofloxacin as prophylactic in close contacts to a case of multidrug resistant tuberculosis provided that the index case is susceptible to these drugs.

Cautions: Hepatic insufficiency, monitoring of liver function is advised; therapy should be stopped if there is evidence of hepatotoxicity (elevation of plasma alanine and aspartate aminotransferases are the earliest features of drug hepatotoxicity), diabetes, and gout.

Contraindications: Liver damage, and porphyria.

Adverse effects: Most serious is the hepatotoxicity; liver tenderness, hepatomegaly, jaundice and fulminating liver failure that can be fatal; hyperuricemia and gouty arthritis occur uniformly and not considered to be a reason to halt therapy; also anorexia, and nausea and vomiting, dysuria, occasional mild fever, and malaise.

Dose and administration: Oral treatment and prophylaxis, ADULT and CHILD 15 to 30 mg/kg daily as a single dose, max. 2 gm/d; for intermittent supervised therapy, 50–70 mg/kg twice or thrice weekly.

Rifampicin

A semisynthetic derivative of rifamycin B and act by inhibiting DNA-dependent RNA- polymerase resulting in block in RNA synthesis. Rifampin exerts broad-spectrum antibacterial effect and is effective against most gram-positive as well as many gram-negative organisms. S. aureus, coagulase-negative staphylococci, *E. coli*, Pseudomonas, indole-positive and indole-negative Proteus, and Klebsiella, *N. meningitidis*, *H. influenzae* are particularly susceptible. Of the mycobacteria, *M. tuberculosis, M. kansasii, M. scrofulaceum, M. intracellulare* are sensitive, while *M. fortuitum* is highly resistant.

After absorption from gastrointestinal tract, it is eliminated rapidly in the bile and exhibits an enterohepatic recycling. Distributed throughout the body and achieve effective concentrations in many organs and fluids, including CSF.

A potent inducer of hepatic drug metabolizing enzymes and eliminated principally as deacylated metabolite in feces.

Mode of action

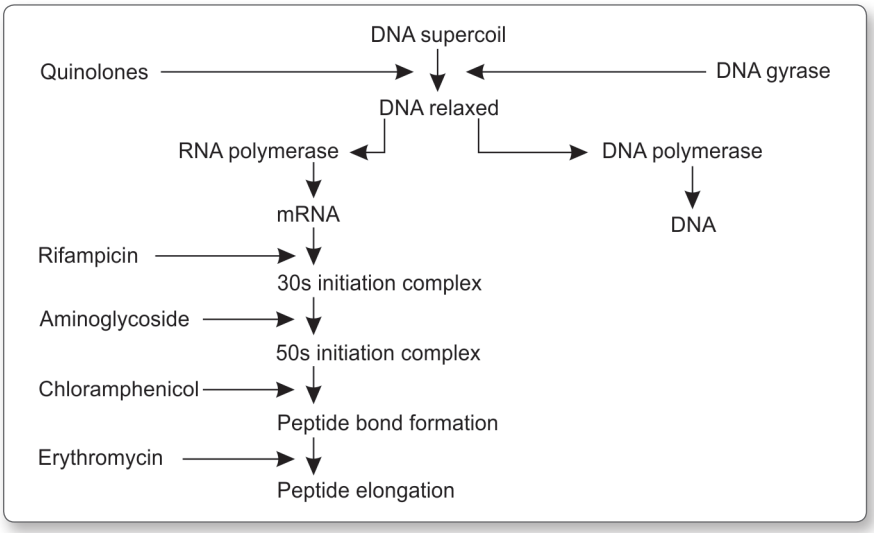


Fig. 8.15: Mechanism of action of Quinolone, Rifampicin, Aminoglycoside Chloramphenicol and Erythromycin

Indications: Treatment of tuberculosis in combination with other drug an alternative to Isoniazid as prophylactic in close contacts to a case of Isoniazid-resistant tuberculosis provided that the index case is susceptible to this drug.

Leprosy, brucellosis, *Haemophilus influenzae* infection, legionnaires disease, prophylaxis of meningococcal meningitis, in combination with Ceftriaxone or Vancomycin for treatment of meningitis caused by Penicillin-resistant strains of pneumococci, in combined therapy against serious staphylococcal infections such as osteomyelitis and prosthetic valve endocarditis.

Cautions: Patients with hepatic impairment need hepatic function and blood counts monitoring, alcoholism, during concomitant use of oral contraceptives, patients should be advised to use additional means of contraception, pregnancy, breastfeeding, porphyria; patients should be warned about harmless orange-red color to urine, feces, saliva, sputum, tears, and sweat.

Contraindications: Jaundice and liver damage.

Adverse effects: Gastrointestinal symptoms including anorexia, nausea, vomiting, diarrhea; cholestatic jaundice and occasionally hepatitis; light-chain proteinuria commonly and acute renal failure rarely, thrombocytopenic purpura, urticaria, rashes, when taken intermittently less often than twice weekly a flu-like syndrome characterized by fever,

chills, myalgias, anemia, thrombocytopenia and sometimes associated with acute tubular necrosis.

Dose and administration: Tuberculosis treatment and prophylaxis, ADULT < 50 kg, 450 mg once daily, 50 kg and over 600 mg once daily or as 10 mg/kg/d; CHILD 10 mg/kg (max. 600 mg) daily; for intermittent supervised therapy, 600 mg twice or thrice weekly.

ANTILEPROSY DRUGS

Chemotherapy of leprosy

Chemotherapy of leprosy, like that of tuberculosis requires simultaneous use of two to three drugs to overcome problem of resistant development by *M. leprae* against any single drug.

For multibacillary leprosy (lepromatous, borderline lepromatous and borderline leprosy).

Three drugs regimen for at least 2 years; Rifampin 600 mg (450 mg for adults weighing < 35 kg) once in a month under supervision, Dapsone 100 mg daily and Clofazimine, 50 mg daily and 300 mg once in a month under supervision.

For paucibacillary leprosy (tuberculoid, borderline tuberculoid and intermediate leprosy). Two drugs regimen with Rifampin and Dapsone for at least 6 months (dose and administration similar to that for multibacillary variety).

Dapsone, Clofazimine, Rifampicin

Dapsone

It is diaminodiphenyl sulfone and like sulfonamides act by inhibiting microbial folate synthesis. Well-absorbed after oral administration and widely distributed throughout body fluids and tissues and tends to accumulate in skin, muscle, liver and kidney. Dapsone is principally cleared through kidney after acetylation.

Indications

Leprosy, treatment and prophylaxis of Pneumocystis carinii pneumonia, dermatitis herpetiformis.

Cautions

Dose adjustment required in renal failure, cardiac or pulmonary disease; anemia; hemolysis in G-6-PD deficient patients, breastfeeding, pregnancy; best to avoid in porphyria.

Adverse effects

Dose-related and not common at dose used for leprosy, hemolysis in G-6 PD deficient patients, methemoglobinemias rather common, neuropathy, allergic dermatitis, anorexia, nausea, vomiting, pruritus, tachycardia, headache, insomnia, psychosis, during therapy of lepromatous leprosy, erythema nodosum leprosum often develops.

Dose and administration

Oral leprosy, 100 mg daily or 1–2 mg/kg daily.

Clofazimine

It is a Phenazine dye and act by binding with mycobacterial DNA. Clofazimine is active against both Dapsone-sensitive and Dapsone-resistant bacilli and against *M. intracellulare*.

Variable absorption from gut and a major portion of drug is excreted in feces. Clofazimine is stored widely in reticuloendothelial tissues and skin.

Indications

Leprosy in combination with other drug, chronic skin ulcers (Buruli ulcer) produced by *M. ulcerans*, prophylaxis against erythema nodosum leprosum.

Cautions

Hepatic and renal impairment; pregnancy and breastfeeding; may discolor soft lenses; best to avoid if persistent abdominal pain and diarrhea.

Adverse effects

Nausea, vomiting (hospitalize if persistent), abdominal pain; headache; tiredness; brownish-black discoloration of lesions and skin including areas exposed to light, reversible hair discoloration; dry skin; red discoloration of feces, urine and other body fluids; also rash; pruritus, acne-like eruptions, anorexia, eosinophilic enteritis, bowel obstruction, dry eyes, dimmed vision, macular and subepithelial corneal pigmentation; elevated blood sugar, weight loss, spinal infarction, lymphadenopathy.

Dose and administration

Oral leprosy, 50–100 mg daily, in lepromatous lepra reactions, dose increased to 300 mg daily for maximum of 3 months.

Rifampicin

(See Section – III, page no 289)

SECTION-IV QUINOLONES AND OTHER BROAD SPECTRUM ANTIMICROBIALS

- Quinolones
- Macrolides
- Chloramphenicol
- Sulfonamide
- Tetracyclines.

QUINOLONES

- Advantages
- Names
- Chemistry
- Pharmacokinetics
- Antibacterial spectrum
- Mechanism of action
- Clinical use
- ADRs
- Cautions and contraindications
- Drug interaction.

Advantages

Currently the fluoroquinolones are one of the most popular antibiotics. Their advantages include—

1. Active against gram-negative as well as gram-positive bacteria. Thus they can be used instead of more toxic drugs, i.e. Aminoglycosides and Chloramphenicol.
2. They have low toxicity.
3. Cross-resistance dose not develop easily.
4. Their penetration into prostate, bones, joints (but not CSF) is good.
5. Most of them can be given orally.
6. They are only moderately expensive.

Names

Of some popular fluoroquinolones are listed below:

i. Ciprofloxacin
ii. Fleroxacin
iii. Gatifloxacin
iv. Levofloxacin
v. Lemofloxacin

vi. Moxifloxacin
vii. Norfloxacin
viii. Ofloxacin
ix. Pefloxacin
x. Sparfloxacin
xi. Trovafloxacin.

Chemistry

Basic structure of Quinolone is shown below. Nalidixic acid contains no fluorine atom but all the fluoroquinolones have a fluorine atom at C_6.

Pharmacokinetics

Fluoroquinolones achieve peak serum levels within 1–3 hours of oral administration, oral bioavailability being 80%–95%.

Oral absorption is impaired by divalent cations, including those in antacids.

They are distributed widely in body fluids and tissues, with concentrations in urine, kidney, lung, prostate tissue, stool, bile, macrophages and neutrophils higher than serum levels. Fluoroquinolone concentrations in CSF, bone and prostate fluid are lower than in serum.

Concentrations of Pefloxacin and Ofloxacin in ascitic fluid are close to serum levels and both of them and Ciprofloxacin have been detected in human breast milk.

The Quinolones, Nalidixic acid and cinoxacin have limited distribution profile and bactericidal concentrations are not achieved in most areas except in urinary tract.

Ciprofloxacin, Clinafloxacin, Ofloxacin, Levofloxacin, Lemofloxacin and Cinoxacin excrete predominantly through kidney; whereas eliminations of Pefloxacin, Nalidixic acid, Sparfloxacin, Trovafloxacin, Moxifloxacin are principally by the liver.

Antibacterial Spectrum

The quinolones are effective against enteric gram-negative bacilli; *P. aeruginosa* is resistant.

Fluorinated analogs (Ciprofloxacin, Pefloxacin, Enoxacin, Lemofloxacin, Levofloxacin) have greatly improved antibacterial activity against many gram-positive and gram-negative organisms that provides a basis of classification.

Mechanism of Action

These synthetic bactericidal drugs act by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, resulting in blockade of nucleic acid synthesis.

Clinical Uses

1. **UTI** All types
   a. Uncomplicated
   b. Complicated
   c. Prostatitis and so forth. In prostatitis, response is highly satisfactory.
2. **STD**
   a. Gonorrhea—Fluoroquinolones are very effective in uncomplicated and disseminated gonorrhea.
      In chlamydial infection, Norfloxacin is useless, Ciprofloxacin is not satisfactory but Ofloxacin is satisfactory though Doxycycline is more satisfactory.
3. **Typhoid**: Today, in the adults, Ciprofloxacin is very often preferred. It has also been tried to eliminate carrier state of typhoid.
4. **Diarrhea and gastroenteritis**: Even in infective diarrhea, antibiotics are often not needed of course fluoroquinolones are very popular.
5. **Skin**: An soft tissue infection use of fluoroquinolones is justified.
6. **Osteomyelitis**: Provided the osteomyelitis has been caused by gram-negative aerobes, Ciprofloxacin is very effective.
7. **RTI**: Bronchitis due to *H. influenzae* responds very quickly to Ciprofloxacin.
8. **Eyes**: Ciprofloxacin ophthalmic preparations are widely used and most pathogens are usually susceptible.
9. **Ear**: Ciprofloxacin has been used in malignant otitis media induced by pseudomonas.

ADRs

1. GIT nausea, vomiting and diarrhea.
2. CNS headache, dizziness.
3. Skin rash, deterioration of liver function tests.
4. Cartilage damages: Fluoroquinolones can cause cartilage damage and therefore, they should not be given at growing ages for fear of interference with the development of proper tallness in future. However ciprofloxacin can be given in children, suffering from severe shigella dysentery and cystic fibrosis (risk of damage due to diseases> that due to ADR). Alternatively, in shigella dysentery in children, Ceftriaxone can be used.

Cautions and Contraindications

Dose adjustments in patients with creatinine clearance less than 50 ml/min are required for Cinoxacin, Norfloxacin, Ciprofloxacin, Ofloxacin, Enoxacin and Lemofloxacin but not for Nalidixic acid, Trovafloxacin and Pefloxacin.

They should be avoided during pregnancy, nursing mother and the normally cleared Fluoroquinolones in patients with hepatic failure.

These drugs are not generally recommended for use in prepubertal children, although in some cases the benefits may outweigh the risks of Quinolone therapy and requires careful assessment.

Drug Interaction

Fluoroquinolone should not be concurrently used with Theophylline for fear of Theophylline accumulation in the body leading to symptoms (even seizure).

MACROLIDES

Nature

These are bacteriostatic (erythromycin may be bactericidal in high concentrations) antibiotics and act by inhibiting microbial protein synthesis.

Antimicrobial Spectrum

Macrolides have antibacterial spectrum similar (not identical) to that of Penicillin and are effective against gram-positive organisms including pneumococci, streptococci, staphylococci and corynebacteria.

Also susceptible are mycoplasma, legionella, *Chlamydia trachomatis, C. psittaci, C. pneumoniae*, helicobacter, listeria and *Mycobacterium kansasii, M. scrofulaceum*.

Of the gram-negative organisms Neisseria species, *Bordetella pertussis, Bartonella henselae* and *B. quintana* (agents of cat scratch disease and bacillary angiomatosis), some rickettsia species, *Treponema pallidum*, campylobacter and *H. influenzae* are susceptible.

Azithromycin and Clarithromycin also have activity against *M. leprae* and Toxoplasma gondii.

Azithromycin is most active against Chlamydia and least active against staphylococci and streptococci.

Against *H. influenzae* both Azithromycin and Clarithromycin are more active.

Resistance

Against macrolides is due to—

- Reduced permeability to drugs
- Production of inactivating enzymes by organisms
- Alteration of ribosomal binding site

Erythromycin base is destroyed by gastric acid and must be administered with enteric coating.

Pharmacokinetics

After being absorbed, both Azithromycin and Clarithromycin are extensively distributed in tissues and secretions except the brain and CSF, to achieve adequate concentrations for producing antibacterial effect.

Erythromycin, however, has limited distribution profile.

Both renal and nonrenal routes are used in elimination, nonrenal being more prominent.

Macrolides, except Azithromycin—drug-metabolizing enzymes inhibitors—

Erythromycin, Clarithromycin, Azithromycin, and Spiramycin.

Erythromycin

Indications

- Mycoplasma pneumonia infections
- Campylobacter enteritis
- First-line drug for chlamydial urogenital infections in pregnant women
- *Chlamydial pneumoniae*
- Diphtheria, pertussis
- Effective alternative to penicillins in hypersensitive patients for pharyngitis, scarlet fever, erysipelas and cellulitis due to *S. pyogenes*
- For tetanus and for prophylaxis against recurrences of rheumatic fever.

Adverse effects

Nausea, vomiting, abdominal discomfort, diarrhea, antibiotic associated colitis, hypersensitivity reactions including urticaria, rashes, cholestatic jaundice and other reactions—

- Reversible hearing loss after large doses
- Chest pain and arrhythmias including prolongation of QT interval and ventricular tachycardia.

Clarithromycin

Indications

- Eradication of *H. pylori.*
- First-line therapy for prophylaxis and treatment of disseminated

infection caused by *M. aviumintracellulare* in AIDS patients and for treatment of pulmonary infections in nonHIV-infected patients.
- Toxoplasmosis encephalitis dose reduction required in renal impairment.

Adverse effects

As Erythromycin, also reported headache, taste disturbances, stomatitis, glossitis, hepatitis and Stevens-Johnson syndrome; on IV infusion, local tenderness, phlebitis.

Spiramycin

- **Indications**: Respiratory tract infections, genital infections, skin and soft tissue infections caused by streptococci, pneumococci and meningococci, diphtheria, prophylaxis of fetus against transmission of maternal toxoplasmosis in pregnancy.
- **Cautions**: Breastfeeding
- **Contraindications**: Known hypersensitivity to macrolides.
- **Adverse effects**: Nausea, vomiting, diarrhea, allergic skin reactions.

CHLORAMPHENICOL

- Source and history
- Mechanism of action
- Indications
- Cautions
- Contraindications
- Clinical uses
- Adverse action

Source and History

It was obtained from a streptomyces in 1974, found in a soil sample from a mulched field in Venezuela and from a compost heap in Illinoids.

It is a broad-spectrum, bacteriostatic antibiotic and act by inhibiting peptidyl transferase step of microbial protein synthesis.

Chloramphenicol is effective against both gram-positive and gram-negative aerobic and anaerobic organisms and also against rickettsiae. *H. influenzae, N. meningitidis* and some strains of bacteroids are particularly susceptible and against them Chloramphenicol may produce bactericidal effect.

Resistance of organisms against Chloramphenicol is principally due to production of Chloramphenicol acetyltransferase enzyme that inactivates the drug.

After absorption the drug is widely distributed to all tissues and body fluids, including central nervous system and CSF, in adequate antibacterial concentrations.

Hepatic glucuronidation is the principal way of drug clearance.

Mechanism of Action

See Figure 8.15.

Indications

1. Severe rickettsial infections such as typhus or rocky mountain fever in children.
2. Alternative to a β-lactam for bacterial meningitis due to Penicillin-resistant strain of pneumo or meningococcus and in Penicillin-allergic patients.
3. Alternative to tetracyclines for acute and chronic brucellosis, eye and ear infections caused by susceptible organisms.

Cautions

Dose must be reduced in hepatic impairment, in newborns less than a week old and in premature infants; repeated courses and prolonged treatment are not recommended; periodic blood counts and monitoring of plasma concentration (in neonates) are required; in neonates (may cause gray baby syndrome).

Contraindications

Pregnancy, breastfeeding, porphyria.

Clinical Uses

The decision to use Chloramphenicol is influenced by its rare but serious toxic effect. There is a case for initiating treatment of bacterial meningitis with Chloramphenicol plus Benzyl penicillin untill the causal organism is identified. When the organism is *H. influenzae*, type-B, Chloramphenicol should be continued and the Benzyl penicillin stopped. Similarly in the initial treatment of brain abscess Chloramphenicol is given with Penicillin. It may be used for salmonella infection, but Ciprofloxacin is preferred.

It penetrates well into the ocular aqueous and vitreous humors after either topical or systemic administration and is effective treatment for ocular infection.

Adverse Action

GIT upset tends to be mild. Optic and peripheral neuritis with prolong use is occasionally seen. Bone marrow depression is of two types:

1. **Dose dependent**: Reversible depression of crythrocyte, platelet and leukocyte formation that occurs early in the treatment.
2. **An idiosyncratic, nondose related**: Usually fatal aplastic anemia which tends to develop during or even weeks after prolonged treatment and sometimes on reexposure to the drug, it has also occurred with eyedrops. It may be detected at an early and recoverable stage by frequent examination of blood.

The gray syndrome occurs in neonates as circulatory collapse in which the skin develop a cyanotic gray color. It is caused by high Chloramphenicol plasma concentration due to failure of liver to conjugate, and of the kidney to execrate the drug.

SULFONAMIDES

General Concept

The discovery of the antimicrobial action of sulfonamide and initial clinical trials in the 1930s are landmarks in the use of pharmacological agents to treat infections. Sulfonamides are true metabolites; they block a specific step in the biosynthetic pathway of folic acid.

Chemistry

Nearly all currently used sulfonamides are derivatives of sulfonamide. A free amino (NH_2) **group is required in the para position**. Sulfonamides substituted in the amino group becomes active only if the substituent is removed in vivo. Substitution on the R_2 amide group influences the absorption, distribution and solubility of the various compounds.

