LECTURE NOTES

For Health Science Students

Pharmacology

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INTRODUCTION

Pharmacology is a medical science that forms a backbone of the medical profession as drugs form the corner stone of therapy in human diseases. Therefore, it is of utmost importance to describe the pharmacological basis of therapeutics in order to maximize the benefits and minimize the risks of drugs to recipients. This lecture note on pharmacology is primarily a note for undergraduate health science students such as health officer, nursing, midwifery and laboratory technology students. However, other health professionals whose career involves drug therapy or related aspects should also find much of the material relevant.

The goal is to empower the practitioner through an understanding of the fundamental scientific principles of pharmacology. The effects of prototypical drugs on physiological and pathophysiological processes are clearly explained to promote understanding. Other related drugs are touched briefly. The selection of the drugs is based on the national drugs list for Ethiopia and on the accumulated experience of teaching pharmacology to many health profession students.

The chapters open with a list of objectives to guide the reader, and most end with questions which challenge the reader's understanding of the concepts covered with in the chapter. Most sections have an introduction that provides an overview of the material to be covered.

Readers are encouraged to refer the references mentioned for further information and we hope that this material will be a valuable companion in our pursuit of a fundamental understanding in a most fascinating area of clinical knowledge, pharmacology.

The Authors

April 2004:

Table of Contents

List of Abbrevations

ACE=	angiotensin converting enzyme
ACH=	Acetylcholine
ACTH=	Adrenocorticotropic hormone
AIDS=	Acquired Immuno deficiency syndorme
ANS=	Autonomic nervous system
B.C.G vaccine=	Bacille Calmette-Guerin Vaccine
CAMP=	Cyclic adenosine Monoposphate
CHO=	Carbohydrate
CMS=	Cytomegalovirus
CNS=	Central nervous system
CSF=	Cerebrospinal fluid
CTZ=	Chemoceptor trigger zone
CVS=	Cardiovascular system
DKA =	Diabetic ketoacidosis
DNA=	Deoxyribonucleic acid
EBV=	Epstein-barr virus
FSH=	Follicle Stimulating hormone
GABA=	Gamma amino butyric acid
GIT=	Gastrointestinal Tract
HBV=	Hepatitis B virus
HDL=	Hgh Density lipoproteins
HHV=	Human Herpes Virus
HIV=	Human Immunodeficiency viru
HSV=	Herpes simplex virus
5-HT=	5-Hydroxytryptamine
IDDM=	Insulin dependent Diabetes Mellitus
IM=	Intramusular
INH=	Isoniazid

CHAPTER ONE

GENERAL PHARMACOLOGY

Learning Objectives

At the end of this chapter the student will be able to:

1. Define various terminologies used in Pharmacology.
2. Know about nature and sources of drugs.
3. Understand pharmacodynamics like mechanism of drug action, dose relation ship and pharmacokinetics like absorption, distribution, metabolism and excretion (ADME) of drugs.
4. Understand theoritical pharmacokinetics like half-life, order of kinetics, steady state plasma concentration.
5. Understand drug safety and effectiveness like factors affecting drug action and adverse drug reactions.
6. Understand new drug development and evaluation.

I. Introduction to Pharmacology

A. Definitions:

1. **Pharmacology:** Pharmacology is the study of interaction of drugs with living organisms. It also includes history, source, physicochemical properties, dosage forms, methods of administration, absorption, distribution mechanism of action, biotransformation, excretion, clinical uses and adverse effects of drugs.
2. **Clinical Pharmacology:** It evaluate the pharmacological action of drug preferred route of administration and safe dosage range in human by clinical trails.
3. **Drugs**: Drugs are chemicals that alter functions of living organisms. Drugs are generally given for the diagnosis, prevention, control or cure of disease.
4. **Pharmacy**: It is the science of identification, selection, preservation, standardisation, compounding and dispensing of medical substances.