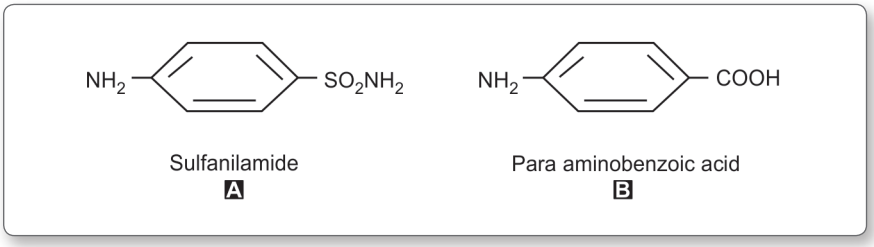


Fig. 8.16: Chemistry of sulfonamide

Classification of Sulfonamide

Sulfonamides may be classified depending on their pharmacokinetic properties as follows:

a. Well-absorbed by mouth with intermediate half-life ($t_{1/2}$ 10 hours), i.e. Sulfadiazine.
b. Well-absorbed by mouth with long half-life ($t_{1/2}$ 40 hours), i.e. Sulfamethopyrazine.
c. Poorly absorbed—Calcium sulfaoxalate has been used for preoperative bowel preparation and for gut infections but is now rarely used.
d. Topical application: Silver sulfadiazine is used for prophylaxis and treatment of infected burns, leg ulcers and pressure sores because of its wide antibacterial spectrum.
e. Miscellaneous: Sulfadiazine is used in inflammatory bowel diseases.
f. Sulfonamid-Trimethoprim combination: Sulfamethoxazole + Trimethoprim is the optimum synergistic effect against most susceptible bacteria is achieved with 80 mg Trimethoprim+400 mg Sulfame-Thoxazole.

Sulfonamides and Cotrimoxazole

Sulfonamides were the first effective chemotherapeutic agents to be employed for bacterial infections. As most of the organisms, once susceptible, have been reported to be resistant and due to their potential toxicity and the fact that more effective antibiotics are available, the Sulfonamides alone are no longer recommended for systemic infections.

A few of them are used topically such as in eye infections and in infected wound and burn injury.

In combination with Trimethoprim as Cotrimoxazole, Sulfamethoxazole, however, is used for systemic bacterial infections.

Individually, both Sulfonamides and Trimethoprim are bacteriostatic and act by inhibiting dihydrofolate synthase and dihydrofolate reductase respectively, resulting in block of folic acid synthesis.

In contrast, the combined preparation Cotrimoxazole produces killing effect by blocking sequential steps in folate synthesis.

Most gram-positive and gram-negative organisms are susceptible to Sulfonamides and Trimethoprim but resistance rapidly develops when these drugs are used alone. Particularly relevant are *Strep. pyogenes, Strep. pneumoniae, H. influenzae,* Nocardia, Actinomyces, and *Chlamydia trachomatis*. Methicillin-resistant strains of *S. aureus* although resistant to Trimethoprim or Sulfonamides alone, may be susceptible to Cotrimoxazole. *P. aeruginosa, B. fragilis* and enterococci usually are resistant.

Resistance

Against Sulfonamides and Trimethoprim can result from reduced cell permeability to these drugs and overproduction or production of altered target enzymes.

After oral administration of combined preparation, Trimethoprim is better absorbed and more widely distributed in the body. Trimethoprim, being a weak base, concentrates in acidic prostatic and vaginal fluids. Both the Sulfonamides and Trimethoprim are eliminated principally through kidneys.

Cautions

All Sulfonamides and their derivatives, including carbonic anhydrase inhibitors, Thiazides, Frusemide, Bumetanide, Torsemide, Diazoxide, and sulfonylurea hypoglycemic drugs, are cross-allergic. Plenty of fluid is to be taken and monitoring of blood count is required in prolonged therapy. Hepatic function monitoring also is required in AIDS patients receiving cotrimoxazole. Dose adjustment is needed in renal insufficiency and therapy with Sulfonamides and/or Trimethoprim in pregnancy and in breastfeeding requires careful assessment of risks in the baby.

Sulfonamides and Cotrimoxazole are not recommended for use in infants below 6 weeks except for treatment or prophylaxis of pneumocystis pneumonia.

Adverse Effects

Most common adverse effects are fever, skin rashes, exfoliative dermatitis, photosensitivity, urticaria, nausea, vomiting, diarrhea, crystalluria, various types of nephrosis and allergic nephritis.

Stevens-Johnson syndrome and toxic epidermal necrolysis, although rare, is a particularly serious and potentially fatal type of reaction associated with use of sulfonamides.

Hemolytic anemia, particularly in glucose-6-phosphate-dehydrogenase deficient patients, aplastic anemia, granulocytopenia, thrombocytopenia, or leukemoid reactions have also been reported after sulfonamides therapy. Risk of kernicterus in newborns if taken near the end of pregnancy.

Trimethoprim may produce megaloblastic anemia, leukopenia and granulocytopenia. Nausea and vomiting, drug fever, vasculitis, renal damage and central nervous system disturbances occasionally occur.

Sulfonamide-procaine antagonism the idea is that, Sulfonamide compete with PABA and inhibits the growth of bacteria. But procaine on hydrolysis produces PABA. So procaine reduces the effectiveness of Sulfonamide by increasing the conc. of PABA. This is called procaine sulfonamide antagonism.

Prevention of Crystalluria

1. Stoppage of the drug and ensure plenty of water intake
2. Alkalinization of urine by $NaHCO_3$

3. Using best soluble Sulfonamides, i.e. Sulfisoxazole
4. Using triad of Sulfonamides, i.e. Sulfadiazine, Sulfamerazine and Sulfathiazole.

Cotrimoxazole

- **Indications**
  1. Urinary tract infections
  2. Acute exacerbation of chronic bronchitis
  3. Typhoid fever
  4. Shigellosis, pneumocystis carinii pneumonia
  5. Acute otitis media in children
  6. Toxoplasmosis, nocardiasis.
- **Cautions**: Monitoring of blood counts is required in prolonged therapy; adequate fluid intake is to be maintained; also see notes above
- **Contraindications**: Porphyria
- **Adverse effects**: As above.

Sulfacetamide

- **Indications**: 10% solution for treatment and prophylaxis of mild infections, conjunctivitis, blepheritis, keratitis; 20% solution for moderate conjunctivitis and ophthalmia neonatorum; 30% solution for severe conjunctivitis, corneal ulceration including dendritic ulceration, trachoma of as 10% eye ointment.
- **Spectrum of** activity sulfonamides are effective against a broad range of micro-organism. They inhibit the growth of micro-organisms or their multiplication, rather than direct killing effect on sensitive microbes.
- **Pharmacokinetics**: Sulfonamide for systemic use are absorbed rapidly from the gut. Sulfadiazine enters CSF more readily than others. The principal metabolic path is acetylation and the capacity to acetylators is genetically determined in a bimodal form, i.e. there are slow and fast acetylators but the difference are of limited practical importance in therapy.
- **Mode of action**: See Figure 8.2 and its description in page no. 262.
- **Resistance**: Micro-organisms develop an altered metabolic pathway that by passes the reaction inhibited by the drug. Sulfonamide resistant bacteria do not require extracellular PABA like mammalian cells, can utilize preformed folic acid.

Some allergic reaction including rash, fever, hepatitis, agranulocytosis, purpura, aplastic anemia, serum sickness like syndrome and polyarteritis, nodosa, rarely severe skin reaction including erythema multiformis bulb (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell's syndrome) can occur. Hemolysis may occur in glucose-6-phosphate dehydrogenase deficient subjects.

TETRACYCLINES

Introduction and Chemistry

TCs are a large group of drugs with a common basic structure and activity. They contain the Naphthacene nucleus which is made up of by fusion of 4 (four) partially unsaturated Cyclohexane radical hence the name Tetracycline.

Mode of Action

They are broad-spectrum bacteriostatic antibiotics and act by inhibiting protein synthesis. (See page no. 265)

TCs enter micro-organisms in part by passive diffusion and in part by an energy dependent process of active transport. As a result susceptible cells concentrate the drug so that the intracellular drug concentration is much higher than the extracellular one. Once inside the cell, TCs hind reversibly to receptor on the '30s' subunit of the bacterial ribosome in a position that blocks the binding of aminoacyl tRNA to the acceptor site on the in RNA ribosome complex. This effectively prevents the addition of new amino acids to the growing peptide chain, inhibiting protein synthesis. The selective inhibition of protein synthesis in micro-organisms may be explained by largely the failure of mammalian cells to conc. Tetracyclines.

Spectrum

Tetracyclines are effective against wide range of aerobic and anerobic gram-positive and gram-negative bacteria, rickettsiae, chlamydia, legionella, mycoplasma, atypical mycobacteria, spirochaetes and against some protozoa.

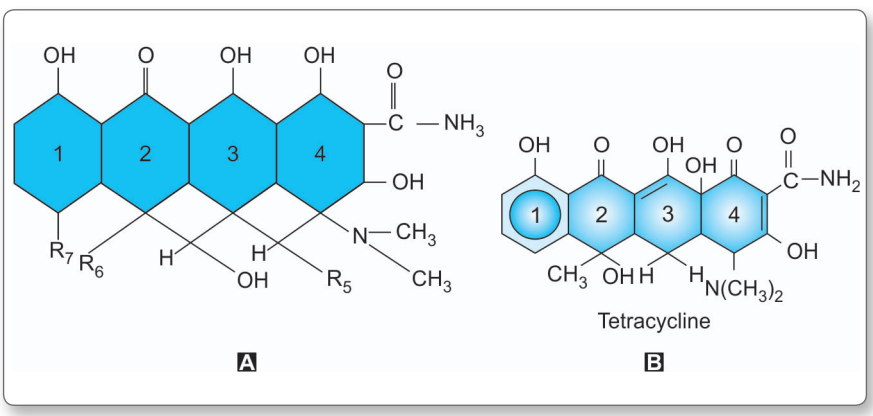


Fig. 8.17: Naphthacene nucleus where R's represents monovalent atoms like Cl, H radical like CH_3, OH, $N(CH_3)_2$ and so forth

Generally they are more active against organisms. Most strains of enterococci and *Pseudomonas aeruginosa* are resistant, although most of *Pseudomonas pseudomallei* (causative agent of melioidosis) are sensitive.

Also susceptible are *Haemophilus ducreyi* (chancroid), brucella, *Vibrio cholerae, Legionella pneumophila, Campylobacter jejuni, Helicobacter pylori*, Yersinia pestis, *Yersinia enterocolitica* and actinomyces is particularly relevant.

A variable number of anaerobes, i.e. Bacteroides spp. are sensitive to Tetracyclines particularly to the most active congener.

Resistance

Emergence of resistances to Tetracyclines is quite frequent and are due to decreased accumulation of drug, protection of ribosomal binding site of the organisms and production of inactivating enzymes by the organisms.

Classification of Tetracycline

Oral bioavailability is—

1. Lowest for Chlortetracycline (30%)
2. Intermediate for Oxytetracycline, Demeclocycline and Tetracycline (60%–80%)
3. High for Doxycycline and Minocycline (95%–100%).

Drug Interaction

- **Tetracyclines** chelate divalent and trivalent metal ions which can impair their oral absorption.

These drugs distribute widely into prostate, bone marrow, bone, dentine, enamel of unerupted teeth and reticuloendothelial cells of liver.

Penetration into CSF, synovial fluid, mucosa of maxillary sinus, and fetal circulation is excellent.

Relatively high concentrations also are found in breast milk.

Primary route of elimination of these drugs except that of doxycycline, is the kidney.

- **Contraindications**: Tetracyclines should not be given to pregnant patients and to patients with renal insufficiency (doxycycline may be given). Neither they are recommended for lactating mother and for treatment of common infections in children under the age of 8 years.
- **Adverse effects**: Epigastric burning and distress, abdominal Discomfort, nausea, vomiting and diarrhea may occur.
  - Esophagitis, esophageal ulcers and pancreatitis have been reported.
  - Photosensitivity particularly with Demeclocycline and Doxycycline also is seen.

Children may develop permanent brown discoloration of teeth. This risk is highest when Tetracycline is given to neonates, babies prior to first dentition and to pregnant mothers.

Tetracyclines are potentially hepatotoxic, pregnant women are particularly susceptible to this risk.

Oxytetracycline and Tetracycline appear to be less hepatotoxic. Jaundice appear first, and azotemia, acidosis and irreversible shock may follow. These drugs can be deposited in skeleton throughout childhood.

Long-term therapy may produce leukocytosis, atypical lymphocytes, toxic granulation of granulocytes and thrombocytopenic purpura.

Increased intracranial pressure and tense bulging of fontanels (Pseudotumor cerebri) in young infants are in reports.

Renal tubular acidosis, proteinuria, aminoaciduria glycosuria—a form of Fanconi syndrome, has been seen after outdated Tetracyclines ingestion.

Hypersensitivity reactions, though rare, may follow the use of any of the Tetracyclines and includes Morbilliform rashes, urticaria, fixed drug eruptions, generalized exfoliative dermatitis and severe reactions like angioedema and anaphylaxis. Hypersensitivity to one Tetracycline generally confers cross-reactivity to all other members of this class.

Therapy with tetracyclines may lead to the superinfections that result in intestinal functional disturbances, anal pruritus, vaginal or oral candidiasis or enterocolitis with shock and death. Pseudomembranous colitis due to an overgrowth of toxin producing *C. difficile* is particularly relevant.

- **Indications** Mycoplasmal pneumonia, chlamydial pneumonia, lymphogranuloma venereum, trachoma, rickettsial infections (epidemic typhus, scrub typhus, rickettsial pox, Q fever), uncomplicated gonococcal infections, syphilis, brucellosis, exacerbations of chronic bronchitis, acne, actinomycosis, Lyme disease, tularemia, cholera, eye infections (conjunctivitis, blepharitis).

DOXYCYCLINE

- **Indications**: Chronic prostatitis, sinusitis, malaria treatment and prophylaxis; also see under Tetracycline (except eye infections).

SECTION-V DRUGS USED TO TREAT MALARIA AND KALA-AZAR

ANTIMALARIALS

- Introduction
- Life cycle of malarial parasite
- Receptors on RBCs and malaria
- Some terms related to antimalarials
- Special dangers of P. falciparum malaria
- Classification of antimalarials and their mode of action
- Individul drug: Chloroquine, primaquine, quinine, artemisinin
- Management of malaria

LEISHMANECIDALS

- Causative organism
- Life cycle of Leishmania donovani
- Clinical features of kala-azar includes
- Limitations of anti-kala-azar treatment
- Leishmanecidals agents – Sodium stibogluconate

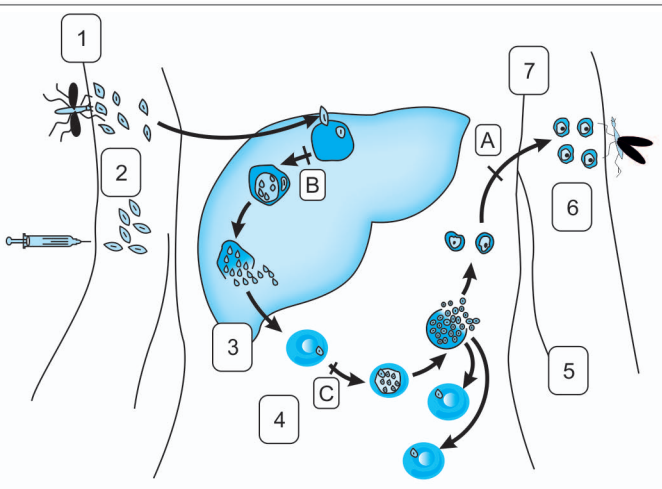
ANTIMALARIALS

Introduction

a. **Incidence**: Nearly 100 million or 10 crores of people, all over the world, are attacked by malaria every year of which about 1% (mostly children) die.

b. **Cause**: Malaria is caused by a protozoa belonging to the subphylum of sporozoa and the genus plasmodium. Four species are clinically important.

c. **Prognosis**: The P. vivax induced malaria is usually not lethal but as a notorious tendency to relapse after cure of a clinical attack, so that special step should be taken to eradicate the parasite and prevent relapse.



Alphabets showing site of drug action and numbers showing different stages of parasitic development.
(A) – Drug effective against gametocytic form primaquine.
(B) – Drug effective against exoerythrocytic form primaquine.
(C) – Drug effective against erythrocytic form artemisinis, chloroquine, quinine.
(1) – An infected mosquito injects sporozoites.
(2) – Sporozoites migrate to the liver, where they form merozoites.
(3) – Merozoites are released and invade red blood cells.
(4) – In the red blood cell, the merozoites becomes a trophozoite.
(5) – In the red blood cell, the trophozoite multiplices producing new merozoites. these are released by RBC rupture and infect other RBCs.
(6) – Some merozoites become gametocytes.
(7) – The female mosquito picks up gametocytes from an infected human. The sexual cycle occurs in the mosquito where sporozoites are formed.

Fig. 8.18: The life cycle of malarial parasite in man and mosquito

Life Cycle of Malarial Parasite

Man is infected by sporozoites injected by the infected mosquitoes. The sporozoites disappear rapidly from the circulation and localize in the parenchymal cells of liver. Where they grow, segment and spurulate. This constitute the **preerythrocytic stage** of infection during which the subject remains symptom-free. On reaching maturity, merozoites are released from the liver cells and enter erythrocytes to start the blood cycle **erythrocytic cycle**, among all but, vivax malaria, proportion of this parasites infect more tissue cells and this stage of infection constitutes the **exoerythrocytic cycle**. This cycle may continue **for several** years and responsible for relapse in the infected patients.

Schizogony occurs in the infected erythrocytes as a result of growth and segmentation of merozoites. When the erythrocytes bursts, the liberated merozoites infect more red blood cells and start a new cycle.

Some Terms Related to Antimalarials

Schizontocides are drugs which kill the schizonts of MP. There may be hepatic schizont or blood schizont. Formation of schizont

a. In the liver, sporozoites → schizonts → merozoites
b. In the blood, merozoites → schizonts → merozoites

Thus there can be **hepatic (tissue) schizontocide**, i.e. Primaquine, proguanil or blood schizontocides, i.e. Chloroquine, Mefloquine, quinine, proguanil and so forth.

In general, hepatic schizontocides kill the hepatic MPs, but cannot kill the blood schizonts. Therefore, if plasmodium falciparum are completely removed from the blood, there should be no relapse, but with P. vivax, relapse is a possibility if a course of blood schizontocides alone be used.

Clinical cure drugs which remove clinical symptoms (fever) cause clinical cure. Clinical symptoms are due to the erythrocytic phase of the schizogony. Therefore, drugs which eradicate the erythrocytic an endemic area, for radical cure.

Tissue schizontocides are drugs those kill the MPs in the liver in both exoerythrocytic and preerythrocytic stage, i.e. Primaquine, Proguanil.

Blood schizontocides kill the blood schizonts, i.e. Chloroquine, Quinine, Amodiaquine, Mefloquine, Pyrimethamine, Proguanil, Quinacrine, Tetracycline and Clindamycin.

Gametocides Kill the blood gametocytes of MP, i.e. Primaquine, Chloroquine.

Sporontocides make the gametocytes noninfective within the mosquitoes body, i.e. Pyrimethamine, Proguanil.

Special Dangers of P. Falciparum Malaria

An RBC infected by Plasmodium falciparum has a special tendency to adhere with healthy RBCs. In this way several RBCs may cling together to form what is known as rosette (a sort of a circular ornament). Such rosette can block capillaries of vital organ (cerebral vessels → cerebral malaria → which can cause death). Flaciparum malaria or malignant malaria must be treated promptly.

Classification of Antimalarials and their Mode of Action

Antimalarials may be grouped into two depending on their mode of action.