5. **Pharmacodynamics:** The study of the biological and therapeutic effects of drugs (i.e, "what the drug does to the body").
6. **Pharmacokinetics:** Study of the absorption, distribution metabolism and excretion (ADME) of drugs ("i.e what the body does to the drug").
7. **Pharmacotherapeutics:** It deals with the proper selection and use of drugs for the prevention and treatment of disease.
8. **Toxicology:** It's the science of poisons. Many drugs in larger doses may act as poisons. Poisons are substances that cause harmful, dangerous or fatal symptoms in living substances.
9. **Chemotherapy:** It's the effect of drugs upon microorganisms, parasites and neoplastic cells living and multiplying in living organisms.
10. **Pharmacopoeia:** An official code containing a selected list of the established drugs and medical preparations with descriptions of their physical properties and tests for their identity, purity and potency e.g. Indian Pharmacopoeia (I.P), British Pharmacopoeia (B.P).

B. Drugs are obtained from:

1. **Minerals:** Liquid paraffin, magnesium sulfate, magnesium trisilicate, kaolin, etc.
2. **Animals:** Insulin, thyroid extract, heparin and antitoxin sera, etc.
3. **Plants:** Morphine, digoxin, atropine, castor oil, etc.
4. **Synthetic source:** Aspirin, sulphonamides, paracetamol, zidovudine, etc.
5. **Micro organisms:** Penicillin, streptomycin and many other antibiotics.
6. **Genetic engineering:** Human insulin, human growth hormone etc.

Out of all the above sources, majority of the drugs currently used in therapeutics are from synthetic source.

II. Pharmacodynamics

Involves how the drugs act on target cells to alter cellular function.

A. Receptor and non-receptor mechanisms: Most of the drugs act by interacting with a cellular component called receptor. Some drugs act through simple physical or chemical reactions without interacting with any receptor.

- Receptors are protein molecules present either on the cell surface or with in the cell e.g. adrenergic receptors, cholinoceptors, insulin receptors, etc.
- The endogenous neurotransmitters, hormones, autacoids and most of the drugs produce their effects by binding with their specific receptors.
- Aluminium hydroxide and magnesium trisilicate, which are used in the treatment of peptic ulcer disease act by non-receptor mechanism by neutralizing the gastric acid.

Many drugs are similar to or have similar chemical groups to the naturally occurring chemical and have the ability to bind onto a receptor where one of two things can happen- either the receptor will respond or it will be blocked.

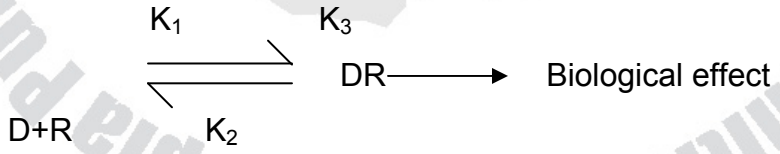
A drug, which is able to fit onto a receptor, is said to have affinity for that receptor. Efficacy is the ability of a drug to produce an effect at a receptor. An agonist has both an affinity and efficacy whereas antagonist has affinity but not efficacy or intrinsic activity.

When a drug is able to stimulate a receptor, it is known as an agonist and therefore mimics the endogenous transmitter.

When the drug blocks a receptor, it is known as antagonist and therefore blocks the action of the endogenous transmitter (i.e. it will prevent the natural chemical from acting on the receptor).

However, as most drug binding is reversible, there will be competition between the drug and the natural stimulus to the receptor.

The forces that attract the drug to its receptor are termed chemical bonds and they are (a) hydrogen bond (b) ionic bond (c) covalent bond (d) Vander waals force. Covalent bond is the strongest bond and the drug-receptor complex is usually irreversible.



Where D = Drug, R= receptor DR= Drug receptor complex (affinity)

K_1 = association constant

K_2 = dissociation constant

K_3 = intrinsic activity

When first messengers like neurotransmitters, hormones, autacoids and most of drugs bind with their specific receptors, the drug receptor complex is formed which subsequently causes the

synthesis and release of another intracellular regulatory molecule termed as second messengers e.g. cyclic AMP, calcium, cyclic GMP, inositol triphosphate (IP_3), diacylglycerol and calmodulin which in turn produce subcellular or molecular mechanism of drug action.

B. Site of drug action:

- A drug may act:

(i) Extracellularly e.g: osmotic diuretics, plasma expanders.