- **First group** includes Chloroquine, Mefloquine, Quinine, etc.
- **Food vacuoles**: They appears in the food vacuoles of the malarial parasites. The food vacuoles which is normally acidic, becomes alkaline due presence of the drugs. The parasites cannot digest Hb (Hb is the food of the parasites).
- **Hb accumulation**: It is lethal for the survival of parasites. The parasites within the RBC digest the Hb, so that the Haem should accumulate, but a polymerase enzyme polymerizes the Haem to form hemozoin which is harmless to parasites. Chloroquine inhibits the polymerase enzyme and prevents the formation of hemozoin.
- **DNA synthesis inhibition**: Chloroquine inhibits the **DNA synthesis** of the parasites.
- **The second group** of drug includes Pyrimethamine, Sulfonamide, Chloroguanides, etc. All cells require folic acid for DNA synthesis. Human cells cannot synthesize folic acid so that folic acid must be supplied in the food. But bacteria and protozoa must synthesize their own folic acid from dihydropteroate and PABA with the help of enzyme folic acid synthetase. Sulfonamides prevent this conjugation of PABA in the bacteria. The active form in which the cell utilizes folic acid is folinic acid or tetrahydrofolic acid. Conversion of folic acid to folinic acid or dihydrofolic acid to tetrahydrofolic acid is achieved by dihydropteroate reductase (an enzyme). In the bacteria Trimethoprim inhibits the DHFR. Treatment in Plasmodium genus, the plasmodium DHFR can be inhibited by Pyrimethamine, Proguanil. So they are the counterparts of Trimethoprim. Further as there is combination product TMP-SMZ (Cotrimoxazole), similar antiplasmodial agents are Sulfadoxine + Pyrimethamine or Sulfone (Sulfonamide analogue + Pyrimethamine). These agents therefore are antifolates. Uses of these antifolates cannot synthesize of DNA and RNA in the MPs. In the MPs due to use of these antifolates DNA cannot be synthesized.

Individual Drugs: Chloroquine, Primaquine, Quinine, Artemisinin with Lumefantrine

Chloroquine

- Introduction and chemistry
- Pharmacokinetics
- Mechanism of action
- Indications
- Contraindications
- ADRs.

Introduction and chemistry: It is the prototype among the antimalarials. Chemically it is a 4-aminoquinoline derivative.

Pharmacokinetics: After oral administration, absorption is complete: distribution is good, V_d is abnormally large about 13000 liters, because the drug tends to be deposited in various tissues, thus increasing the V_d. This necessitates that a **large initial loading dose must be given**. 900 mg base is given orally in the 24 hours. Otherwise plasma level of drug will be too low to be blond schizonticidal effect. Its conc. is very high in RBC infected by MP and the vacuoles in the blood schizont are still richer in Chloroquine.

Resistance to Chloroquine is due to decreased concentration of the drug in the RBCs.

Verapamil can sensitizes the erythrocyte's ability to concentrate Chloroquine. The drug crosses placenta and BBB. It is dealkylated by hepatic MFO system. Some of the degraded products retain antimalarial action. Excretion is mostly, via urine.

Mechanism of action: Already discussed in the mode of action of antimalarials under the heading of first group.

Indications

1. In malaria
2. Amebiasis
3. SLE
4. Rheumatoid arthritis.

Contraindications

1. Patients with psoriasis or porphyria
2. In presence of retinal or visual field abnormalities
3. History of liver damage
4. Alcoholism
5. Hematological or neurological disorder.

ADRs: It is largely a safe drug. GI upset, nausea, vomiting are fairly common. Visual disturbance may be mild, i.e. blunting of vision due to lose of accommodation resulting from loss of vision due to retinopathy. It has some Quanidine like action on heart and can cause T. wave changes, arrhythmia.

Primaquine

- Introduction
- Indications
- Cautions
- Contraindications
- Adverse effects.

Introduction: It is a synthetic 8-aminoquinoline and is highly effective against dormant liver forms of P. vivax and P. ovale.

The drug is well-absorbed orally and is widely distributed.

It is rapidly metabolized into metabolites which have high potential for hemolysis. The metabolites are excreted in the urine.

Indications: Radical cure of P. vivax and P. ovale malaria, with Clindamycin an alternative to cotrimoxazole for pneumocystis carinii infection.

Cautions: Pregnancy, breastfeeding, G-6-PD deficiency, diseases associated with granulocytopenia, i.e. Rheumatoid arthritis, lupus erythematosus.

Contraindications: Hemolytic anemia.

Adverse effects: Anorexia, nausea, vomiting, jaundice, less commonly mild diarrhea, hemolytic anemia in G-6-PD deficient patients, agranulocytosis, cardiac arrhythmia.

Quinine

- Introduction
- Indications
- Cautions
- Contraindications
- Adverse effects.

Introduction: It is a rapidly acting, highly effective blood schizonticide that act by an unknown mechanism and effective against all four species of human malaria parasites. The drug is gametocidal against P. vivax and P. ovale but not against P. falciparum and neither against dormant liver forms of any species. Quinine is rapidly absorbed from gut and distributes widely in the body. Loading dose administration allows achievement of peak levels within a few hours. It is primarily metabolized in liver and excreted in urine.

Indications: First-line drug for treatment of severe, uncomplicated falciparum malaria in an area with documented Chloroquine-resistant malaria, with Clindamycin first-line therapy for babesial infections.

Cautions: Renal insufficiency requires dose adjustment, therapy should be discontinued if signs of cinchonism, hemolysis or hypersensitivity, great cautions required in patients with underlying cardiac abnormalities.

Contraindications: Visual and auditory problems, hemoglobinuria.

Adverse effects

1. Nausea, vomiting and anorexia are common after ingestion
2. Cinchonism includes tinnitus, headahce, dizziness, flushing and visual disturbance
3. CVS disorder cardiac arrhythmias can occur if given IV routes
4. Hypoglycemia can occur due to stimulation of insulin secretion by Quinine
5. Black water fever manifested as intravascular hemolysis hemoglobinuria and dark urine
   This syndrome has a high mortality
6. Hemolysis can occur in G-6-PD deficieny cases
7. Uterine contraction—These effect is minor
8. IV Quinine can produce phlebitis.

Artemether with Lumefantrine

- Indications
- Cautions
- Contraindications
- Adverse effects

Tablet, Artemether 20 mg with Lumefantrine 120 mg.

Indications: Treatment of acute uncomplicated malaria due to plasmodium falciparum mixed infections including P. falciparum in areas with significant drug resistance.

Cautions: ECG required before and during treatment in cardiac disorder including bradycardia, heart failure, history of arrhythmias, QT interval prolongation, electrolyte disturbances, concomitant administration of drugs that prolonged QT interval; patients unable to take food require monitoring (greater risk of recrudescence); severe renal impairment or hepatic impairment.

Contraindications: Pregnancy breastfeeding; family history of sudden death, congenital prolongation of QT interval.

Adverse effects: Abdominal pain, anorexia, diarrhea, nausea and vomiting, headache, dizziness, sleep disorders; palpitations, arthralgia, myalgia; cough, asthenia, fatigue; pruritus, rash.

Management of Malaria

Treatment of clinical attack of P. vivax with radical cure

- Rx.
- Lariago—250 mg tab.
  (Chloroquine phos).

- 4 tab stat. followed by 2 tab.
- After 6 hours 2 tab daily for next two days.
- Primaquine—15 mg tab.
- To be started after the above dose is finished.

Treatment of chloroquine resistant P. falciparum

- Rx.
- Quinine sulfate—300 mg tab
- 2 tab at a time, 3 times a day for 5 days
- Doxycycline—100 mg tab
- 1 tab once daily for 7 days
- Advise: Plenty of glucose drinks or sugarcane (sherbet) by mouth throughout the course of the disease.

Leishmanecidals

Causative organism: Leishmaniasis is the disease produced by protozoan, Leishmania. Several clinical presentation of leishmaniasis are known, of which kala-azar is the most known one.

Life cycle of leishmania donovani: Leishmania donovani is a species of the genus leishmania causing kala-azar. There are two main stages of L. donovani 1. Amastigote (in man) and the 2. Promastigote (in sandfly).

The parasites are injected into the man during its bite → once inside the body of man the parasites excite a cellular reaction → this cellular reaction consists of a large number of macrophages being drawn towoards these protozoal parasites → macrophages engulf the parasites but fail to kill or digest them; rather, the parasites multiply within the macrophages → eventually the → macrophages bursts and liberate the parasites → the liberated protozoa reenter another macrophage.

Lymphocytes also drawn towards these parasite infected macrophages. In kala-azar these lymphocytes fail to destroy the parasite infected macrophages because of their poor efficiency. Also IgG (produced by B. lymphocytes) value in the serum rises but that does not mean that the anti-kala-azar defense is also rising.

Clinical features of kala-azar include

1. Fever
2. Skin pigmentation
3. Hepatosplenomegaly
4. Diarrhea

If not treated, most cases die within 2 years.

Limitations of anti-kala-azar treatment: Treatment against kala-azar is not satisfactory because—

1. Drugs are not so specific
2. Toxicity are common
3. Long drawn course of the treatment
4. Kala-azar being largely seen in populations where health consciousness is incomplete, victims of the disease often drop out after partial improvement.

Leishmanecidals agents – Sodium stibugluconate

Antimonials	Diamidines	Others
Sodium stibogluconate	Pentamidine	Amphotericin B
Meglumine antiniate	Hydroxystibamidine	Ketoconazole
Urea stibamine		Allopurinol, Miltefosine

Sodium stibogluconate

It is the drug of choice for kala-azar. It is a water-soluble pentavalent antimonial containing 1/3rd antimony by weight. The mechanism of action and the basis of selective toxicity to the leishmania amastigotes is unclear, probably—SH (sulphidryl)-dependent enzymes are inhibited and bioenergetics of the parasite is interfered with. It has been shown to block glycolytic and fatty acid oxidation pathways.

Because of frequent failure with 10 mg/kg/day dose used earlier, the WHO now recommends a dose of 20 mg/kg (max 850 mg) daily by IM in buttocks or IV injection for 20–36 days. In poor health patients and those who experience adverse effects, the injection may be given on alternate days. In India, primarily because most patients take irregular and incomplete courses over 25% failure occur.

Recently sodium stibogluconate has been incorporated in liposomes for IV injection. These bodies are taken up by the macrophages. The drug thus reaches selectively at the site where parasites reside; efficacy is improved. However, this has not been made available for general use. Liposome formulations of amphotericin B and ketoconazole also have been prepared for use in kala-azar.

Adverse actions

In general antimonials are toxic drugs, but the sodium stibogluconate is better tolerated. Nausea, vomiting, metallic taste, cough, pain abdomen, pain and stiffness of injected muscle, sterile abscesses, mental symptoms often occur. Liver and kidney damage, ECG changes are possible but are seldom severe. Few cases of shock and death are on record. Sodium stibogluconate, nevertheless, is less toxic than diamidines.

SECTION-VI CHEMOTHERAPY OF FUNGAL DISEASES

- Definition of mycosis
- Types
- Properties
- Essential of fungal cell wall
- Classification of antifungal agents with basis
- Pharmacokinetics and drug interactions
- Antifungal activities/ spectrum
- Mechanism of action of azoles
- Indication
- Adverse drug reactions
- Contraindications

DEFINITION OF MYCOSIS

Fungal diseases are called mycoses (Single, Mycosis).

TYPES

3 types of mycoses are known—

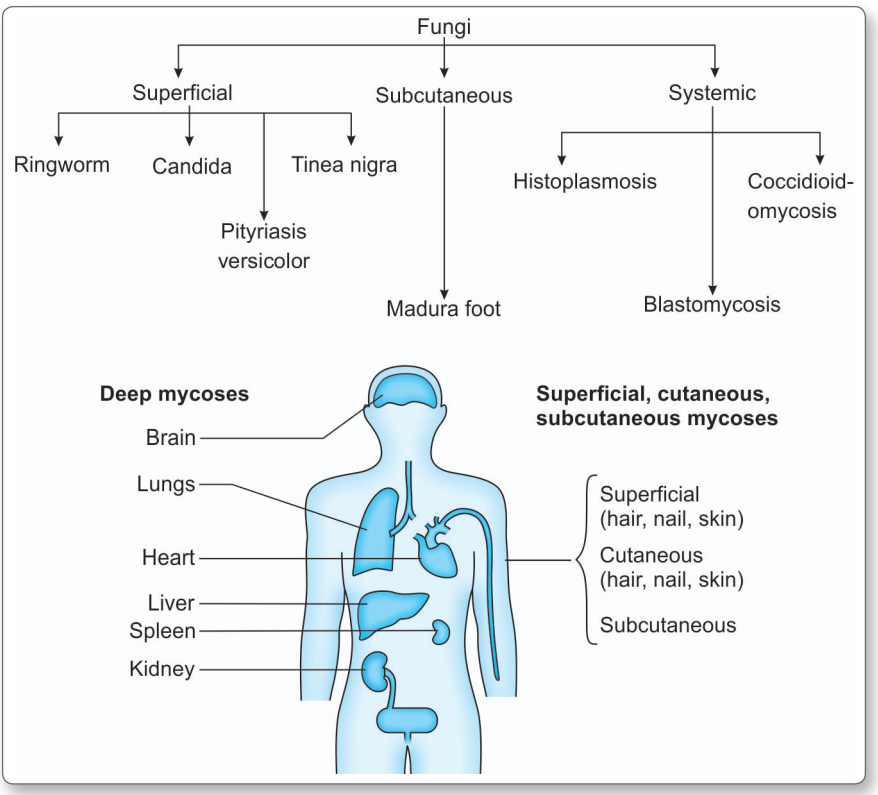


Fig. 8.19: Classification of fungi

1. **Superficial mycosis** are the commonest variety and are caused by dermatophytes. Major subgroups of mycoses are—
   a. Ringworm or tinea, caused by the fungus called dermatophytes.
   b. Candidiasis produced by candida group of fungus. In both the subgroup, many subgroups exist. Other notable members of superficial mycosis are—
   c. Tinea nigra and so forth.
2. **Subcutaneous mycosis** are caused by different species of fungus lesions are characterized by subcutaneous granuloma or chronic skin ulcers. Madura foot is a special example.
3. **Systemic mycosis** includes such diseases like—
   a. Blastomycosis. b. Histoplasmosis.

Because of widespread use of immunosuppressive chemotherapy and the prevalence of AIDS have been contributed to a rise in the incidence of systemic mycoses that demand prolonged treatment with antifungal agents.

PROPERTIES

Fungi are generally multicellular and flamentous. They are ubiquitous in distribution and are aerobic mostly, they are gram-positive and nonpathogenic. Only a few are pathogenic and cause diseases in plants, man and animals and less than a dozen can be fatal.

ESSENTIALS OF THE FUNGAL CELL WALL

A fungal cell has a rigid cell wall, which contains heavy amount of polysaccharides. Inner to the cell wall lies cell membrane. It may be remembered, that in mammalian cell membrane, cholesterol molecules are present whereas in the fungal cell membrane the substitute is ergosterol rather than cholesterol.

CLASSIFICATION OF ANTIFUNGAL AGENTS

a. Chemical structure
b. Clinical use.
   i. For superficial mycoses
      a. Clotrimazole, miconazole, griseofulvin and nystatin.
      b. Topical use polyene macrolides—Nystatin, Amphotericin-B, Natamycin.
   ii. Systemic use (a) Azoles, e.g. Ketoconazole, Fluconazole (b) Nonazoles Griseofulvin.
   iii. For subcutaneous and systemic mycoses (a) Polyene compounds (Amphotericin-B), (b) Pyrimidine derivative (Flucytosine), and (c) Azoles (Ketoconazole, Itraconazole, Fluconazole).

PHARMACOKINETICS AND DRUG INTERACTIONS

Absorption after oral administration varies from person to person. Presence of Cimetidine can retard the absorption from GIT. It can increase the effects of Warfarin and some newer antihistamines like Astemizole on heart.

ANTIFUNGAL ACTIVITIES/SPECTRUM

Clotrimazole is the prototype of Azole antifungals used topically and are effective against dermatophytes and Ketoconazole is used against systemic mycosis. Clotrimazole can cause local irritation.

Ketoconazole is orally used and is a broad spectrum antifungal, effective against both dermatophytes as well as systemic mycoses. But it has got some limitation that is, for vulvovaginal candidiasis Clotrimazole topically and Griseofulvin orally may be used but Ketoconazole is not a good choice due to its greater risk of ADRs.

MECHANISM OF ACTION OF AZOLES

They act by 2 ways—

a. They inhibit the biosynthesis of ergosterol in the fungal cell membrane, this is the fundamental action.
b. Conversion of Lanosterol to Ergosterol is blocked, this is the MOA when such members of this group of drug, i.e. Ketoconazole are given orally, Ketoconazole accumulates in the infected tissues and inhibits the biosynthesis of Ergosterol.

INDICATION

Ringworms failed to respond to griseofulvin but effective against systemic mycoses like aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis.

ADVERSE DRUGS REACTIONS

It can produce GI upsets like nausea and vomiting.

A special ADR is endocrine defects (1) fall in testosterone level, gynecomastia, libido, menstrual abnormality and corticosteroid activity. All these effects are due to Ketoconazole induced inhibition of P-450 isoenzyme required in steroid and androgenic hormone biosynthesis. However on withdrawal of Ketoconazole, reversion occurs.

CONTRAINDICATIONS

1. Nursing mother
2. Pregnancy
3. Persons suffering from liver diseases.

SECTION-VII ANTIVIRAL AGENTS

- Brief idea about virus
- Classification of antiviral drugs
- Individual drugs—Interferon

BRIEF IDEA ABOUT VIRUS

Viruses are unique group of living agent extremely small in size, usually beyond the resolution of light microscope, possess highest state of parasitism and may be responsible for a wide range of infections. They can infect animals, plant and bacteria and accordingly may be grouped as animal, plant and bacterial viruses. Last group are known as bacteriophase or simply as phages. Viruses are tiny packages of protein coated nucleic acid. The virus particle is called a virion. It has a protein overcoat called capside and a nucleic acid core. The nucleic acid may be either DNA or RNA and may be single-stranded or double-stranded. In some viruses the capsid is surrounded by thin structure called viral envelop. The capsid in many viruses is not smooth but studded with knob like structure of polypeptides, called capsomeres.

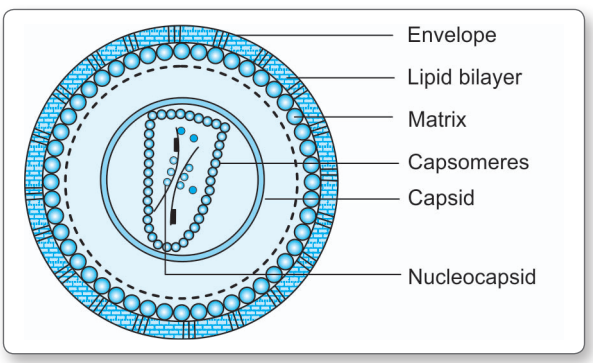


Fig. 8.20: The virion

CLASSIFICATION OF ANTIVIRAL DRUGS

1. Drugs used against respiratory viral infection.
   Amantadine, Rimantadine, Ribavirin
2. Drugs used against herpes and cytomegalovirus
   Acyclovir, Foscarnet, Vidarabine
3. Drugs used against HIV infection
   Didanosine, zidovudine, lamivudine, stavudine
   Protease inhibitors:Saquinavir, indinavir
4. Interferon

INDIVIDUAL DRUGS — INTERFERON

- History
- Source
- Properties
- Types of interferon
- Mechanism of action
- Uses of interferon
- Current status
- Adverse actions

History

In 1957, the British virologist Isaac and his Swiss colleague Lindermann discovered interferon.

Source

It is produced by virus-infected cells in intact animal and also in tissue culture.

Properties

1. Nonspecific in its action.
2. Produced by infected cell, not by a healthy cell.
3. Interferon is smaller than virus.
4. It is protein in nature (glycoprotein). Molecular weight varies between 20,000 to 30,000.
5. More heat stable than virus proteins and resists inactivation by acid or very alkaline pH.
6. Antiviral antibodies cannot inactivate interferon.
7. Interferon is species specific.
8. Nucleic acid of nonviral origin, rickettsia and endotoxins can induce interferon production.
9. It can be purified by chromatography and electrophoresis.

Types of Interferon

At least three varieties of interferon have been identified so far, they are—

a. Leukocyte interferon—Produced by leukocyte (alfa interferon).
b. Fibroblast interferon—Produced by fibroblast (prime source is the fore skin of circumcised infants) (beta interferon).
c. Immune interferon produced by T lymphocytes (more potent than other two) (gamma interferon).

Mechanism of Action

Interferon acts by interfering with virus multiplication within the cells. It causes the virus infected cell to manufacture a protein which is called "Translation inhibiting protein TIP". TIP interferes with viral mRNA in the cell to synthesize viral proteins.

Uses of Interferon

Alfa interferon is used in—

1. Hairy cell leukemia
2. Genital warts (papilloma virus)
3. AIDS related Kaposi's sarcoma
4. Hepatitis B and C viruses (2 million units daily or twice daily for 16–24 weeks can decrease the pathologic activity).

Current Status

In recent years, it has gained a renewed importance because of its antiviral and anticancer properties. It is in short supply and as a result efforts are been made by different research centers to find out avenues for mass production. Attempts at production of synthetic interferon have not yet met with success. Recombinant DNA technique employing *E. coli* is being tried and appears to be successful.

Adverse Actions

It includes fever, headache, malaise.

On the respiratory tract, histamine cause bronchoconstriction, SRS-A is also a potent bronchoconstricter. Profound hypotension and respiratory embracement together can lead to generalized shock.