(ii) On the cell surface e.g.: digitalis, penicillin, catecholamines

(iii) Inside the cell e.g.: anti-cancer drugs, steroid hormones.

C. Dose Response relationship

The exact relationship between the dose and the response depends on the biological object under observation and the drug employed.

When a logarithm of dose as abscissa and responses as ordinate are constructed graphically, the "S" shaped or sigmoid type curve is obtained.

The lowest concentration of a drug that elicits a response is minimal dose, and the largest concentration after which further increase in concentration will not change the response is the maximal dose.

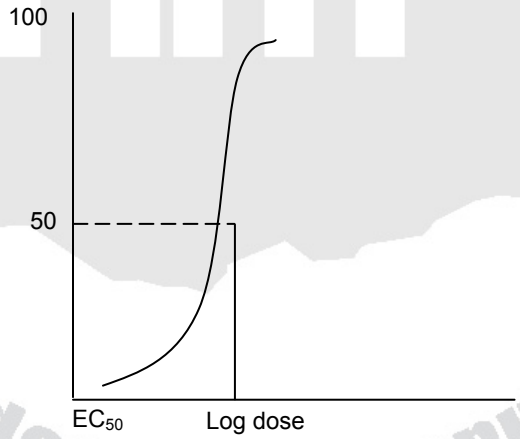


Fig 1.1: Log dose response relationship.

1. Graded dose effect: As the dose administered to a single subject or tissue increases, the pharmacological response also increases in graded fashion up to ceiling effect.

- It is used for characterization of the action of drugs. The concentration that is required to produce 50 % of the maximum effect is termed as EC_{50} or ED_{50}.

2. Quantal dose effect: It is all or none response, the sensitive objects give response to small doses of a drug while some will be resistant and need very large doses. The quantal dose-effect curve is often characterized by stating the median effective dose and the median lethal dose.

Median lethal dose or LD_{50}: This is the dose (mg/kg), which would be expected to kill one half of a population of the same species and strain.

Median effective dose or ED_{50}: This is the dose (mg/kg), which produces a desired response in 50 per cent of test population.

Therapeutic index: It is an approximate assessment of the safety of the drug. It is the ratio of the median lethal dose and the median effective dose. Also called as therapeutic window or safety.

$$\text{Herapeutic index (T. I)} = \frac{LD_{50}}{ED_{50}}$$

The larger the therapeutic index, the safer is the drug. Penicillin has a very high therapeutic index, while it is much smaller for the digitalis preparation.

D. Structural activity relationship

The activity of a drug is intimately related to its chemical structure. Knowledge about the chemical structure of a drug is useful for:

(i) Synthesis of new compounds with more specific actions and fewer adverse reactions
(ii) Synthesis of competitive antagonist and
(iii) Understanding the mechanism of drug action.

Slight modification of structure of the compound can change the effect completely.

III. Pharmacokinetics

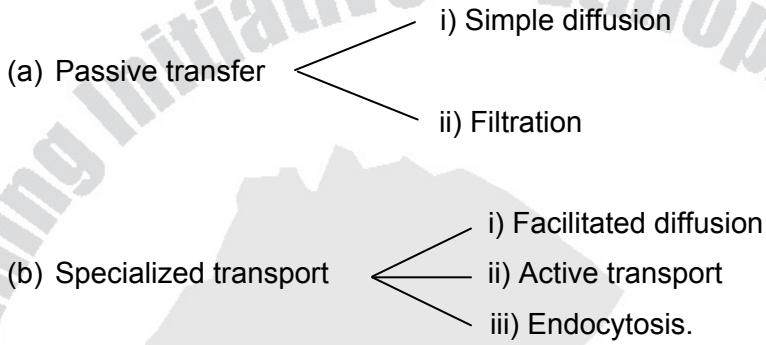
Pharmacokinetics deals with the absorption, distribution, metabolism and excretion drugs in the body.