SECTION-VIII CHEMOTHERAPY OF NEOPLASTIC DISEASES

- Introduction
- Cell kinetics
- Goal of treatment
- Chemosensitivity of different tumors
- Classification of anticancer agents
- Some chemotherapy schedules
- Precancerous conditions
- The European 10 - points code against cancer
- Mechanism of action
- Principal adverse effects

INTRODUCTION

Cancer is the 2nd highest killer disease (1st being the CHD). In the developed countries, nearly 30% of the persons face the risk of developing cancer in his lifetime.

CELL KINETICS

The cell cycle is divided into several phases, i.e. Go Gi(Gap-l), S (synthesis), G_2 (Premitotic) interval, M (Mitosis). The resting phase is designated as G_0. In the G_1-phase genes required for replication are activated as cells prepare to enter the S-phase. During the S-phase there is a pronounced increase in DNA synthesis. The G_2-phase, a period in which DNA repair progresses. It is the transition time between DNA synthesis and mitosis. Cancer chemotherapeutic agents may be cell cycle specific and cell cycle nonspecific. Resting cells do not respond to cell cycle specific agents. However, they may respond to alkylating agents or to other drugs that combine directly with the DNA. The drugs like Vincristine is cell cycle specific and acts in the metaphase of mitosis (M-phase).

Details of the explanation of all the techniques, whether alone, sequentially of concurrently is beyond the scope of this book. This account will be substantially confined to drugs only.

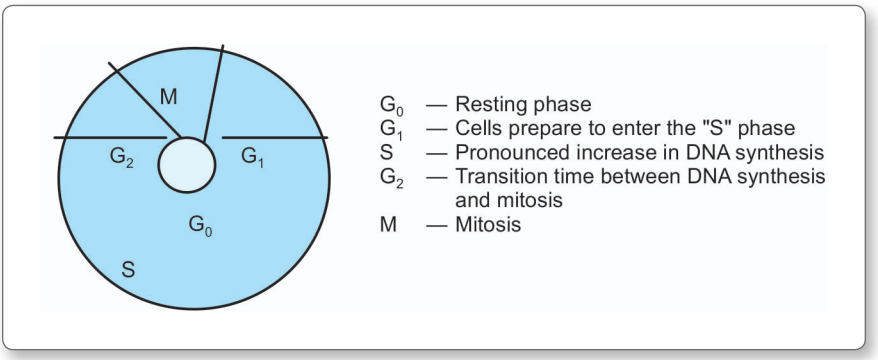


Fig. 8.21: Cell cycle

GOAL OF TREATMENT

There are 3 goals—

1. To cure the disease where possible.
2. To keep the patient symptom-free and increase the period of survival.
3. To give "palliation" to the patient.

Approach attempts to cure or palliate cancer employ, five principal approaches or mode. They are—

1. Surgery, including lasers
2. Radiotherapy
3. Chemotherapy
4. Endocrine therapy
5. Immunotherapy including cytokines.

CHEMOSENSITIVITY OF DIFFERENT TUMORS

i. Highly sensitive
   a. Teratoma of testis
   b. Hodgkin's diseases
   c. High-grade non-Hodgkin's diseases
   d. Wilm's tumor
   e. Embryonal rhabdomyosarcoma
   f. Choriocarcinoma
   g. Acute lymphoblastic leukemia (ALL) in children
   h. Ewing sarcoma
ii. Moderately sensitive:
   a. Small cell carcinoma of lungs
   b. Breast carcinoma
   c. Low-grade non-Hodgkin's lymphoma
   d. Acute myeloblastic leukemia (AML)
   e. Ovarian cancer
iii. Relatively insensitive:
   a. Gastric carcinoma
   b. Bladder carcinoma
   c. Squamous cells carcinoma of head and neck
   d. Soft tissue sarcoma
   e. Cervical cancer
iv. Resistant tumor:
   a. Melanoma
   b. Squamous cells carcinoma of lungs
   c. Large bowel cancer.

CLASSIFICATION OF ANTICANCER AGENTS

a. Alkylating agent: Nitrogen mustard, Cyclophosphamide, Chlorambucil, Melphalan, Thiotepa and Busulfan.
b. Antimetabolites—
   i. Folic acid antagonist—Methotrexate.
   ii. Purine antagonist—6-Mercaptopurine, 6-Thioguanine.
   iii. Pyrimidine antagonist—5-Fluorouracil, Cytarabine and Arabinoside.
c. Antibiotics—Bleomycin, Dactinomycin, Doxorubicin, Daunorubicin, Mitomycin-C and Mithramycin.
d. Plant alkaloids—Vinblastine, Vincristine.
e. Nitrosources—Carmustime, Lomustine and Semustine.
f. Random synthetics—Cisplatinum, Dicarbazine, Hexamethyl-melamines, Procarbazine and Hydroxyurea.

g. Enzymes L-Asparaginase.
h. Hormones:
   i. Adrenocorticoids—Prednisolone, Dexamethasone
   ii. Androgen—Testosterone
   iii. Estrogen—Diethylstilbestrol
   iv. Antiestrogen—Tamoxifen
   v. Progestogen—Hydroxyprogestron, Megistrol acetate.

SOME CHEMOTHERAPY SCHEDULES

COPP For treatment of Hodgkin's lymphoma—
1. Endoxin (Cyclophosphamide)–650 mg/m^2 IV day 1+8
2. Vincristine (Oncovin)—1.4 mg/m^2 IV. days 1+8
3. Procarbazine (Natural)—100 mg/m^2 PO days 1–14
4. Prednisolone—40 mg/m^2 PO days 1–14 in cycle land 4.
   Total 6 cycles of 2 week each with 2 week interval.

CHOP this regime for treatment of highgrade non-hodgkin's lymphoma.
1. Cyclophosphamide—75 mg/m^2 IV days land 8
2. Doxorubicin (Hydroxydaunorubicin)—25 mg/m^2 IV days 1 and 8
3. Vincristine—1.4 mg/m^2 lV days 1 and 8
4. Prednisolone—50 mg/mg/m^2 IV days 1 and 8.
   Repeated every 28 days from day 1.

CMF this regime is used to treat a case of infiltrating ductal cell carcinoma of breast,
1. Endoxin—400 mg/m^2 PO days to 14
2. Methotrexate—40 mg/m^2 lV days 1+8
3. 5- Fluorouracil—600 mg/ m^2 lV days 1+8.
   Repeated every-4 weeks.

FAM to treat gastrointestinal tumors (malignant neoplasis of the esophagus, stomach, colon, rectum, pancreas or liver).
1. 5- Fluorouracil—600 mg/ m^2 lV days 1,8,29,36 (weekly interval)
2. Doxorubicin (abriomycin)—30 mg/ m^2 IV days 1,29, (monthly interval)
3. Mitomycin-C—10 mg/ m^2 lV days 1 (2 monthly interval)
   To be repeated in every 8 weeks.

MACC to treat small cell lung cancer.
1. Methotrexate—40mg/ m^2 lV day 1
2. Doxorubicin—40 mg/ m^2 IV day 1
3. Endoxan—400 mg/m^2 IV day 1
4. CCNU—30 mg/PO day 1.
   To be repeated every 3 weeks.

BEP to treat testicular tumors (all types and germ cell tumor of ovary)
1. Bleomycin—30 mg/m^2 IV weekly
2. Etoposide—50–100 mg/m^2 IV day 1 to 5
3. Cysplatin—50–100 mg/m^2 lV day 1 to 5
   To be repeated every 3 weeks, total cycle-4.

VACA to treat Ewing's sarcoma, Osteosarcoma.
1. Vincristine—1.5 mg/ m^2 IV day 1
2. Doxorubicin (adriamycin)—50 mg/ IV day 1
3. Cyclophosphamide—600–800 mg/ IV day 1
4. Actinomycin—0–5 mg or 500 mg/m^2 IV day 2 to 6 cycles.

PRECANCEROUS CONDITIONS

Some examples are given below.
i. Undescended testis—It is an abnormality of development of testes.
ii. Paget's disease of bone—It is a condition of middle to late adult life has a risk of osteosarcoma.
iii. Solar keratosis—A warty skin lesion due to sun exposure.
iv. Leukoplakia—A whitish patch in the mouth or vulva.
v. Dysplasia—It means deranged development so that there is a atypical cytologic alterations involving cell size, shape and organization.
vi. Carcinoma in situ—It has the microscopic feature of cancer but the cells are still confined to there normal anatomical limit.
vii. Adenomatous polyp of the large intestine is a benign tumor.

THE EUROPEAN 10-POINT CODE AGAINST CANCER

- Reducing tobacco smoking.
- Avoiding the alcohol drinking.
- Avoid being overwight.
- Take care in the sun. Too much sunlight can cause skin cancer.
- Observe the health safety regulation at work—some chemicals and processes are known to cause cancer. Proper protection and safety regulations should be maintained.
- Cut down on fatty foods.
- Eat plenty of fresh fruit and vegetables and other foods containing fiber.
- See your doctor if there is any unexplained change in your normal health which last for more than 2-weeks.
- Specially for woman, have regular cervical smear test. The Pap smear test can detect abnormal changes in very early cancer of cervix.
- Examine your breast monthly. Woman over age of 50 should be screened by mammography at regular interval.

MECHANISM OF ACTION

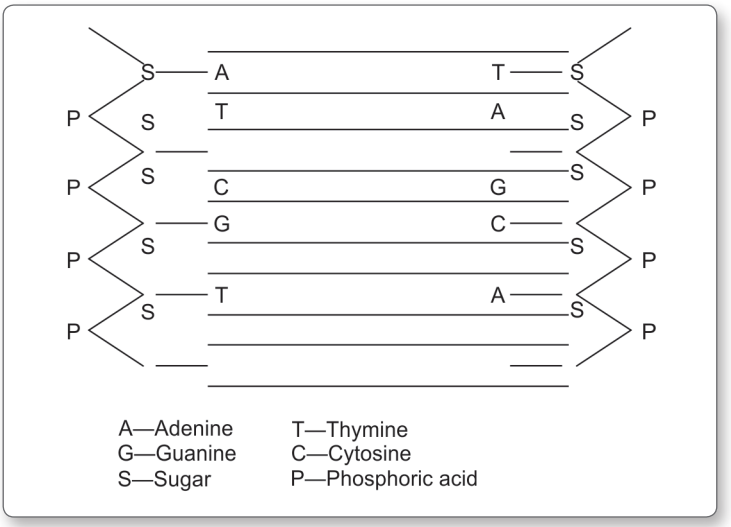


Fig. 8.22: Structure of DNA (Proposed by Watson and Click)

It is very much essential to know the structure of DNA, because it is concerned to the clear understanding of mechanism of action of most of the anticancer agents, so it is mentioned here.

Structure of DNA

Watson and click proposed the helix structure of DNA in which the two polynucleotide chains are wound about a common axis in the form of a double helix. These two polynucleotide chains are antiparallel, i.e. they run in opposite direction.

Alkylating Agents

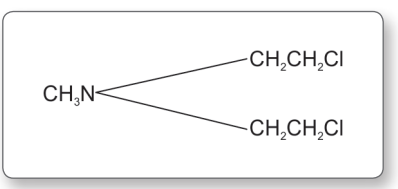


Fig. 8.23: Nitrogen mustard

The alkylating agents transfer alkyl groups to the important cell constituents by combining with sulfadryl, Amino, Carboxyl and Phosphate group. They are cell cycle nonspecific.

Antimetabolites

1. Folic acid antagonist—Methotrexate inhibits nucleic acid synthesis by blocking the enzyme dihydrofolate reductase.
2. Thioguanine is metabolized to ribonucleotide which enters the pathway of nucleic acid synthesis by substituting for guanine.
3. 5-Fluorouracil is incorporated into mRNA in place of uracil. ANTIBIOTICS—Bleomycine binds with DNA and blocks RNA formation. HORMONAL AGENTS—Estrogen is used in prostatic carcinoma along with castration. Tamoxifen, an antiestrogen is used in breast cancer, which competes with estradiol for estrogen receptor and inhibits estrogen stimulated growth of tumor.

Miscellaneous

Agents L-asparaginase is an enzyme used to treat leukemia. Apparently some malignant cells require exogenous asparagine, though normal cells can synthesize their own. Thus a metabolic difference between normal and neoplastic cells appears to exist for this drug.

Adverse action

Cytotoxic drugs act against all cells that are multiplying. Bone marrow, mucosal surfaces, gut, hair follicles, reticuloendothelial system, germ cells all are dividing more rapidly than many cancers and so they are also the targets for cytotoxic drugs.

PRINCIPAL ADVERSE EFFECTS

1. Nausea and vomiting.
2. Bone marrow and lymphoreticular system: Pancytopenia and immunosuppression (depression of both antibody and cell mediated immunity) leading to infection.
3. Gut lining and other mucosal surfaces: Diarrhea, mouth ulcers.
4. Hair: Alopecia due to effect on hair bulb (recovers within 2 to 6 months after cessation of treatment). Scalp hypothermia may be tried as a preventive measure.
5. Delayed wound healing.
6. General immunosuppression.
7. Germ cells sterility, teratogenesis, mutagenicity.
8. Secondary cancers.
9. Local toxicity: If extravasation occurs.
10. Various organ damage, i.e.
    a. Pancreatitis ← Asparaginase.
    b. Pulmonary fibrosis ← Bleomycin.

c. Cardiotoxicity ← Cisplatin.
d. Cardiotoxicity ← Doxorubicin.
e. Cholestasis ← Mercaptopurine.
f. Pulmonary fibrosis ← Methotrexate.
g. Peripheral neuropathy ← Vincristine.

Abbreviation

+ve	:	Stimulation positive
AA	:	Amino acid
ADRs	:	Adverse drug reactions
AGs	:	Aminoglycosides
BBB	:	Blood brain barrier
BEP	:	Bleomycin etoposide and platocin
BP	:	Blood pressure
cAMP	:	Cyclic adenosine monophosphate
CHOP	:	Cyclophosphamide hydroxy doxorubicin, Oncovin and Prednisolone
CMF	:	Cyclophosphamide, Methotrexate and Fluorouracil
CO^-	:	Keto
CO	:	Cardiac output
$COOH^-$	:	Carboxyl
COPP	:	Cyclophosphamide, Oncovin, Procarbaxine and prednisolone
CSF	:	Cerebrospinal fluid
DHFA	:	Dihydrofolic acid
DHFR	:	Dihydrofolate reductase
dL	:	Deciliter
e.g.	:	Given example
FAM	:	Fluorouracil, Adrenomycin and Mitomycin-C
GABA	:	Gamma aminobutyric acid
GIT	:	Gastrointestinal tract
i.e.	:	That is
IM	:	Intramuscular
IV	:	Intravenous
INH	:	Isonicotinic acid hydrazide
MACC	:	Methotrexate adrinomycin cyclophosphamide
MBC	:	Minimum bacteriocidal concentration
Mg	:	Milligram
MIC	:	Minimum inhibitory concentration
MOA	:	Mode of action
MPs	:	Malarial parasites
MIT	:	Methyl thiotetrazole
NAG	:	N-Acetyl glucosamine
NAM	:	N-Acetyl muramic acid+ve

NH_2	:	Amino group
NMJ	:	Neuromuscular junction
PABA	:	Para-aminobenzoic acid
PAS	:	Para-aminosalicylic acid
PBP	:	Penicillin binding protein
PGs	:	Prostaglandin
PID	:	Pelvic inflammatory diseases
PR	:	Peripheral resistance
SIADH	:	Syndrome of inappropriate antidiuretic hormone
SRS-A	:	Slow reacting substances of anaphylaxis
STD	:	Sexually transmitted diseases
TB	:	Tuberculosis
THEA	:	Tetrahydrofolic acid
TI	:	Therapeutic index
TIP	:	Translation inhibiting protein
TMR-SMG	:	Trimethoprim- Sulfamethoxazole
VACA	:	Vincristine adriamycin cyclophosphamide and actinomycin D
-ve	:	Inhibition/negative

CHAPTER

9

Short Answer Questions (SAQs)

Approximately seven hundred SAQs have been presented in this text; which have been prepared/designed through search of more than one text, with an objective of making the question more specific, significant reliable and valid.

In this era of MCQs they (SAQs) are even considered as very traditional, fundamental and time tested methods of study beyond doubt. Like many areas of the world, now in Bangladesh students are still assessed for 70% of marks in present undergraduate (MBBS) curriculum in their written examination in every subject. Whereas, MCQs and marks for formative assessment covers only 30%.

So the students are asked to prepare themselves for each chapter of the text thoroughly so that commonly asked SAQs may be answered very easily.

GENERAL PHARMACOLOGY

1. Define Pharmacology? Name its 10 important branches. Why a medical Pharmacologist puts attention about 2 of its important branches?
2. Define Pharmacogenetics? Give its 5 examples of medical importantance.
3. Name 5 experimental animals and name the organs or tissues on which experiment is done and also the reagents used.
4. What are the branches of clinical pharmacology; which completes the definition of interaction between drugs and human body?

5. Define drugs. What are its characteristics?
6. Diazepam is a drug, give its—
   a. Chemical
   b. Proprietary
   c. Generic name.
7. "Antisnake venom serum" is officially an essential drug in India but need not be so in New Zealand"—Why?
8. What are the differences between—Tetracycline and Cap Tetracycline 250 mg, 6 hourly for 7 days meal?
9. What are the criterias to be filled up for listing a drug as essential drugs?
10. What are the forms of medicine, present with examples.
11. What are the approaches or ways of entering a drug in the body? Summarizes by a picture.
12. What are the ranges of molecular weight of most of the drugs? Why tPA needs IV administration to be reached in the blood?
13. Streptomycin, Insulin, Benzyl, Penicillin and Heparin are administered parentally never orally—Why?
14. What are the 3 varieties of drug-receptor binding?
15. Diagrammatically show the usual story of Pharmacokinetics.
16. How mammalian cell membrane is formed? What are the 4 types of proteins in the cell membrane (CCER)?
17. How you can apply Henderson-Hasselbalch equation in the management of acidic drug poisoning in clinical medicine? What is ion-trapping?
18. Make a list of 5 acidic and 5 alkaline drugs.
19. Show the summary of passages of molecules through cell membrane and biological membrane.
20. List the factors influencing drug absorption following oral ingestion.
21. Define bioavailability. Write notes on 'concentration Vs time graph' What are the modifying factors?
22. What is bioequivalent of drugs? What are the criterias of bioequivalence?
23. Define V_d. How it can be determined? What are the 6 factors influencing V_d?
24. What are the consequences of plasma protein binding of drugs?
25. What is the effect of very high V_d on half-life of a drug? Give its clinical importance with examples?
26. What is drug sequestration and tissue storage? Is there any difference between these? Name 4 stored drugs with their tissues.
27. Define drug biotransformation. Does it differ from metabolism? What will be the effects of metabolism on drug? What is the purpose of drug metabolism?
28. What are the kinetics of excretion of drugs? Points the differences?
29. What are the phases/steps of drug metabolism? Name the conjugation reactions? What are the results after conjugation in phase II?

30. What is enzyme induction and enzyme inhibition? Name 5 inducers and 5 inhibitors.
31. Lists the factors influencing biotransformation of drug.
32. What is microsomes? What do you mean by MFO? What are its components? Name 5 drugs which follow metabolism through MFO system.
33. Calculate the following pharmacokinetic principles—
    a. Clearance (Cl)
    b. Maintenance dose (MD)
    c. Dosing interval (DI)
    d. Fraction oral ('F' oral)
    e. Steady state concentration (Css)
    f. Half-life ($t_{1/2}$)
    g. Volume of distribution (V_d)
    h. Loading dose (LD).

$$\text{Css} = \frac{\text{'F' oral} \times \text{MD}}{\text{Cl} \times \text{DI}}$$

$$\text{Cl} = \frac{\text{'F' oral} \times \text{MD} \times 1}{\text{DI} \times 1\ \text{mg/ml}}$$

$$= \text{Liter/h/70 kg}$$

$$\text{MD} = \frac{\text{Css} \times \text{Cl} \times \text{DI}}{\text{'F' oral} \times 1}$$

$$\text{'F' oral} = \frac{\text{DI} \times \text{Cl} \times \text{Css}}{\text{MD}}$$

34. Define receptors. Classify them—
    a. According to location
    b. According to function
    c. According to MOA of activation.
35. Define 'serpentine receptors'. Show schematically the sequences of activation via Gs, Gi and Gq proteins (membrane receptors).
36. Describe the sequences after activation of intracellular (cytosolic/nuclear) receptors.
37. Show diagrammatically the sequences of activation of transmembrane (tyrosine kinase) receptors.
38. What happens, when receptors containing ligand gated channels become activated by agonists?
39. What do you mean by receptor desensitization and internalization?
40. Define—
    a. Affinity
    b. Efficacy
    c. Potency
    d. Agonists
    e. Antagonists
    f. Partial agonists

g. Inverse agonists
h. Reverse agonists.

41. 'Dose-response' curves in log scale is more popular—Why?
42. Classify agonists and antagonists.
43. What are the three points on which 'dose-response' curve depends? Give the relationship between EC_{50} or ED_{50} and potency.
44. Depicted pictorially the following (a) high potency; high efficacy, (b) low potency; high efficacy, (c) low potency; low efficacy.
45. Define therapeutic index and therapeutic window; Show diagrammatically.
46. Same dose can produce different effects on different persons—Explain.
47. In the same person same dose can elicit different responses in different times—Explain.
48. Explain the clinical relevancy of—
    a. Down regulation
    b. Up regulation
    c. Overshoot phenomenon
49. Drugs are usually selective not specific – Explain.
50. i. What are the variations of combined effects of drugs?
    ii. Write notes on—(a) difference, (b) synergism, (c) antagonism
51. Define titrated dose. What are the advantages of—"Fixed dose combinations?
52. Why once fixed dose combinations were mushrooming?
53. What are FDCs? Give its disadvantages?
54. What are the importance of measurement of plasma drug concentration?
55. Give 3 examples of pharmacogenetic abnormalities in phase II drug metabolism.
56. List the factors which can modify drug action with examples of each.
57. How
    a. Route
    b. Dose
    c. Diet
    d. Age
    e. Presence of concomitant disease
    f. Environment can modify drug action?
58. Define drug interactions (DI) and classify them.
59. How coadministration of Omeprazole reduces the absorption of Ketoconazole?
60. Why the concentration of free Warfarin increases if it is given concomitantly with Indomethacin?
61. Explore the condition where excess Chloroquine ingestion can produce vomiting (a sign of toxicity) but in some persons even a single tablet of Chloroquine can produce vomiting. (These persons are Chloroquine intolerant).

62. How Probenecid prolongs the action of Penicillin?
63. Define and classify adverse drug reactions (ADRs).
64. What are the understanding of ADRs?
65. What are the factors which can modify ADRs?
66. What do you mean by—
    a. Side effects
    b. Toxic effects
    c. Drug allergy.
67. Write notes on
    a. Idiosyncrasy
    b. Toxic effects
    c. Drug allergy.
68. What is—
    a. Drug dependence
    b. Carcinogenicity
    c. Mutagenicity
    d. Photoallergy
    e. Cytotoxicity?
69. Consider the following points relevant to drug toxicity
    a. Epidemiology
    b. Classification
    c. Factors influencing (toxicity).
70. Define rational use of drugs. Give its criteria.
71. List the criterias for rational prescribing.
72. What is polypharmacy? Name 5 diseases which need polypharmacy.
73. What are the problems of irrational use of drugs?
74. What is P-drug? What are the significances of "SANES" or "CASES" in selecting P-drug?
75. Name 4 Conditions where P-drug varies.

AUTACOIDS AND NSAIDs

1. Define autacoids. Who introduced the term? Name 3 autacoids and 2 eicosanoids. How they differ from classical hormones?
2. What do you mean by mast cell and nonmast cell histamines? What are the settings of histamine release? Name 4 histamine liberators.
3. What are the types of histamine receptors? Mention their sites and the effects of their activation.
4. Why anaphylactic shock is treated by AD, not by NA?
5. What are the antagonists of histamine?
6. Classify antihistamines. Mention 3 differences between 1st and 2nd generation of classical antihistamines.
7. Mention the appropriate antihistamines used in—
    a. Allergy
    b. Motion sickness

   c. Ménière's disease
   d. Hyperemesis gravidarum
   e. With Morphine in AMI.
8. Set the antihistamines for the following adverse effect—
   a. Sedation
   b. Cardiac arrhythmia
   c. Teratogenicity
   d. Convulsion.
9. Give the pharmacological importance of Serotonin.
10. How Bradykinin and Kalidin are produced? What are their effects? How ACE inhibitors produce hypotension and cough?
11. Name 4 eicosanoids. Mention their 4 physiological functions and role in 2 pathological conditions.
12. What are the common properties of NSAIDs? Name the mediators of acute and chronic inflammation.
13. Write short notes on COX. What will be the effects of inhibition of COX's?
14. Give the chemical classification of NSAIDs.
15. Why aspirin is clinically used in—
   a. Pyrexia
   b. Inflammation
   c. Gout
   d. AMI
   e. PDA?
16. Name 3 important adverse effects of NSAIDs. Why acute Paracetamol poisoning is pharmacologically so important?
17. DMARDs are a special class of drugs used in rheumatoid arthritis—Explain.
18. Why aspirin is contraindicated in—
   a. Peptic ulcer
   b. Labor pain
   c. Bronchial asthma
   d. Viral fever in child?
19. What is the treatment strategy in gout?
20. Aspirin is more anti-inflammatory than paracetamol yet paracetamol is preferred in some clinical conditions where aspirin could be used—Explain.
21. Concomitant use of H_2 blockers or antacids do not give protection against aspirin induced gastritis—Why?
22. It is not antacid not H_2 blocker or PPI, but Misoprostol is used in Aspirin-induced gastritis—Justify.
23. How gold compounds and Chloroquine acts as DMARDs?
24. Write notes on 'safe Aspirin'.
25. Why there is some overlapping between the pharmacological and adverse effects of Aspirin?

ENDOCRINE PHARMACOLOGY

1. Define diabetes mellitus (DM) and clarify the key words in it.
2. Name the 4 polypeptides comes from islets of Langerhans of pancreas. What are the types of DM? Mention 5 important clinical features of type-1 DM.
3. Name 5 complications which can occur in chronic cases of DM. What is your idea about usual natural history of type II DM?
4. What do you mean by glycated hemoglobin (HbAlc)? Give its clinical significance.
5. Where there is coexistence of type-II DM with hypertension?
   a. What could be happened without tight control of hypertension?
   b. What could be happened without tight control of blood sugar?
   c. In type-I DM, without tight control of blood sugar, what could be happened?
   d. What would be the effect on blood sugar, after the tight control of blood sugar?
6. What are the points should be included in the goals of treatment of DM?
7. Differentiate between oral hypoglycemic and oral antidiabetic drugs.
8. List the 5 groups of oral antihyperglycemics with examples.
9. Tell the effects of insulin on the following target cells.
   a. Liver
   b. Muscle
   c. Adipose tissue.
10. How insulin lowers blood glucose?
11. What are the ways of classifying insulin? What is Lispro? Human insulin is least, porcine is more and beef insulin is most antigenic—Why?
12. Mention the following points in insulin regimen—
    a. Types
    b. Daily dose of insulin
    c. How many dose presupposing the meals.
13. What are the indications of insulin?
14. What is insulin resistance? Give its management.
15. Can you remember some (4) great pharmacological effects of Metformin? How it causes lactic acidosis?
16. What are the different varieties of hyperthyroidism, present with their incidence?
17. What are the 5 measures used to treat hyperthyroidism?
18. What are the logics behind using β-blockers in hyperthyroidism?
19. "In pregnancy with hyperthyroidism, it is Propylthiouracil not Carbimazole is used"—Why?
20. "In the treatment of hyperthyroidism, Carbimazole administration does not give immediate relief, clinical improvement requires 3 to 4 weeks to be manifested"—Why?

21. What is the significance of—
    a. High serum TSH level
    b. Low serum TSH level
    c. Name 3 indications of Levothyroxine.
22. What do you mean by bone remodeling? Name the 3 factors facilitating osteoporosis.
23. What are the disadvantages of hormone replacement therapy (HRT)? What are its alternatives?
24. Define and classify
    a. Ecbolics
    b. Tocolytics.
25. Compare Oxytocin, Ergometrine and Prostaglandin as oxytocics.
26. "Contraction of Ergometrine is sustained in nature, without any relaxation in between, and same effect occurs throughout the uterus, but the nature of contraction of Oxytocin is rhythmic intermittent in type and contraction is confined only in the fundus and body, whereas it causes relaxation in the cervix"—How can you correlate these properties of above mentioned ecbolics in the management of 2 obstetrical conditions—
    a. Induction of labor
    b. Control of PPH.
27. "The uterine arteries run perpendiculars to the long axis of the muscle, i.e. these arteries are compressed by the contracting myometrium, so what would be if it is (Ergometrine) administered to induce labor?
28. Name the factors which initiate labor pain.
29. What are the stages of labor?
30. Tell the indication of—
    a. PGE_2 (Dinoprostone)
    b. $PGF_{2\alpha}$ (Carboprost).
31. Define steroids. Exemplify the 3 groups of steroids coming from the different histological layers of adrenal cortex.
32. Name 5 compounds which contain PCC nucleus. Mention the pharmacological actions of glucocorticoids.
33. Make a list of synthetic glucocorticoids. What is your idea about super steroids?
34. How glucocorticoids protect us from stress? What will happen in Addison's disease, if exogenous cortisol is not given?
35. Name and justify the 5 inflammatory and 3 immunological conditions, where glucocorticoids may be used.
36. Name 10 adverse conditions which can follow long-term glucocorticoids therapy.
37. After a prolonged therapy with glucocorticoids, withdrawal should be tapered and gradual—What are the logics?

38. Explain the following relative contraindications of glucocorticoids—
    a. Diabetes mellitus
    b. Hypertension
    c. Peptic ulcer
    d. Edema
    e. Presence of tuberculosis
    f. Osteoporosis.
39. Make a list, mentioning at least 5 members causing inhibition of adrenocorticosteroids.
40. What are the great assets of Raloxifene over Tamoxifen in its antiatherogenic effect?
41. What are the 4 major varieties of hormonal contraceptives?
42. How combined pill (hormonal contraceptives) acts?
43. Cite 3 factors on which adverse effect of contraceptive pills depend upon.
44. Cite 7 severe adverse effects of hormonal contraceptives.
45. What are the 5 contraindications of OCPs?
46. What are the 5 noncontraceptive benefits of OCPs?
47. Name 5 drugs (from 2 groups) which can cause contraceptive failure.
48. Glucocorticoids are indicated in miliary tuberculosis, in tubercular osteoarthritis, etc. but is severely contraindicated in pulmonary tuberculosis—Why?
49. Mention the points of Henoctis principle.
50. Justify the use of glucocorticoids in the management of insulin resistance.

CARDIOVASCULAR SYSTEM

1. Name 5 physiological functions and 5 clinical conditions where there is involvement of angiotensin-II.
2. What are the different varieties of angiotensin II and their receptors?
3. Classify ACE inhibitors. Mention 3 general features of ACE inhibitors.
4. Name 5 important indications of ACE inhibitors.
5. How Ramipril gives renal protection in diabetic nephropathy?
6. "Some blacks (in USA) are somehow resistant to hypotensive effects of Ramipril"—How this resistance can be minimized? Why K^+ sparing diuretics should not be concomitantly used with Ramipril?
7. Why Ramipril is more cardio–and renoprotective than other members of ACE inhibitors?
8. Define and classify hypertension. Why asymptomatic hypertensive need treatment?
9. What should be the degree of reduction of BP? Do you know about "J-shaped curve"—What is it?

10. Hypertension often coexists with other diseases such as—
(a) diabetes, (b) gout, (c) hyperlipidemia. What things should be kept in mind during managing such hypertensives?
11. Points the nonpharmacological management of hypertension.
12. Make a list of 10 groups of antihypertensive drugs.
13. Which modified Thiazides is called lipid neutral Thiazides? What are its traditional adverse effects?
14. Describe the current status of ACE inhibitors. (5 points)
15. Name 5 ARBs and 3 chemical groups of CCBs with examples of each.
16. CCBs are not 1st line drugs is hypertension JNC. CCBs are 1st line drugs in hypertension with other drugs—WHO. Where lies the controversy?
17. Why it is dangerous to use Nigedipine in diabetic nephropathy? (afferent arterioles are relaxed)
18. "Sudden stoppage of β-blockers is dangerous"—Give 3 points in favor.
19. Why combination of β-blockers with ACE inhibitors is not very logical?
20. Select the appropriate antihypertensive where there is coexistence of following diseases—
    a. Blacks (in USA and in India)
    b. Patients with hypelipidemia
    c. Patients with angina
    d. Patients with diabetes
    e. Patients with pregnancy.
21. Comment on the following antihypertensive combination
    a. ACEI + low dose Thiazide
    b. ACEI + K^+ sparing diuretics
    c. ACEI + CCBs
    d. ACEI + β-blocker
    e. CCBs + Diuretics
    f. Diuretics + DPH
    g. β-blocker + DPH or CCBs.
22. What are the (10) factors which helps in developing classical/exertional/stable angina?
23. What are the dangers and aim of treatment of angina?
24. What are the antiangina drug and how they act as an antiangina agent?
25. Among the antiangina drugs nifedipine mainly close/block the 'L' channels (or slow channels) so it is principally used as arterial dilators to reduce BP even Nifedipine is sometimes rarely used in angina, whereas Verapamil-Diltiazem is commonly used in this indication but in supraventricular trachycardia Nifedipine is never used but Verapamil-Diltiazem is commonly used"—Why?

26. Define CCF/CHF. Suggest its prognosis and mention its causes. What is starling heart?
27. Describe the pathophysiology of heart failure.
28. What do you mean by ventricular remodeling? State 4 important causes.
29. Explain the role of—
    a. Diuretics
    b. ACEI
    c. Vasodilators
    d. β-blockers on ventricular remodeling.
30. Justify the role of ACEI in CHF.
31. Tell the effects of digitalis on—
    a. CVS
    b. ANS
    c. Kidneys.
32. Recently in some cases of CHF use of Carvedilol is encouraged. What are the reasons?

Cardiac Electrophysiology

[Not applicable for undergraduate student, but for postgraduate students, specially essential for the students of MD in cardiology]

33. Draw and label AP of fast response and explain its ionic basis.
    a. Phase '0' is due to what?
    b. What are the 2 causes of phase —I?
    c. What are the 3 causes responsible for phase—II?
    d. Mention the 3 causes responsible for phase—III?
    e. What is the cause of phase—IV?

Cardiac Pathophysiology

34. Draw and label reentry phenomenon. Mention one benign and one life-threatening (PVT) cardiac arrhythmia due to reentry.
35. Classify common tachyarrhythmias.
36. Classify antiarrhythmias drugs.
37. State the MOA of—
    a. Propranolol
    b. Amiodarone as an antiarrhythmic drug.
38. What is Torsades de pointes?
39. Name 4 drugs which can precipitate torsades de pointes.

Hypolipidemic Drugs

40. What are the plasma lipids? Why the plasma lipids form lipoproteins? What is apolipoproteins?
41. Classify plasma lipoproteins.

42. Why the lay people call the—(a) cholesterol of LDLs as bad cholesterol. (b) cholesterol of HDLs as good cholesterol?
43. Classify primary hyperlipidemias depending on clinical practice?
44. State the plasma lipoproteins; as risk factor for development of atherosclerosis- CHD-CVD.
45. How antioxidants can prevent atherosclerosis?
46. How bile acid sequestrates (resins) lowers plasma LDLs?
47. Explain the advantages and disadvantages of the following hypolipidemic combinations—
    a. Statin + fibrate
    b. Statin + resin + niacin.
48. How LPL increasers and fabric acid derivatives reduce VLDL and increases HDL cholesterol level?
49. What are their indications and adverse effects? Why clofibrate is nowadays virtually obsolete?
50. Classify 5 groups of antihyperlipidemic drugs.

ANS PHARMACOLOGY

1. Define and classify ANS.
2. List the functional tissues.
3. Name the sites where ACh is released.
4. Clarify neurotransmitters, neuromediators and neuromodulators.
5. How you can classify neurotrasmitters?
6. Prove that ACh and NA are classical examples of peripheral neurotransmitter.
7. Yet there are 50 NTs been discovered, among which 6 demands special attention in medical pharmacology or in clinical medicine [ACh-NA, DA-5HTs; NMDA-GABA]—Why?
8. What are the postganglionic and sympathetic target organs?
9. Be clear from confusion between
    a. Neuroeffector junction
    b. Neuromuscular junctions.
10. What are the 6 important sites where ACh are found?
11. Why the cholinergic receptors are classified and termed as muscarinic and nicotinic receptors?
12. Mention the groups and subgroups of muscarinic and nicotinic receptors.
13. Why we emphasize study on the structure and functions of ANS? [we often manipulate the functions of ANS pharmacologically in clinical medicine, because basic study on ANS demands special attention]
14. Classify cholinoceptor activators?
15. What are the ways of classifying cholinoceptor activators?
16. Mention the clinical importance of BuChE/pseudocholinesterase. Name 3 naturally occurring alkaloids with their sources.

17. How ACh or Pilocarpine acts on eye?
18. Clarify the relationship among
    a. ACh-cholinesters
    b. Cholinesterase
    c. Anticholinesterase [ACh, AChE, AntiAChE]
19. How DFP (di-isopropylfluorophosphate) or echothiophate acts? Give their clinical uses.
20. What do you mean by ageing in case DFP poisoning? Is there any relationship between—ageing and Pralidoxime?
21. What are the clinical uses of AntiAChE?
22. Give the clinical uses of 5 Atropine analogues.
23. How Atropine and Adrenaline causes mydriasis?
24. Make a 10 member list of nondepolarzing NMJ-blockers.
25. Compare the CVS effects of—
    a. AD
    b. NA
    c. ISOP.
26. Classify the sympathomimetics with their basis.
27. "DA and AD both are Catecholamine, have an action on α and β-receptors. AD is bronchodilator but DA is not – Why?
28. Give the important clinical indications of DA and Dobutamine.
29. What are the 3 or 4 major types of shock?
30. "In hypovolemic/hypotensive shock, it is not NA but DA is used:- Give reasons.
31. Classify Adrenoceptor blockers.
32. What are the 5 AD-reversal effects of phenoxybenzamine?
33. What are the therapeutic uses of α-blockers?
34. Give the medical treatment of BPH.
35. What are absolute contraindications of β-blockers?
36. "As an adverse effect, depression and sleep disturbance is more pronounced with Propranolol than Atenolol"—Why?
37. "Concomitant use of nonselective β-blocker is very dangerous" Why?
38. "Sudden withdrawal of short acting β-blocker is very dangerous"—Why?
39. Justify the use of propranolol in—
    a. Hyperthyroidism
    b. Pheochromocytoma.
40. How VMA is produced? How much VMA is excreted per 24 hours through urine? Name the clinical conditions where VMA excretion is increased with examples.
41. What are the difference between reuptake I and II?

42. Can we say AD is not a NT? How we can explain?
43. Define and exemplify autoreceptor regulation.
44. Make a chart of 10 members showing the clinical uses of adrenergic drugs.
45. How does α-methyldopa lowers BP? Why it is preferred as antihypertensive in pregnancy?

RENAL PHARMACOLOGY

1. Why we need some highlights on renal physiology before going to study on diuretics?
2. Make a list by 5 members of drugs which act on kidneys.
3. What is nephron? How many nephrons are there in each kidney? What are the parts of a nephron for our purpose, we can view? Mention the amount of GFR/min and 24 hours.
4. What do you mean by cotransport system? Is there any difference between by cotransport of protein in the ascending limb and that of distal tubule? Why efficacy of thiazide diuretic is much lesser than that of loop diuretics?
5. Classify diuretics—
   a. Depending on site of action
   b. Depending on efficacy.
6. Why loop diuretics are called high celling diuretics?
7. Why physiologically Frusemide is called high celling and that of anatomically loop Diuretics?
8. In acute pulmonary edema due to LVF, after IV administration of Frusemide, clinically improvement starts before the onset of Diuresis"—Why?
9. How you can prove that in addition to diuresis, Frusemide has vasodilatory effect?
10. How Frusemide causes hypokalemia and Thiazide causes gout? It is said, Thiazides may have extra benefits in osteoporotic bedridden patients"—How?
11. Thiazides as antihypertensives are extremely popular in the elderly, in subdiuretic dose—Why?
12. Name 3 important members of K^+ sparing diuretics. How spironolactone acts as a diuretic?
13. Give 3 indications of Spironolactone and 2 adverse effects.
14. What is $Na^+ - K^+$ exchange? Name 2 drugs which can block this exchange? What will be the effects of blocking this exchange?
15. Spironolactone is not effective in " Addison's disease" as a diuretic but Triamterene and Amilorides are—Why?
16. In hypertension, ACEIs are extremely popular nowadays, Diuretics are also popular but ACEIs and K^+ sparing diuretics should not be given together because of what reason?