A. Biotransport of drug: It is translocation of a solute from one side of the biological barrier to the other.

1. Structure of biological membrane: The outer surface of the cell covered by a very thin structure known as plasma membrane. It is composed of lipid and protein molecules. The

membrane proteins have many functions like (a) contributing structure to the membrane (b) acting as enzyme (c) acting as carrier for transport of substances (d) acting as receptors. The plasma membrane is a semipermeable membrane allowing certain chemical substances to pass freely e.g. it allows water, glucose, etc. but it won't allow sucrose until it is converted into glucose and fructose.

2. Passage of drug across membrane.



(a) ***i) Simple diffusion:*** Movement of a solute through a biological barrier from the phase of higher concentration to phase of lower concentration. No need of energy e.g. highly lipid soluble drugs.

ii) Filtration: Is the process by which water soluble drug of relatively low molecular weight crosses the plasma membrane through pores as a result of hydrodynamic pressure gradient across the membrane e.g. urea and ethylene glycol.

(b) ***i) Facilitated diffusion***: It means the passage of drug across the biological membrane along the concentration gradient by the protein carrier mediated system also called as carrier mediated diffusion. It depends on number of carrier e.g. tetracycline, pyrimidine.

ii) Active transport: The process by which drugs pass across the biological membrane most often against their concentration gradient with the help of carriers along with the expenditure of energy e.g. alpha methyl dopa, levodopa, 5-fluoro-uracil, 5 bromouracil.

iii) Endocytosis: It is the process by which the large molecules are engulfed by the cell membrane and releases them intracellularly e.g. protein, toxins (botulinum, diphtheria)

Differences amongst different transport systems

Characteristics	Simple diffusion	Facilitated	Active transport
Incidence	Commonest	Less common	Least common
Process	Slow	Quick	Very Quick
Movement	Along concentration gradient	Along concentration gradient	Against concentration gradient
Carrier	Not needed	Needed	Needed
Energy	Not required	Not required	Required

B. Drug absorption: Absorption is the process by which the drug enters in to the systemic circulation from the site of administration through biological barrier. In case of intravenous or intra-arterial administration the drug bypasses absorption processes and it enters into the circulation directly.

1. Routes of drug administration:

a) From the alimentary tract:

(i) Buccal cavity: e.g. nitrates
(ii) Stomach: e.g. aspirin, alcohol
(iii) Intestine: e.g. most of non ionized and ionized drugs.
(iv) Rectum: e.g. rectal suppositories, bisacodyl laxatives.

Advantages of oral route: This route is safe, convenient and economical.

Disadvantages of oral route: Onset of drug action is slow, irritant drugs cannot be administered and it is not useful in vomiting and severe diarrhea, gastric acid and digestive enzymes may destroy some drugs, and water soluble drugs are absorbed poorly.

b) From the parenteral route:

(i) **Intradermal**: This is given into the layers of the skin e.g. B.C.G. vaccine
(ii) **Subcutaneous**: Non-irritant substances are given into subcutaneous tissue e.g. insulin
(iii) **Intramuscular**: Soluble substances, mild irritants, suspensions and colloids can be injected by this route. These injections can be given to deltoid or gluteal muscle. This route is one of the more common routes e.g. multivitamins, streptomycin, etc.

Advantages: rate of absorption is uniform, onset of action is faster than oral and it can be given in diarrhoea or vomiting.

Disadvantages: Pain at local site of injection, the volume of injection should not exceed 10 ml.

(iv) **Intravenous**: Drugs directly given into a vein, produce rapid action, no need of absorption as they enter directly into blood, can be given as bolus e.g. furosemide, morphine, dopamine or as continous infusion e.g. fluids during shock or dehydration.

Advantages: It can be given in large volumes, production of desired blood concentration can be obtained with a well designed dose.

Disadvantages: Drug effect cannot be halted if once the drug is injected, expertise is needed to give injection.

(v) **Intrathecal**: Injected into subarachnoid space of spinal cord e.g. spinal anaesthetics.

(vi) **Intraperitonial**: Injections given into the abdominal cavity e.g. infant saline, glucose.

(vii) **Intra-articular**: Injected directly into a joint e.g. hydrocortisone.

c) Transcutaneous route:

i) **Iontophoresis:** Galvanic current is used for bringing about the penetration of drugs into the deeper tissue e.g. salicylates.

ii) **Inunctions:** Absorbed when rubbed in to the skin e.g. nitroglycerin ointment in angina pectoris.

iii) **Jet injection:** With help of high velocity jet produced through a micro fine orifice; No need of needle and therefore painless. e.g. mass inoculation programmes.

iv) Adhesive units: A transdermal therapeutic system produce prolonged systemic effect e.g. scopolamine for motion sickness.

d) Topical/ local route:

The absorption through skin is a passive process. The absorption occurs more easily through the cell lining e.g. dusting powder, paste, lotion, drops, ointment, suppository for vagina and rectum.

e) Inhalation:

Drugs may be administered as dry powders, and nebulized particles when sprayed as fine droplets get deposited over the mucous membrane producing local effects and may be

absorbed for systemic effects e.g. salbutamol spray used in bronchial asthma and volatile general anaesthetics.

2. Bioavailability:

It is the rate and amount of drug that is absorbed from a given dosage form and reaches the systemic circulation following non-vascular administration. When the drug is given IV, the bioavailability is 100%. It is important to know the manner in which a drug is absorbed. The route of administration largely determines the latent period between administration and onset of action. Drugs given by mouth may be inactive for the following reasons:

a) Enzymatic degradation of polypeptides within the lumen of the gastrointestinal tract e.g. insulin, ACTH.

b) Poor absorption through gastrointestinal tract e.g. aminoglycoside antibiotic.

c) Inactivation by liver e.g. testosterone during first passage through the liver before it reaches systemic circulation.

3. Factors affecting drug absorption and bioavailability:

a) Physico-chemical properties of drug

b) Nature of the dosage form

c) Physiological factors

d) Pharmacogenetic factors

e) Disease states.

a) Physico-chemical properties of drug:

i) **Physical state**: Liquids are absorbed better than solids and crystalloids absorbed better than colloids.

ii) **Lipid or water solubility**: Drugs in aqueous solution mix more readily than those in oily solution. However at the cell surface, the lipid soluble drugs penetrate into the cell more rapidly than the water soluble drugs.

iii) **Ionization:** Most of the drugs are organic compounds. Unlike inorganic compounds, the organic drugs are not completely ionized in the fluid. Unionized component is predominantly lipid soluble and is absorbed rapidly and an ionized is often water soluble component which is absorbed poorly. Most of the drugs are weak acids or weak bases. It may be assumed for all practical purposes, that the mucosal lining of the G.I.T is impermeable to the ionized form of a weak organic acid or a weak organic base. These drugs exist in two forms.

Acidic drugs: rapidly absorbed from the stomach e.g. salicylates and barbiturates.

Basic drugs: Not absorbed until they reach to the alkaline environment i.e. small intestine when administered orally e.g. pethidine and ephedrine.

b) Dosage forms:

i) **Particle size:** Small particle size is important for drug absorption.

Drugs given in a dispersed or emulsified state are absorbed better e.g. vitamin D and vitamin A.

ii) **Disintegration time and dissolution rate.**

Disintegration time: The rate of break up of the tablet or capsule into the drug granules.
Dissolution rate: The rate at which the drug goes into solution.

iii) **Formulation:** Usually substances like lactose, sucrose, starch and calcium phosphate are used as inert diluents in formulating powders or tablets. Fillers may not be totally inert but may affect the absorption as well as stability of the medicament. Thus a faulty formulation can render a useful drug totally useless therapeutically.

c) Physiological factors:

i) **Gastrointestinal transit time:** Rapid absorption occurs when the drug is given on empty stomach. However certain irritant drugs like salicylates and iron preparations are deliberately administred after food to minimize the gastrointestinal irritation. But some times the presence of food in the G.I tract aids the absorption of certain drugs e.g. griseofulvin, propranolol and riboflavin.

ii) **Presence of other agents:** Vitamin C enhances the absorption of iron from the G.I.T. Calcium present in milk and in antacids forms insoluble complexes with the tetracycline antibiotics and reduces their absorption.

iii) **Area of the absorbing surface and local circulation:** Drugs can be absorbed better from the small intestine than from the stomach because of the larger surface area of the former. Increased vascular supply can increase the absorption.