17. What is chloride driven Na^+ transport. How CA inhibitors cause this?
18. Mention 2 clinical use and 3 adverse effects of Acetazolamide.
19. Name 4 members of osmotic Diuretics. What is Mannitol? What are its routes for diuretic action? How it acts? Give its 3 clinical use.
20. Justify the use of Thiazides in idiopathic hypercalciuria and renal stone formation.
21. Thiazide is contraindicated in DM, but indicated in nephrogenic "diabetes insipidus"—Explain.
22. "In all varieties of edema (cardiac, renal, hepatic) Frusemide is useful, but Frusemide is most popular in edema of CHF specially in early stages—Why?
23. Both Thiazides and loop Diuretics possesses antihypertensive whereas Frusemide is in CHF—Why?
24. Justify the use of Thiazide in nephrogenic diabetes insipidus and Spironolactone in ascites due to cirrhosis.

CNS PHARMACOLOGY

1. What are the 3 major groups of tracts in the CNS?
2. List the monoaminergic tracts with their functions.
3. Correlate the deficiency or excess of action of these tracts and the cause of the following disease—
   a. Schizophrenia
   b. Depression
   c. Parkinsonism
   d. Epilepsy
   e. Alzheimer's diseases.
4. What are the 3 major DA'ergic pathways? Tell their functions.
5. Why the drugs used to schizophrenia causes parkinsonism? Is there any approach to minimize this?
6. What are the functions of serotonergic and cholinergic tracts?
7. Why glutamate (NMDA) receptors have demanded attention in clinical medicine recently?
8. Why anxiolytics, sedatives and hypnotics are considered as very commonly used drugs?
9. Define and classify anxiolytics. Why the term anxiolytic–sedative is very popular? How sedatives differ from hypnotics?
10. What is sleep-wake cycle? What are phases of sleep? How many cycles are found in a single night? What are the stages of NREM phase?
11. Why SMS (slow wave sleep) are more pronounced in infants and reduced in old persons?
12. Define hypnotics. Name the conditions, depending on which one should prescribe hypnotics.
13. Define GABAergic neuron. Name 4 sites where BDZ receptors are found and correlate the activation of these receptors by BDZ and the following effects—

a. Anxiolysis
b. Hypnosis
c. Muscle relaxation
d. Ataxia.

14. Name 5 clinical uses of BDZs in clinical medicine.
15. Name 4 advantages and 3 disadvantages of BDZ as anxiolytic agent.
16. Why among others Flurazepam, Temazipum and Triazolum are preferred as hypnotics?
17. Match the hypnotics, mentioned below with the different type of insomnia.
    a. Triazolam (3) Who have a long latency period.
    b. Temazepam (1) Who awake repeatedly during the night sleep.
    c. Flurazepam (2) Reduces the sleep latency period.
18. What are the 4 general rules of indicating hypnotics in chronic insomnia?
19. Some BDZ have long $t_{1/2}$ values, yet their duration of action is relatively short—How this can be explained?
20. Classify BDZs on the basis of their duration of action.
21. What are the subtypes of BDZ receptors? Mention 4 advantages of selective BDZ agonists.
22. Zolpidem is chemically a nonBDZ? How it acts? Does it possesses muscle relaxing and antiseizure effect? What are its 3 advantages over BDZ?
23. "Why the barbiturates are no longer popular?
24. What the 5 effects of G/A must be produced?
25. "All professional anesthesiologists are specialists"—Explain.
26. What are the 3 divisions/phases of anesthesia?
27. Classify the 3 divisions of G/As
28. Mention the factors which can change the protocol of G/As?
29. Make a protocol for surgical procedure with G/A of long duration.
30. In modern days, why the stage of G/A cannot be cleanly demarcated?
31. Name the stages of G/A and explain this nomenclature.
32. State the Overton-Meyer principle or what is "fluidization" and give its relationship with G/As. Or how one can refuse the depolarization of the neuron with G/As.
33. Classify G/A and name 6 members of them.
34. What do you mean by the tension or pressure of the anesthetic gases? What is the relationship between blood solubility and the tension or pressure of anesthetic gas?
35. Why induction by ether is slower than that of nitrous oxide?
36. What is MAC? Give its relationship with potency of inhalation anesthetics.
37. Explain "Oxygen inhalation is must in postoperative phase where nitrous oxide is being used" or explain diffusion hypoxia and its management.

38. Justify the rationality of combining nitrous oxide with Halothane and oxygen.
39. What are the advantages of ether, why it is not yet obsolete in poorer countries as an anesthetic?
40. What is the disadvantage, why it is obsolete in developed countries in modern days?
41. What are the advantages of Halothane?
42. What are the disadvantages of Halothane?
43. "Halothane anesthesia should not be repeated within 3 months"—Why?
44. Why Enflurane is less hepatotoxic than Halothane and it is contraindicated in renal failure?
45. It is said Isoflurane is safer in IHD among the halogenated volatile liquids—Why?
46. Name 4 clinical indications and its (isoflurane) limitation in prolonged use.
47. Name 3 Barbiturates of inducing agents in G/A. Give its onset of action and duration of action as an inducing agent.
48. Thiopental is used as inducing agent and it is maintained by inhalation anesthesia. However for short duration of G/A. Opioid or such drugs has to be used. Non use of opioid in this case what can cause?
49. How Ketamine causes dissociative anesthesia?
50. Ketamine anesthesia is popular in hypovolemic shock, in hypotension but not in hypertensives—Why?
51. Ketamine injection is risky in patients with IHD—Why?
52. Ketamine has many advantages even it is not very popular—Why?
53. List 4 clinical condition where Ketamine is used as IV anesthetics.
54. What are the aims of preanesthetic medication, point at least 5 drugs.
55. Define and classify epilepsy.
56. What are the causes of epilepsy?
57. What are the classical methods of producing experimental epilepsy in animals?
58. Classify antiepileptic drugs (both depending on chemicals and clinical use).
59. What are the common 4 approaches by which antiepileptics act?
60. What are the 4 components of guideline in the treatment of epilepsy?
61. What do you mean by the "use-dependent action" of phenytoin? Give its clinical use?
62. How phenytoin causes—
    a. Osteomalacia
    b. Gum hyperplasia
    c. Megaloblastic anemia.
63. What do you mean by "fetal hydantoin" syndrome?
64. How phenobarbitone acts as an antiepileptics?

65. List the antiepileptics developed after 1990. Give the M/A of Lamotregene, Gabapentin and Vigabatren.
66. Name 4 neurodegenerative diseases? Why treatment of PD receives most importance in pharmacology than other neurodegenerative diseases? Present the prognosis of PD.
67. Define and classify parkinsonism? What do you mean by drug-induced parkinsonism? Name three groups of drugs which can cause secondary parkinsonism.
68. Interrelate between the
    1. DAergic and GABAergic
    2. Cholinergic fibers
        i. Neostriatum
        ii. Substantia nigra in the pathogenesis of PD.
69. What are the substances, which causes loss of DAergic neurons of substantia nigra?
70. Mention the strategies or pharmacology of PD.
71. List the drugs used in the treatment of PD.
72. Why Carbidopa is combined with Levodopa?
73. How
    1. Amantadine
    2. Selegiline
    3. Procycline hydrochloride act as an antiparkinsonian agents?
74. Why the response of Levodopa begins to fall after a few years?
75. Why a dose of Levodopa which did not produce involuntary movement at first cause's involuntary movements later on?
76. Nausea, vomiting and anorexia are frequent when Levodopa is taken without Carbidopa—Why?
77. Levodopa without Carbidopa if taken can cause tachycardia ventricular extrasystole but combined use can reduce this incidence of cardiac arrhythmia—Explain.
78. What do you mean by fluctuation of motor performance or 'on-off' phenomenon in PD? State the strategy to combat 'on-off' phenomenon.
79. How we can classify psychiatric disorders? List them.
80. What is schizophrenia? What are its (+ve) and (–ve) signs? Present the dopaminergic theory of schizophrenia?
81. Classify the following terms—
    a. Psychosis
    b. Antischizophrenic drugs
    c. Neuroleptics
    d. Psychotropics.
82. What are the affective disorders? What is depression and what are its types?

83. What is biogenic amine theory of depression? What are its drawbacks?
84. Classify the antidepressants based on Harvey, RA and Champe, P (series editors) Why bupropion and mianserin are called atypical antidepressants?
85. How MARI act?
86. What are the 2 characteristics of SSRI, which distinguish them from TCAs. How they act? What are their clinical uses?
87. Combination of SSRI and MAOI be dangerous—Why?
88. What are the drawbacks of MAOI? Write notes on cheese reaction. How MAOIs act?
89. What are the 3 indications of MAOI?
90. Explain the following interactions—
    a. Concomitant use of MAOI + SSRIs
    b. Levodopa + MAOI
    c. Ephedrine containing drug + MAOI.

CLINICAL PHARMACOLOGY

1. Give the pharmacotherapy or treatment of hypertension with diabetes mellitus.
2. Give the pharmacotherapy or treatment of hypertension with IHD.
3. Give the pharmacotherapy or treatment of hypertension with hyperlipidemia.
4. Give the pharmacotherapy or treatment of hypertension with gout.
5. Give the pharmacotherapy or treatment of hypertension with bronchial asthma.
6. Give the pharmacotherapy or treatment of nephritic syndrome.
7. Give the pharmacotherapy or treatment of diabetic nephropathy.
8. Give the pharmacotherapy or treatment of CHD/CCF.
9. Give the pharmacotherapy or treatment of pulmonary TB.
10. Give the pharmacotherapy or treatment of enteric fever.
11. Give the pharmacotherapy or treatment of vivax malaria.
12. Give the pharmacotherapy or treatment of falciparum malaria.
13. Give the pharmacotherapy or treatment of rheumatoid arthritis.
14. Give the pharmacotherapy or treatment of status epilepticus.
15. Give the pharmacotherapy or treatment of COPD.
16. Give the pharmacotherapy or treatment of gonorrhea.
17. Give the pharmacotherapy or treatment of CAP/HAP.
18. Give the pharmacotherapy or treatment of hyperlipidemia.
19. Give the pharmacotherapy or treatment of glaucoma.
20. Give the pharmacotherapy or treatment of PID.
21. Give the pharmacotherapy or treatment of food poisoning.
22. Give the pharmacotherapy or treatment of shigellosis.

23. Give the pharmacotherapy or treatment of sinusitis.
24. Give the pharmacotherapy or treatment of common cold.
25. Give the pharmacotherapy or treatment of otitis media.

CHEMOTHERAPY

1. Penicillins are the classical examples of "magic bullet" of Paul Ehrlich—Explain.
2. What are the 5 major mechanisms of action of chemotherapeutic agents? Give examples of each.
3. Mention 4 criterias of cell wall synthesis inhibitors.
4. Why Penicillin is ineffective in infections caused by mycoplasma?
5. What do you mean by 'remodeling' of bacterial cell wall synthesis? What is the effect of cell wall synthesis inhibitors on this remodeling?
6. Make a (5 members/group) list of antibiotics. Which group act by inhibition of bacterial protein synthesis? Which group/member of this list is bactericidal?
7. Name 4 groups of bactericidal and bacteriostatic antibacterial agents.
8. Mention the basis of classifying AMAs.
9. Clarify the points why antimicrobials act as 'magic bullet'.
10. What do you mean by natural and acquired microbial resistance? What are the various means of development of acquired resistance?
11. What do you mean by multidrug resistant microbials? Give 2 examples. Do you think multidrug resistant tuberculosis and falciparum malaria are a problem in our country recently? Name 3 tests for microbial resistance.
12. What are the 10 factors/points, a clinician has to keep in mind to make chemotherapy successful?
13. A wild combination of AMAs may not be justifies, in fact unwise combination can worsen the prognosis"—Explain. Give 2 examples.
14. However in some clinical setting a combination of AMAs shall have to be used, give such 5 instances.
15. List the common hazards of antibiotic therapy.
16. What are the 2 major subclasses of inhibitors of bacterial cell wall synthesis?
17. Why Penicillin 'G' is ineffective in salmonella infections and it is to be always administered parenterally, never orally?
18. What were the attempts to overcome the 2 limitations of Penicillin G?
19. How we can define Penicillin chemically?
20. a. Write down the structure of '6-APA'. What are its components?

b. How you will correlate the chemical change or modification of 'R' with the following 3 members of Penicillin such as—
   1. Penicillin G
   2. Amoxicillin
   3. Cloxacillin?

21. What will happen if only Ampicillin is administered in a case of pneumonia caused by *Staph. aureus*?
22. Classify Penicillins depending on bacteriological spectrum.
23. Is there any example of natural microbial resistance of Penicillin? How microbes develop acquired resistance of Penicillin?
24. Why Ampicillin is more effective in shigella infection and its incidence of diarrhea is more than Amoxicillin?
25. What are the antipseudomonal antibiotics? What are the extra advantages of antipseudomonal Penicillins over Aminopenicillin (they are in addition effective against aeruginosa and proteus).
26. What is MRSA? To which antibiotic combination it is sensitive?
27. What do you mean by 'suicide inhibitors'? Name its 3 member and explain the phenomenon.
28. Make a simple list of Cephalosporins.
29. What are the superiority of Cephalosporin to Penicillins?
30. What are 8 advantages of Ceftriaxone to other members of Cephalosporins?
31. Name 6 members of AGs. Why they are so called?
32. Name 4 advantages and 3 disadvantages of AGs.
33. Explain "combination of AGs with Penicillin or Vancomycin acts synergistically".
34. "Ototoxicity is more with Streptomycin and that of nephrotoxicity with Gentamicin"—Explain.
35. How AGs might be beneficial in prehepatic and hepatic coma in clinical medicine?
36. Why neonates or very young baby can develop 'gray baby syndrome' after Chloramphenicol therapy? How it causes anemia and aplastic anemia?
37. What are the clinically important members of TGs? Why they are so called? How they can cause discoloration of teeth, maldevelopment of bone growth and malformation of teeth enamel?
38. List are the clinically important macrolids and why they are so called?
39. What are the advantages of Azithromycin over other members of macrolids?
40. Why *Mycoplasmae pneumoniae* or atypical pneumonia is treated by macrolids not by Penicillins or Cephalosporins?
41. What do you mean by folate antagonist? What are they?

42. How sulfonamides causes
    a. Hemolytic anemia
    b. Thrombocytopenia
    c. Arthritis
    d. Kernicterus
    e. Erythema multiforme.
43. How Pyrimethamine acts as an antimalarial and Methotrexate as an anticancer agent?
44. Why TMP-SMZ (Trimethoprim-Sulfamethoxazole) acts as an antibacterial a mixture of Sulfadoxine, Pyrimethamine as an antimalarial agent?
45. What do you mean by sequential block? How the ideal (TMP:SMZ) ratio of (1:20) in blood is maintained?
46. What do you mean by Fluoroquinolones? Name 10 Quinolones. Why they are so popular recently?
47. How Quinolones act?
48. Explain why Fluoroquinolones should not be used in
    a. Subjects below 18 years
    b. Patients receiving Theophylline
    c. Patients with Warfarin
    d. With coadministration of Enoxacin and Fenoprofen.
49. What are the indications of Metronidazole? How they acts as an antibacterial?
50. What are the (four) aims of chemotherapy of tuberculosis?
51. "In tuberculosis, as a rule, a combination of drugs are used"—What are the reasons?
52. Why tuberculosis needs long drawn treatment?
53. What are the different pools of *M. tuberculosis*? How Rifampicin behaves with these pools?
54. What are the different regimens of antitubercular treatment?
55. Classify antitubercular drugs.
56. What are the advantages of INH over other antitubercular agents?
57. Why INH is included in all antitubercular regimens?
58. "It is INH, which has only one indication and it is tuberculosis"—Explain.
59. Explain—Why the Blacks are more prone to develop peripheral neuropathy and Whites are more susceptible to develop hepatotoxicity?
60. "PZA is ineffective in ECF but acts as a highly effective antitubercular drug". How?
61. How many peoples are attacked by malaria allover the world throughout the year? What are the clinically important species of malarial parasites? Give their prognosis.
62. Why P vivax malaria requires radical cure? How it is done?
63. How Quinine acts as antimalarials? Mention its 8 important adverse effects. Why quinine requires IV glucose infusion?

64. How Artemisinin acts as an Antemalarial agent? Has it any role in radical cure of malaria? What are its toxicities?
65. Classify antimalarials.
66. In which group, Chloroquine belongs to as an antimalarial drug? How it acts as an antimalarial agent? What are its other clinical uses? Why it requires initial loading dose?
67. Mention the major use of Primaquine. Why it is always given orally? What are its adverse effects? Mention its 2 contraindications.
68. Classify amebicides clinically.
69. Write down the treatment of clinical attack of malaria.
70. Write down the Chemoprophylaxis of malaria.
71. What do you mean by clinical cure and radical cure of malaria give examples of each. What are the different forms of Leishmaniasis?
72. Why P.falciparum infections need very prompt treatment?
73. How the transmission of kala-azar varies in India and other parts of the world? Explain the following sign/symptoms of kala-azar
    a. Anemia
    b. Hepatomegaly
    c. Splenomegaly
    d. Fever
    e. Cutaneous pigmentation.
74. Make a list of Leishmanicidal drugs. How sodium stibogluconate acts? What are its adverse reactions? What do you know about liposomal Amphotericin B?
75. Make a list of clinically important helminthes.
76. Select the appropriate anthelmintics against—
    a. Nematodes (M)
    b. Trematodes (P)
    c. Cestodes (N).

    How (i) Mebendazole (ii) Praziquantel (iii) Niclosamide act as anthelmintics? What are the contraindications of Praziquantel? Why use of Niclosamide needs a suitable purgatives?
77. Classify the antiviral drugs according to antiviral spectrum.
78. What are the 3 groups of drugs used against AIDS? What are the indications of Lamivudine? What is the tragedy of continuous uses of single drug in AIDS? How this tragedy can be reduced?
79. Classify mycoses and antifungal drugs. Chemically identify Amphotericin B. Why it is a toxic drug? Write down the advantages of liposomal preparation of Amphotericin B.
80. Classify antifungal azoles. How they act? What are the advantages of Itraconazole over Ketoconazole?
81. Compare Ketoconazole and Itraconazole.
82. What are the goals of cancer treatment?

83. What do you mean by cancer cell burden, debulking and log kill?
84. Classify anticancer drugs.
85. How major six groups of anticancer drugs act?
86. What are the common adverse effects of anticancer drugs? Mention 5 special toxicities of (ACDs) with examples?
87. Name some cancers, where chemotherapy is highly sensitive and life may be prolonged and where chemotherapy is insensitive.
88. What do you mean by cell-cycle specific and cell-cycle nonspecific CCNS or proliferation independent drugs?
89. "CCNS drugs are particularly effective after surgical debulking"—Explain.
90. Leuprolide, Goserelin are becoming popular in the treatment of cancer prostate, Why?
91. What are the major uses of immunosuppressants?
92. Make a list of immunosuppressants.
93. Write notes on "food vacuole" and haem accumulation concerned with the antimalarial actions of Chloroquine.
94. Why Chloroquine needs initial loading dose? Why mefloquine is preferred in Chemoprophylaxis of malaria? Give the schedule.

RESPIRATORY SYSTEM

1. What is asthma? What are the predisposing factors?
2. Classify bronchial asthma. Discuss its pathogenesis.
3. What are the chemical mediators released from mast cell during early phase reaction?
4. What are the approaches of treatment of bronchial asthma?
5. Name the drugs used in bronchial asthma or list the drugs useful for treating asthma.
6. Name the inhalers used in asthma.
7. Classify drugs that are used for prophylaxis and treatment of asthma.
8. Outline the stepwise management of bronchial asthma.
9. Name the drugs used in treating acute asthma. Discuss their role.
10. How will you treat a case of acute severe bronchial asthma or status asthmaticus?
11. Name the therapeutic bronchodilators.
12. Which route do you prefer for bronchodilators? Why?
13. discuss the advantages of use of salbutamol inhaler instead of tablet form.
14. Justify the use of salbutamol nebulizer in the management of acute asthma.
15. What are the disadvantages of prescribing Salbutamol in tablet form instead of inhaler?

16. Mention the disadvantages or adverse effects of—
    a. Salbutamol
    b. Aminophylline
    c. Theophylline.
17. What will happen when theophylline is given to a smoking patient?
18. What will happen when Propranolol is given in a patient of bronchial asthma?
19. List the β_2-antagonist.
20. Ephedrine is no longer used in bronchial asthma—Why?
21. Make a list of (5 members) bronchoconstrictor. Or, Exeamplify the bronchoconstrictor from—
    a. Narcotic analgesic
    b. Muscle relaxant
    c. NSAIDs
    d. Cholinester
    e. β-blockers.
22. Mention the pharmacological effects of xanthine derivatives (Aminophylline).
23. Justify the popularity of using Ipratropium bromide in bronchial asthma.
24. How Theophylline differs from Aminophylline? What is the therapeutic range of Theophylline concentration? What can happen if Aminophylline is given IV rapidly and why?
25. Name the Leukotrienes synthesis inhibitors and receptor blockers. What is their indication?
26. What is cough? Where lies the cough receptors and cough center? Classify cough.
27. Define and classify mucolytics and expectorants.
28. What are the drugs used in cough?
29. What is the main advantage of Ipratropium bromide over Atropine as Antimuscarinic bronchodilator?
30. "Antihistamines have little place in the treatment of bronchial asthma"—Explain.

GASTROINTESTINAL PHARMACOLOGY

1. "Most anticancer drugs produce nausea and vomiting"—What are the known facts?
2. Most of the antiemetics are receptors antagonist of Serotonin, Histamine or Muscarine—How?
3. List antiemetics.
4. What are the 7 indications of antiemetics?
5. Define emetics and exemplify.
6. How Metoclopramide acts as an antiemetic? Justify its use in GER.

7. Why Cisapride is used in GER but not in emesis?
8. What is Barrett's esophagus? Name the 6 factors producing GERD.
9. What is Omeprazole test? How noncardiac chest pain can be differentiated from GERD by this test? How long treatment with Omeprazole is required to eradicate GERD? Define digestants and bitters. What are their examples?
10. Why antacid is used in PUD? What are their types? How they cause rebound acidity? Define laxatives and purgatives. Classify purgatives.
11. What is Sucralfate? How this compound act? Explain its cytoprotective effect. What are the types and causes of diarrhea?
12. Why natural PGs are not used; but synthetic PGE, Misoprostol is used as cytoprotective agent in PUD? Compare its efficacy to H_2 blockers.
13. Compare Omeprazole to Ranitidine. What is the advantage of Lansoprazole over Omeprazole?
14. Pirenzepine is superior to other antimuscarinic used in disorders of GIT explain.
15. Define proton pump inhibitors. Name 4 members of PPI. How they act? What are their clinical uses?

ANTIHEMOSTASIS AGENTS

1. Define hemostasis. What are its steps?
2. What are the antihemostatic drugs?
3. What is primary hemostasis? How you will save life with it?
4. What is intrinsic and extrinsic pathway of blood clotting?
5. What do you mean by secondary hemostasis and blood coagulation?
6. What are the defects in procoagulants?
7. Why inhibition of cyclooxygenase enzyme by Aaspirin leads to inhibition of platelet drugs.
8. Name 5 antiplatelet drugs.
9. How Aspirin acts as antiplatelate drug? Name 5 clinical conditions where its dose is 75–100 mg and why?
10. What is the lethal dose of Aspirin and for dose there is antibiotic effect? 500 mg daily dose can cause some adverse effects. What are those?
11. How heparin acts as anticoagulant?
12. Name 5 characteristics and 5 common features of heparin.
13. What are the reasons that bleeding occurs due to heparin?
14. Why LMWH is preferred in the treatment of DVT?
15. Write 6 points on heparin versus Warfarin.
16. What is APTT (activated partial thromboplastin time)? How it is related with heparin? What is INR? How it is related with Warfarin?
17. Define thrombolytics or fibrinolytics. Name 5 thrombolytics. How they act?

18. Heparin or Aspirin are either coadministered with the thrombolytics or given immediately after the thrombolytics—Why?
19. How the saying of "golden 1st hour" is relevant with fibrinolytics?
20. What do you mean by 'clot selective thrombolytics'? How tPA act as fibrinolytics?
21. Name 5 drugs which can arrest bleeding.
22. What is anemia? What are the causes?
23. Define and classify hematinics. Name 5 iron foods. Comment on milk.
24. What are the oral irons? In most cases of iron therapy, which route is preferred?
25. What is the formula for calculation of parenteral iron (iron required in mg = 4.4 × b.w in kg × D), where D = Hb deficit in gm/100 ml). Why this total amount calculation is mandatory?

CHAPTER

10

Miscellaneous

- Concept of essential drugs
- P-drugs
- Rational use of drugs
- Drugs acting on eye
- Local anesthetics
- Ganglion and neuromuscular blockers
- Prescription writing
- Immunosuppressants
- Management of
  - Erectile dysfunction
  - Osteoporosis
  - Obesity.

CONCEPT OF ESSENTIAL DRUGS

Introduction

A particular drug may be essential in a particular country but need not be so in every country. Thus snake bite is common in India and antisnake venom serum is officially an essential drug in India but need not be so in New zealand which is officially a snake-free country.

WHO experts published EDL (essential drug list) in 1977 and there were 250 drugs. In 1995 the EDL was revised and it became 300 drugs. Now more than 80 countries are practising EDL.

Major Criteria

The major criteria for listing a drug as essential drug include—

1. The pharmacological data of the proposed drug must be adequately known.

2. The prevalence of disease pattern, cost, demographic factors, environmental factors are also important.
3. Where there are several options—
   a. Safety
   b. Efficacy
   c. Availability
   d. Need to the community.

Cost are major criteria for clinching the name. The government prepared list should also consider whether the drug is manufactured within the country. Commonly, the proposed drug is a single drug compound. But that does not mean that combination preparation cannot be included in the list (Neomycin + Bacitracin).

Advantages

1. Reduction in the number or pharmaceutical products to be manufactured, imported, stored, analyzed and distributed from amongst the thousands.
2. Improvement of the quality of drug utilizing management information and monitoring.
3. Stimulation of the local pharmaceutical industries.
4. Solutions of the primary health care problems by providing high priority on safe and cost-effective drugs.
5. Facilitating the use of drugs more economically and rationally.

EDL (Essential Drug List) in Bangladesh

It is that number of essential drugs that have been recommended to be used by the various levels of the health care personnel.

1. Primary health care complex
   a. Village level—15 drugs
   b. Upazilla level—15 + 58 = 73 drugs
2. Secondary level
   a. District hospital—15 + 58 + 78 = 151 drugs
3. At tertiary level
   a. Medical college and Universities—15 + 58 + 78 + 73 = 224 drugs.

P-DRUGS

- **Meaning**: P denotes personal, priority, primary.
- **Selection criteria**: P-drug is selected on the basis of—

1. Safety
2. Availability
3. Need to the community
4. Efficacy
5. Status of the patients—
   a. Cost-effective

b. Availability
c. Safety
d. Efficacy
e. Suitability.

- **Availability**: P-drug is available in case of

1. Child
2. Old age
3. Pregnancy
4. Lactation.

RATIONAL USE OF DRUGS

Criteria for rational prescribing

1. Incorrect clinical or microbiological diagnosis
2. To take proper decision whether chemotherapy is needed or not
3. Improper drug administration or inadequate dosage
4. Poor patient compliance
5. Alteration in bacterial flora during drug administration and superinfection with a resistant organism
6. Infection in a location inaccessible to the drug
7. Failure to use indicated surgical drainage
8. Development of drug resistance by mutant forms of infecting organism
9. Deficiency in host defenses
10. Drug toxicity and hypersensitivity
11. Incompatible chemotherapeutic combination.

DRUGS ACTING ON EYE

Mydriatics and miotics.

Mydriatics

- Definition
- Uses
- Classification
- Mechanism of action
- Differentiation of reflexes
- Pharmacotherapy of glaucoma
- Normal IOP (intra-ocular pressure)
- Glaucoma
- Principles of treatment
- Drugs.

Definition

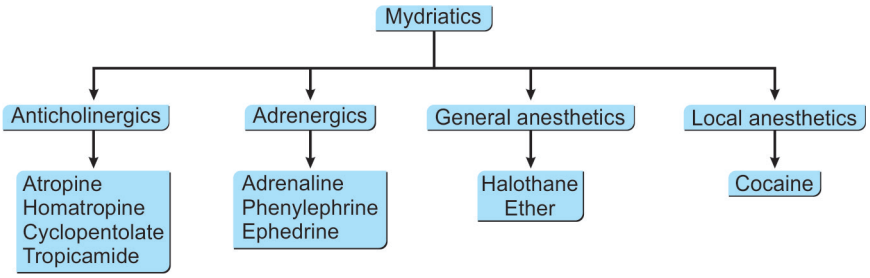
Mydriatics are drugs which cause pupillary dilatation. There may be various reasons why a mydriatic drug should be used—

Uses

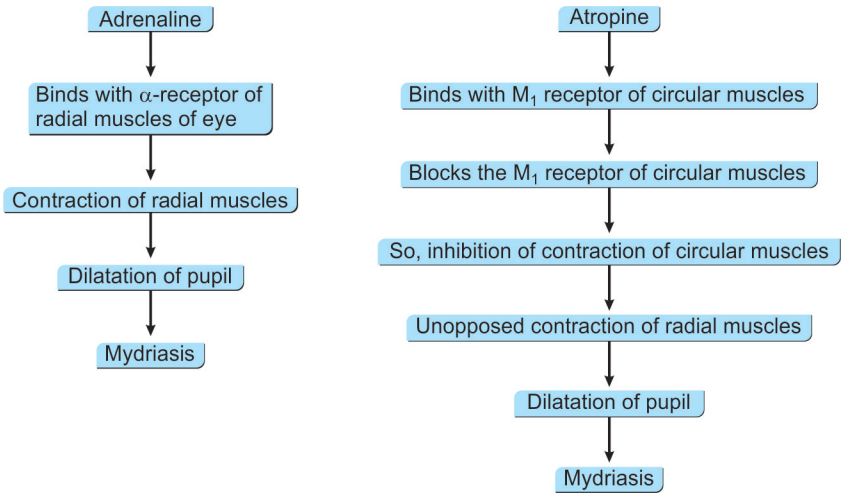
1. Examination of fundus

2. Testing for refraction
3. Prevention of synechiae and so on.

Classification

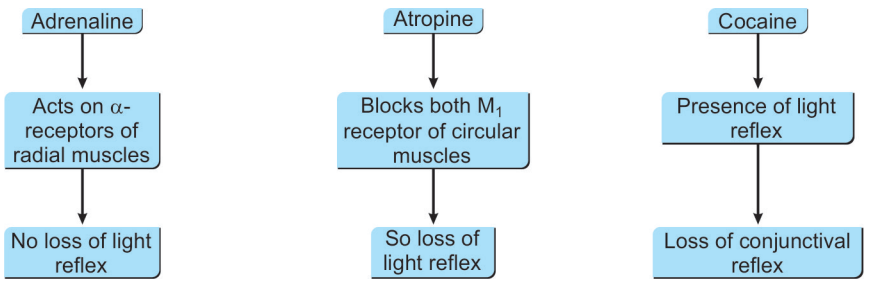


Mechanism of action

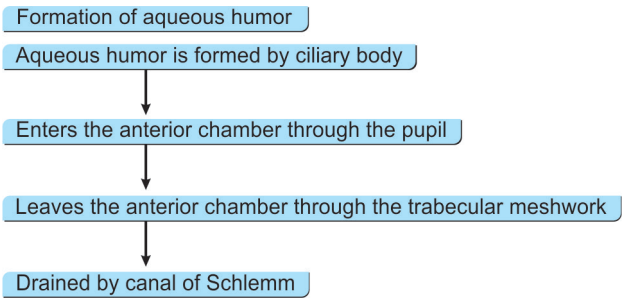


Differentiation of reflexes

Differentiation of mydriasis produced by Adrenaline, Atropine and Cocaine



Pharmacotherapy of glaucoma



Normal IOP (intraocular pressure)

Within 20 mmHg. A common cause of rise of IOP is obstruction of the flow because of the fault in trabecular meshwork.

Glaucoma

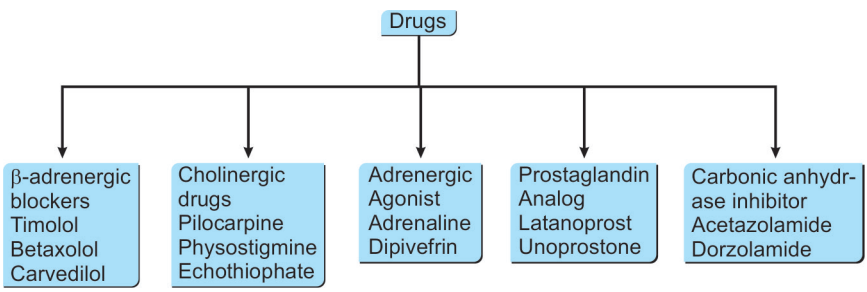
It is characterized by

1. Abnormally high IOP
2. Damage of the optic nerve
3. Glaucomatous cupping
4. Loss of vision which may eventually lead to blindness.

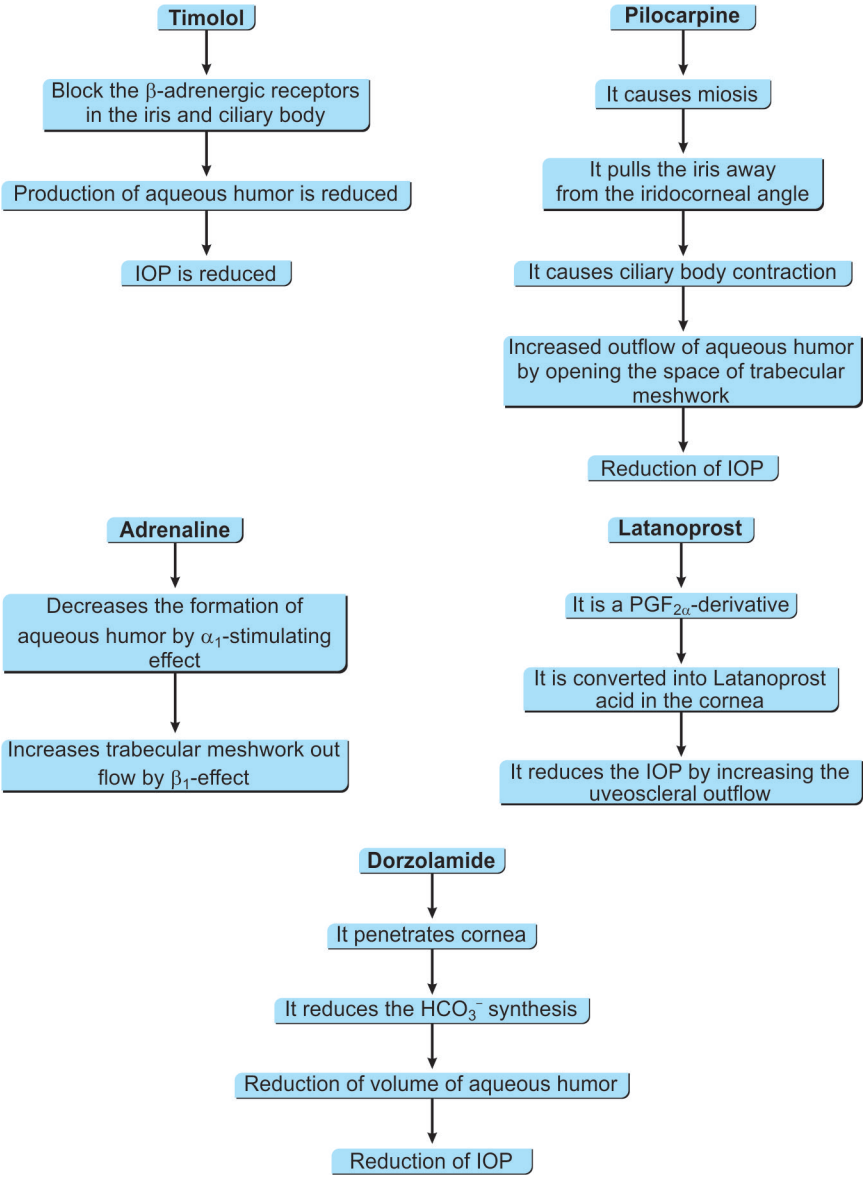
Principles of treatment

1. Decrease the secretion (formation) of aqueous humor.
2. Increase the drainage by opening the space in the trabecular meshwork.
3. Increase the drainage by uveoscleral pathway—Normally, it is not so important in healthy persons, but in glaucomatous subjects, some drugs can cause heavy drainage of aqueous humor through this pathway.

Drugs



Mechanism of Action



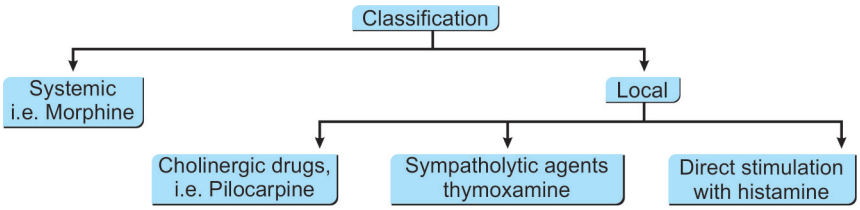
Miotics

- Definition
- Classification
- Mechanism of action
- Causes of miosis.

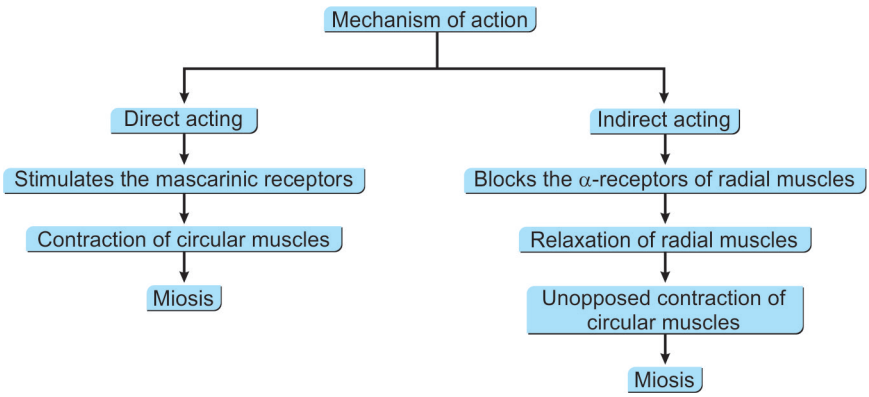
Definition

Miotics are drugs which cause constriction of the pupils.

Classification



Mechanism of action



Causes of miosis

1. Unilateral
   a. Miotic drugs – Pilocarpine
   b. Ocular cause.
2. Bilateral
   a. Morphine
   b. Tumor of the pineal body
   c. Bilateral iritis
   d. During deep sleep.

LOCAL ANESTHETICS

- Differences with general anesthetics
- Scope
- Criteria of a good local anesthetics
- Classification
- Clinical significance
- Mechanism of action
- Different forms of local anesthetics.

Differences with General Anesthetics

1. Local anesthetics are safer, therefore where possible particularly in poor risk patients they preferred.
2. Consciousness is not lost with them.
3. With local anesthetics usually functions of heart, lung and liver are not affected.

Scope

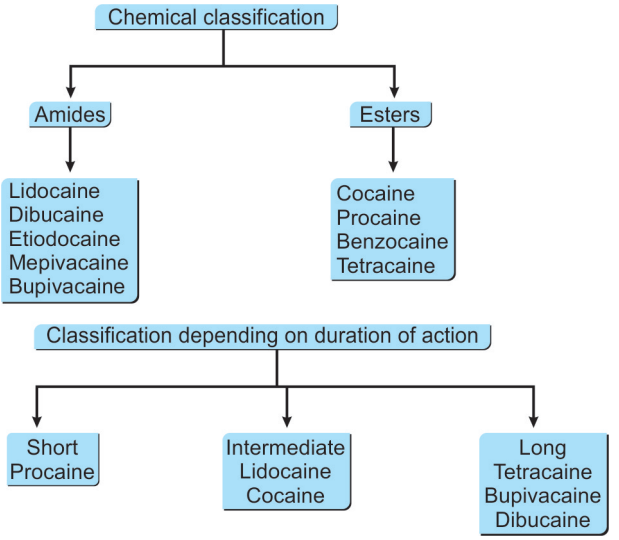
The scope of local anesthetics have now expanded and today in many surgeries where previously general anesthetics were used today local anesthetics are employed.

Criteria of a Good Local Anesthetics

1. Locally as far as practicable, nonirritant
2. It will cause no local tissue damage
3. It must begin to act within a short time
4. It should have a long duration of action
5. Its systemic toxicity should be minimum. Viewed in this way, no local anesthetics in current use can be regarded as ideal.

Classification

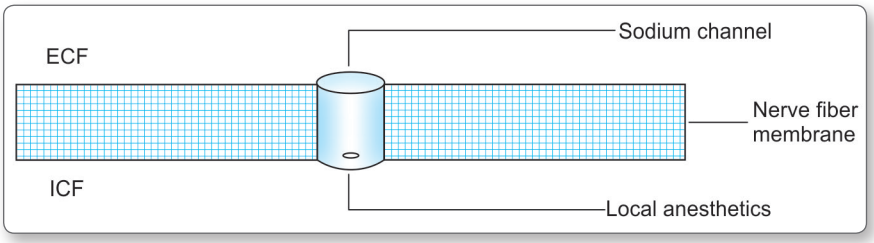
There are two ways of classifying the local anesthetics—



Clinical Significance

See Page 31 (genetic factor).