iv) **Enterohepatic cycling:** Some drugs move in between intestines and liver before they reach the site of action. This increases the bioavailability e.g. phenolphthalein.

v) **Metabolism of drug/first pass effect:** Rapid degradation of a drug by the liver during the first pass (propranolol) or by the gut wall (isoprenaline) also affects the bioavailability. Thus a drug though absorbed well when given orally may not be effective because of its extensive first pass metabolism.

d) Pharmacogenetic factors:

Individual variations occur due to the genetically mediated reason in drug absorption and response.

e) Disease states:

Absorption and first pass metabolism may be affected in conditions like malabsorption, thyrotoxicosis, achlorhydria and liver cirrhosis.

4. Bioavailability curves

Single dose bioavailability test involves an analysis of plasma or serum concentration of the drug at various time intervals after its oral administration and plotting a serum concentration time curve.

$$\text{Bioavailability (F)} = \frac{\text{AUC after oral dose}}{\text{AUC after I.V. dose}}$$

AUC= Area under curve – which provides information about the amount of drug absorbed.

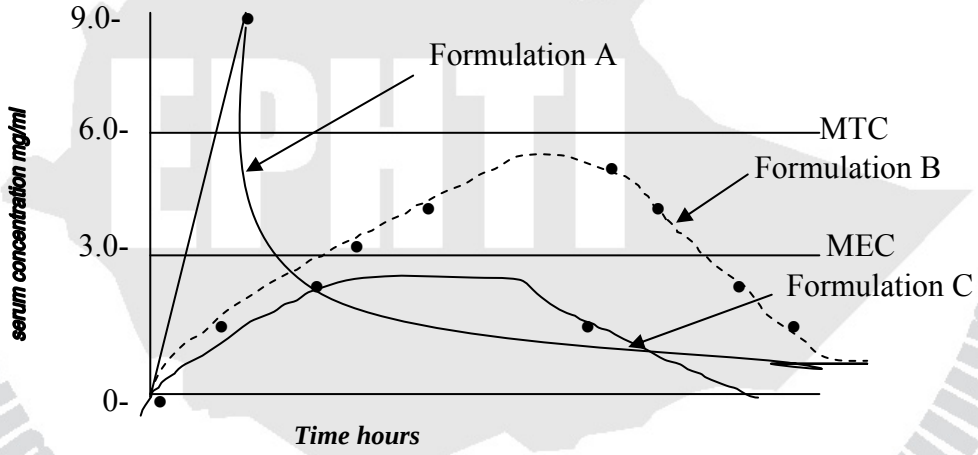


Fig 1.2 : The plasma drug level curves following administration of three formulations (A, B and C) of the same basic drug.

MTC: Minimum toxic concentration

MEC: Minimum effective concentration

Formulation A = would produce quick onset and short duration of action, produce toxic effects.

Formation B = Effect would last much longer and nontoxic

Formulation C = gives inadequate plasma level so therapeutically ineffective.

C) Distribution of drugs

1. **Definition**: Penetration of a drug to the sites of action through the walls of blood vessels from the administered site after absorption is called drug distribution. Drugs distribute through various body fluid compartments such as (a) plasma (b) interstitial fluid compartment (c) trans-cellular compartment.

Apparent Volume of distribution (VD): The volume into which the total amount of a drug in the body would have to be uniformly distributed to provide the concentration of the drug actually measured in the plasma. It is an apparent rather than real volume.

Factors determining the rate of distribution of drugs:

1**. Protein binding of drug:** A variable and other significant portion of absorbed drug may become reversibly bound to plasma proteins. The active concentration of the drug is that part which is not bound, because it is only this fraction which is free to leave the plasma and site of action. (a) Free drug leave plasma to site of action (b) binding of drugs to plasma proteins assists absorption (c) protein binding acts as a temporary store of a drug and tends to prevent large fluctuations in concentration of unbound drug in the body fluids (d) protein binding reduces diffusion of drug into the cell and there by delays its metabolic degradation e.g. high protein bound drug like phenylbutazone is long acting.