Mechanism of Action



Nerve fibers contain sodium ion channels in their membrane. When a nerve fiber stimulated sodium ions enter from the ECF into the ICF, via these sodium channels → an action potential develops. Local anesthetics can block the sodium channels and prevents the development of action potential so the nerve fiber is not stimulated.

Different Forms of Local Anesthetics

1. Surface application—Lignocaine ointment
2. Infiltration anesthesia—Lignocaine HCl 2% injection
3. Regional anesthesia
   a. Spinal
   b. Epidural
   c. IV regional anesthesia.

GANGLION AND NEUROMUSCULAR BLOCKERS

- Introduction
- Muscle relaxants.

Introduction

Ganglion blockers block the transmission at the autonomic ganglia (both sympathetic and parasympathetic). Neuromuscular blockers block the transmission at the neuromuscular junction of somatic nerve and skeletal muscles.

ACh is the chemical transmitter at

1. Parasympathetic nerve endings (M-receptor).
2. ANS ganglia, both sympathetic and parasympathetic (N-receptor).
3. Neuromuscular junction (N-receptor).
   N receptors are of two types—
   a. N_n—At ganglia
   b. M_m—At neuromuscular junction
4. M-receptors are block by antimuscarinic drugs.

5. Ganglion blockers block N_n-receptors but has virtually no effect on N_m-receptors.
6. Neuromuscular blockers block M_m-receptors but has practically no effect on N_n-receptors.

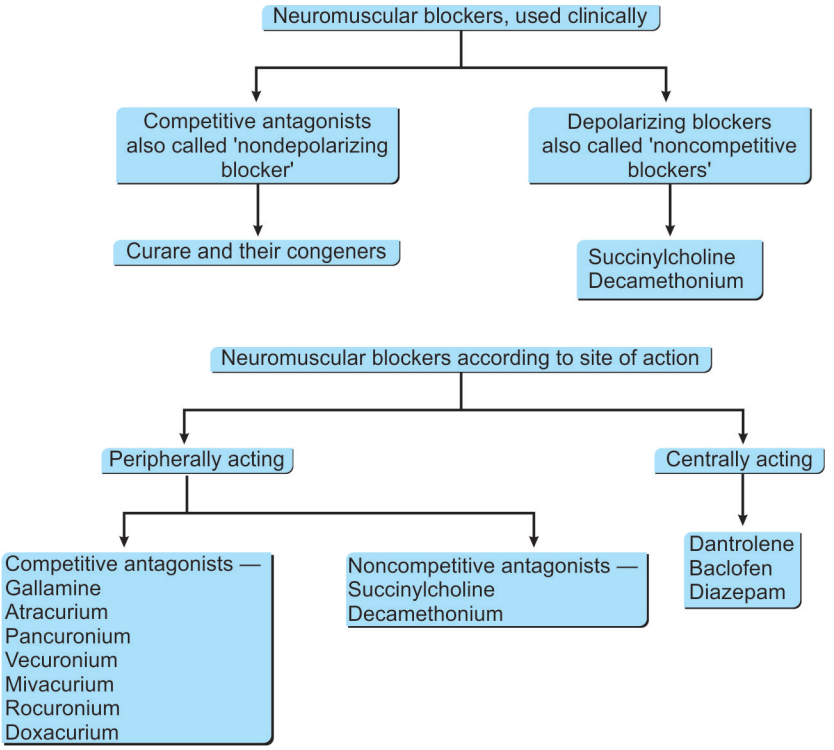
Muscle Relaxants

- Definition
- Classification
- Mechanism of action
- General features
- Clinical uses
- Drug interaction
- Drugs which remove skeletal muscle spasm.

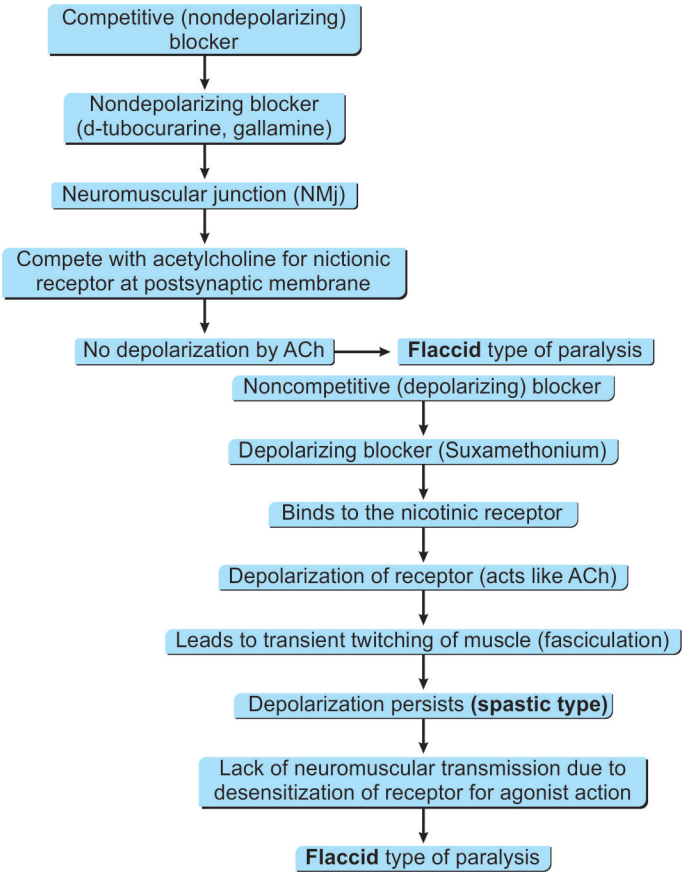
Definition

Neuromuscular blockers block the transmission at the neuromuscular junction of somatic nerves and skeletal muscles.

Classification



Mechanism of action



General features

1. All nondepolarizing blockers have to be given IV.
2. Their onset of action is quick, within a few minutes. However, the onset is quickest with rocuronium (1–2 minutes).
3. March of paralysis with nondepolarizing blockers fast response muscles like those of face and then of fingers are earliest to be paralyzed, afterwards trunk and limb muscles, Diaphragm is the last muscles to be paralyzed.
4. Need of Neostigmine in many (but not in all) nondepolarizing blockers after the operation is over, Neostigmine may be given to terminate the effects of the blocker (particularly on the diaphragm).
5. Histamine release d-TC can cause good deal of histamine release—This is not due to any allergy or immune reaction, rather it is a case of histamine liberation. Histamine can cause fall of BP.
6. Ganglion blocking d-TC can block the Nn of AChR in the ganglia.

7. Blood pressure—Blood pressure can fall due to (a) ganglion blocking (b) histamine release (c) lack of contraction of skeletal muscle.

Clinical uses

1. Neuromuscular blockers are used to produce skeletal muscle relaxation during surgical operations.
2. They are used to control convulsion in epilepsy or convulsion due to local anesthetics.

Drug interaction

1. Neostigmine, a cholinesterase inhibitor cancels the effects of these blockers.

Explanation:

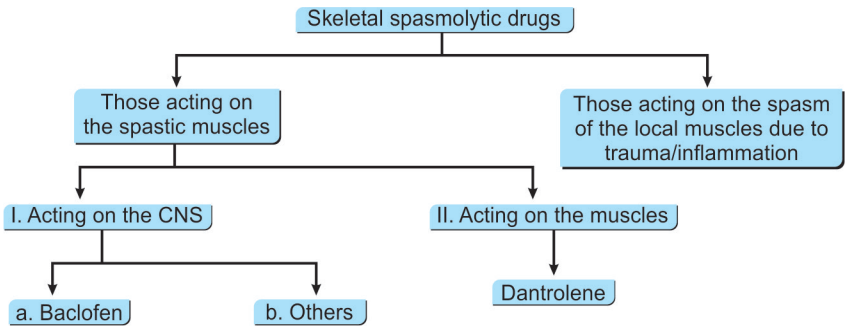
   a. When histamine release due to neuromuscular blocker is feared, there injection of antihistamine should be made sufficiently in advance.
   b. Where reversal of the blocker is needed (for fear of death due to respiratory, i.e. diaphragmatic paralysis, particularly in the recovery room) neostigmine injection should be made. Neostigmine is an anti-AChE drug causing increased availability of the ACh (thus reversing the effect of blockers) in the neuromuscular junction.

2. Aminoglycoside antibiotics augments the effects of these drugs.
3. Many anesthetic agents like halothane, nitrous oxide, notably Isoflurane increase the effect of these drugs.

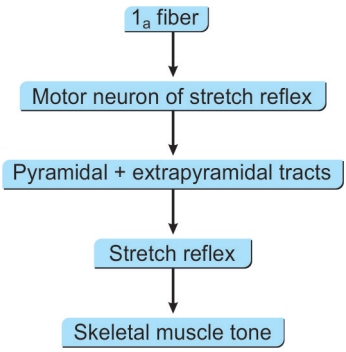
Drugs which removes skeletal muscle spasm

- Classification
- Stretch reflex
- Spasticity
- Excitation—Contraction coupling
- Mechanism of action
- Uses.

Classification



Stretch reflex



Spasticity

The term spasticity means a condition characterized by—

1. Skeletal muscle rigidity.
2. + ve Babinski's sign.
3. Exaggerated tendon jerks.
4. Paralysis/paresis of the effected muscle.

Spasticity is usually seen in upper motor neuron paralysis, i.e. Following CVA. In spasticity, the rigidity occurs because of abnormal functioning of upper motor neuron. These abnormally functioning tracts cause alteration of the activity of basic stretch reflex.

Excitation-contraction coupling

When the motor nerve supplying the skeletal muscle is excited, it (= motor nerve) develops an action potential (AP) ultimately this leads to the "excitation," i.e. development of AP in the muscle fiber, this AP in the muscle fiber membrane cause release of Ca^{++} ions from the sarcoplasmic reticulum the released Ca^{++} ultimately cause "contraction" of the muscle.

Therefore, the linking material between the excitation and contraction is Ca^{++} ions.

Foot notes: 1. Pyramidal tract—Extrapyramidal tracts are within the CNS.
2. Rigidity of parkinsonism is not spasticity. So drugs mentioned above should not be used in rigidity of parkinsonism.

Mechanism of action

Dantrolene is a hydantoin derivative. It prevents the release of calcium ion that follows the development of muscle excitation, i.e. it prevents the excitation contraction coupling.

Uses

1. In addition to depressing skeletal muscle, depresses slightly the cardiac and the smooth muscle

2. It is used in spastic rigidity
3. It is also used in malignant hyperthermia.

PRESCRIPTION WRITING

- Definition
- Preconditions
- Samples.

Definition

A prescription is the clinician's (doctor's) written order for the pharmacist, nurses and the patient. A prescription should be rational and the clinician should, before prescribing, satisfy the following preconditions:

Preconditions

1. **Make a diagnosis**: If a definitive diagnosis cannot be made, make a tentative diagnosis. However, in some cases, no diagnosis or even tentative diagnosis can be made and a prescription for symptomatic relief has to be made. However, no drug should be prescribed merely to satisfy the patient.
2. **Make a choice of the drug**: Some drugs are contraindicated in pregnancy lactation, some others in particular patients. So, for the same disease, different persons may require different drugs.
3. **Therapeutic goal should be selected**: In a diabetic patient requiring insulin, it may be ideal to give insulin three or four times a day and to keep blood sugar level almost normal but if the patient develops repeated hypoglycemic shock and anginal pain during the hypoglycemic episodes, it might be better to revise the therapeutic goal and to give two insulin injections a day. However, ordinarily, the therapeutic goal should aim to give possible maximal benefit, to the patient.
4. **Doses must be appropriate**: This is an extremely important issue. Overdose may be dangerous but under dose also is bad. In the same disease same drug may have to be given in a different dosing regimen in different patient (e.g. in a chronic renal failure case, many drugs have to be given in lower doses).
5. **Prior investigation for possible side effects should be made**: For example, before prescribing Metformin or Ramipril, serum creatinine values should be checked—If serum creatinine values is too high, these drugs should not be prescribed.

Sample

1. Name, professional qualification, address, telephone no. and registration number of the doctor
2. Date .....
3. Name, age, sex and address of the patient
4. R_x
5. Name (proprietary and official) of the drug, strength of the drug and quantity to be taken
6. Quantity to be served by the pharmacist
7. Direction regarding using
8. Caution if any
9. Whether the patient has to report further
10. Signature of the doctor

Pharmacotherapy of some infections

- **Salmonella infections**: Common diseases due to salmonella infections are—
  1. Enteric fever
  2. Gastroenteritis
  3. Septicemia
  4. Some asymptomatic carriers.
- **Enteric fever**: Theoretically following drugs can be used
  1. Ciprofloxacin – 500 mg 12 hourly
  2. Cotrimoxazole – 480 mg 12 hourly
  3. Amoxicillin – 750 mg 4 times a day
  4. Chloramphenicol – 500 mg 4 times a day.

  Treatment to be continued for 14 days.
- **Food poisoning**: Food poisoning may be due to micro-organisms or other than micro-organism. Common bacteria producing food poisoning include
  1. Salmonella (other than S. typhi)
  2. Campylobacter and so on.

  Treatment of food poisoning includes—
  1. Fluid and electrolyte correction
  2. Bowel sedation by Loperamide/Codeine – But only in nonmild cases and not before full one day after the onset of diarrhea.
  3. In nonmild cases particularly in salmonella infections, Ciprofloxacin.
- **Shigellosis**

  Treatment includes—
  1. Fluid or semifluid roughage-free diet
  2. ORS therapy—However, in severe cases IV fluid may be necessary.
  3. Excepting very mild cases no Loperamide/Codeine type of drugs.
  4. Antibiotics are generally not needed.
  5. If given, Ciprofloxacin 500 mg 12 hourly.

- **Cholera**: Fluid and electrolyte replacement is the mainstay of treatment. Fluid should be given by IV route. A 3 day course of tetracycline (250 mg 6 hourly) is to be given.
- **Common cold**: In uncomplicated cases, no antibiotic is necessary. Treatment is only symptomatic—
  1. Paracetamol 0.5 to 1 gm 8 hourly.
  2. Nasal decongestant if nasal congestion is marked, Xylometazoline nasal drop for only a few days.
- **Acute sinusitis**: Acute sinusitis is often a result of virus infection of upper respiratory tract on which bacterial (streptococcus/*H. influenzae/B. catarrhalis*) infection has superimposed.
- **Measures**
  1. Nasal decongestants (Xylometazoline) to ensure drainage of the sinus.
  2. Antibiotics – To tackle the bacteria Amoxicillin – Clavulanic acid type of drug may have to be used.
- **Chronic sinusitis**
  1. Collect discharge from the inflamed sinus and test for bacterial identity and sensitivity → only then select the antibiotic.
  2. Remove underlying pathology (polyp/septal deviation) if any.
  3. Do not use antihistamine.
- **Otitis media**: This is usually a result of virus infection on which bacterial infection has super imposed. Bacteria are same as those of acute sinusitis.
  Treatment includes antibiotics (same as in acute sinusitis).
- **Pneumonia**: Two varieties of pneumonia—
  1. Community acquired pneumonia (CAP)
  2. Hospital acquired pneumonia (HAP)

IMMUNOSUPPRESSANTS

- Use
- Drugs

Use

The major use of immunosuppressants are—
1. In prevention of rejection in organ transplants
2. Autoimmune disorders. However, they are used by superspecialists.

Drugs

These include—
1. Glucocorticosteroids
2. Cyclosporine
3 Cyclophosphamide

4. Azathioprine and Mycophenolate mofetil
5. Antilymphocytic serum
6. Rho(D) immunoglobulin.

1. **Glucocorticosteroids**: They cause—
   a. A reduction of blood lymphocyte counts
   b. Reduction of endogenous proinflammatory materials
   c. Reduction of circulating IgGs.

As immunosuppressants they are used in—
   a. Autoimmune disorders
   b. After organ transplants
   c. Rarely in rheumatoid arthritis
   d. In bronchial asthma (acts as anti-inflammatory agent).

2. **Cyclosporine**: It is a derivative of fungus, is an antibiotic. Its suppresses B and T lymphocyte. Clinically, it is used in combination with glucocorticosteroids to prevent graft rejection after organ transplant.

MANAGEMENT OF

- Erectile dysfunction
- Osteoporosis
- Obesity.

Erectile Dysfunction

- Definition
- Causes
- Incidence
- Treatment
- Mechanism of penile erection and role of PDE-5.

Definition

Inability to maintain penile erection for the successful performance of sexual activity.

Causes

Both organic and psychogenic.

Incidence

ED is estimated to affect upto thirty million man in the United States.

Treatment

Phosphodiesterase (PDE) inhibitors are now considered to be first-line therapy for man with ED.

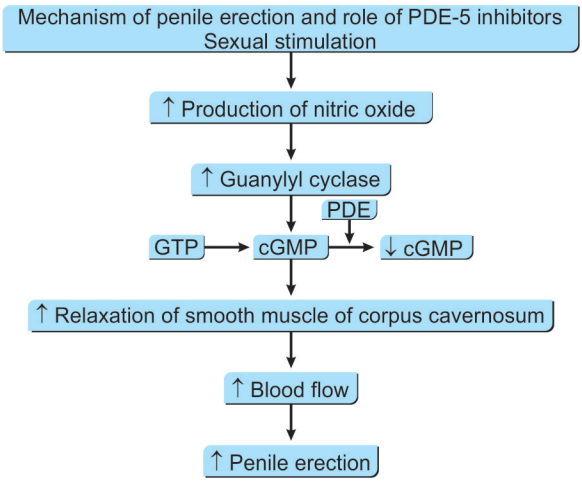
Drugs

1. Sildenafil
2. Vardenafil
3. Tadalafil.

PDE-5 Inhibitors

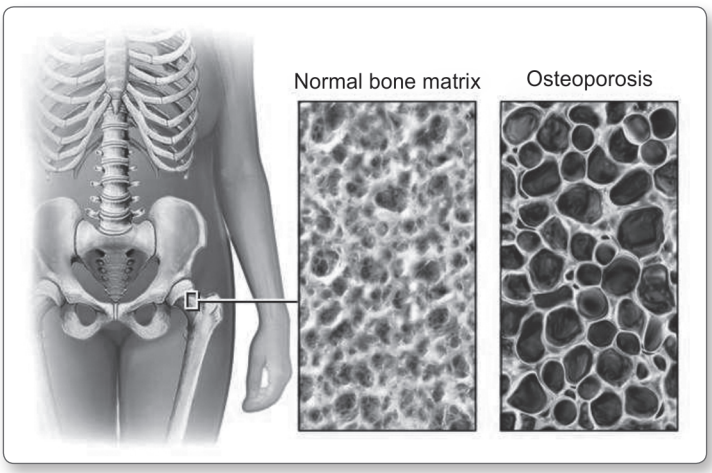
PDE at least eleven isozymes of PED have been characterized.

Mechanism of penile erection and role of PDE-5 inhibitors



- PDE-5 causes the breakdown of cGMP so penile erection is not maintained. On the otherhand PDE-5 inhibitors are indicated for the treatment of ED due to organic or psychogenic causes.

Osteoporosis



- Definition
- Morbidity
- Management.

Definition

Skeletal fragility due to progressive loss of bone mass.

Morbidity

It is characterized by frequent bone fractures, which are a major cause of disability among the elderly.

Management

a. Nondrug measure
b. Drug measure.

a. Nondrug measure

i. Diet adequate in calcium and vitamin D
ii. Weight bearing exercise
iii. Cessation of smoking
iv. Avoidance of glucocorticosteroids.

b. Drug measure

i. Bisphosphonates: The bisphosphonates decrease osteoclastic bone resorption, via several mechanisms, including—1. inhibition of the osteoclastic proton pump necessary for dissolution of hydroxyapatite, 2. decrease in osteoclastic formation/activation, and 3. increased osteoclastic apoptosis (programmed cell death).
ii. Teriparatide: It increases spinal bone density and decreases the risk of vertebral fracture. It is the first approved treatment for osteoporosis that stimulates bone formation.
iii. Selective estrogen receptor modulators (SERMs): They prevents osteoporosis and reduces the risk of hip fracture.
iv. Calcitonin: It reduces bone resorption and imporves bone architecture, relieves pain, and increases function. Unfortunately, tolerance occurs with continuous use.

Obesity

Two classes of drug are used in treating obesity: the anorexiants (appetite suppressants) Phentermine or Sibutramine and a lipase inhibitor, Orlistat.

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