   Low protein bound drug like thiopental sodium is short acting.

2**. Plasma concentration of drug (PC):** It represents the drug that is bound to the plasma proteins (albumins and globulins) and the drug in free form. It is the free form of drug that is distributed to the tissues and fluids and takes part in producing pharmacological effects.

The concentration of free drug in plasma does not always remain in the same level e.g.

i) After I.V. administration plasma concentration falls sharply

ii) After oral administration plasma concentration rises and falls gradually.

iii) After sublingual administration plasma concentration rise sharply and falls gradually.

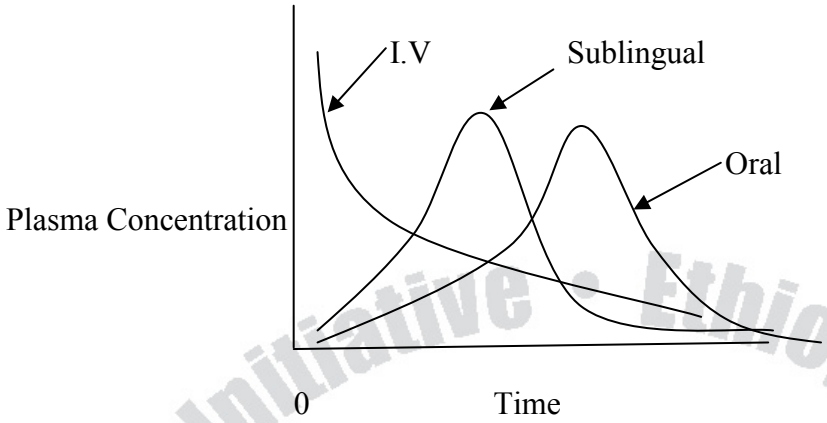


Fig 1.3: Plasma concentration of drug after different routes of administration.

3. **Clearance:** Volume of plasma cleared off the drug by metabolism and excretion per unit time. Protein binding reduces the amount of drug available for filtration at the glomeruli and hence delays the excretion, thus the protein binding reduces the clearance.

4. **Physiological barriers to distribution**: There are some specialized barriers in the body due to which the drug will not be distributed uniformly in all the tissues. These barriers are:
   a) **Blood brain barrier (BBB)** through which thiopental sodium is easily crossed but not dopamine.
   b) **Placental barrier:** which allows non-ionized drugs with high lipid/water partition coefficient by a process of simple diffusion to the foetus e.g. alcohol, morphine.

5. **Affinity of drugs to certain organs:** The concentration of a drug in certain tissues after a single dose may persist even when its plasma concentration is reduced to low. Thus the hepatic concentration of mepacrine is more than 200 times that of plasma level. Their concentration may reach a very high level on chronic administration. Iodine is similarly concentrated in the thyroid tissue.

D. Metabolism of drugs:

Drugs are chemical substances, which interact with living organisms and produce some pharmacological effects and then, they should be eliminated from the body unchanged or by changing to some easily excretable molecules. The process by which the body brings about changes in drug molecule is referred as drug metabolism or biotransformation.

Enzymes responsible for metabolism of drugs:

a) **Microsomal enzymes:** Present in the smooth endoplasmic reticulum of the liver, kidney and GIT e.g. glucuronyl transferase, dehydrogenase , hydroxylase and cytochrome P450

b) **Non-microsomal enzymes:** Present in the cytoplasm, mitochondria of different organs. e.g. esterases, amidase, hydrolase.

Types of biotransformation: The chemical reactions involved in biotransformation are classified as phase-I and phase – II (conjugation) reactions. In phase-I reaction the drug is converted to more polar metabolite. If this metabolite is sufficiently polar, then it will be excreted in urine. Some metabolites may not be excreted and further metabolised by phase –II reactions.

Phase-I: Oxidation, reduction and hydrolysis.

Phase-II: Glucuronidation, sulfate conjugation, acetylation, glycine conjugation and methylation reactions.

Phase - I reactions

a) **Oxidation:** Microsomal oxidation involves the introduction of an oxygen and/or the removal of a hydrogen atom or hydroxylation, dealkylation or demethylation of drug molecule e.g. conversion of salicylic acid into gentisic acid.

b) **Reduction:** The reduction reaction will take place by the enzyme reductase which catalyze the reduction of azo (-N=N-) and nitro ($-NO_2$) compounds e.g. prontosil converted to sulfonamide.

c) **Hydrolysis:** Drug metabolism by hydrolysis is restricted to esters and amines (by esterases and amidases) are found in plasma and other tissues like liver. It means splitting of drug molecule after adding water e.g. pethidine undergoes hydrolysis to form pethidinic acid. Other drugs which undergo hydrolysis are atropine and acetylcholine.

Phase - II reactions (conjugation reactions):

This is synthetic process by which a drug or its metabolite is combined with an endogenous substance resulting in various conjugates such as glucoronide, ethereal sulfate, methylated compound and amino acid conjugates.

Glucuronide conjugation: It is the most common and most important conjugation reaction of drugs. Drugs which contain

a) Hydroxyl, amino or carboxyl group undergo this process e.g. phenobarbitone.

b) Sulfate conjugation: Sulfotransferase present in liver, intestinal mucosa and kidney, which transfers sulfate group to the drug molecules e.g. phenols, catechols, etc.

c) Acetyl conjugation: The enzyme acetyl transferase, which is responsible for acetylation, is present in the kupffer cells of liver. Acetic acid is conjugated to drugs via its activation by CoA to form acetyl CoA. This acetyl group is then transferred to-NH_2 group of drug e.g. dapsone, isoniazid.

d) Glycine conjugation: Glycine conjugation is characteristic for certain aromatic acids

e.g. salicylic acid, isonicotinic acid, p-amino salicylic acid. These drugs are also metabolized by other path ways.

e) Methylation: Adrenaline is methylated to metanephrine by catechol-o-methyl transferase.

Here the source of methyl group is s – adenosyl methionine.

E. Excretion of drugs

Excretion of drugs means the transportation of unaltered or altered form of drug out of the body. The major processes of excretion include renal excretion, hepatobiliary excretion and pulmonary excretion. The minor routes of excretion are saliva, sweat, tears, breast milk, vaginal fluid, nails and hair.

The rate of excretion influences the duration of action of drug. The drug that is excreted slowly, the concentration of drug in the body is maintained and the effects of the drug will continue for longer period.

Different routes of drug excretion

a) **Renal excretion:** A major part of excretion of chemicals is metabolically unchanged or changed. The excretion of drug by the kidney involves.

i) Glomerular filtration
ii) Active tubular secretion
iii) Passive tubular reabsorption.

The function of glomerular filtration and active tubular secretion is to remove drug out of the body, while tubular reabsorption tends to retain the drug.

i) **Glomerular filtration:** It is a process, which depends on (1) the concentration of drug in the plasma (2) molecular size, shape and charge of drug (3) glomerular filtration rate. Only the drug which is not bound with the plasma proteins can pass through glomerulus. All the drugs which have low molecular weight can pass through glomerulus e.g. digoxin, ethambutol, etc.

In congestive cardiac failure, the glomerular filtration rate is reduced due to decrease in renal blood flow.

ii) **Active tubular secretion:** The cells of the proximal convoluted tubule actively transport drugs from the plasma into the lumen of the tubule e.g. acetazolamide, benzyl penicillin, dopamine, pethidine, thiazides, histamine.

iii) **Tubular reabsorption:** The reabsorption of drug from the lumen of the distal convoluted tubules into plasma occurs either by simple diffusion or by active transport. When the urine is acidic, the degree of ionization of basic drug increase and their reabsorption decreases. Conversely, when the urine is more alkaline, the degree of ionization of acidic drug increases and the reabsorption decreases.

b) **Hepatobiliary excretion:** the conjugated drugs are excreted by hepatocytes in the bile. Molecular weight more than 300 daltons and polar drugs are excreted in the bile. Excretion of drugs through bile provides a back up pathway when renal function is impaired. After excretion of drug through bile into intestine, certain amount of drug is reabsorbed into portal vein leading to an enterohepatic cycling which can prolong the action of drug e.g. chloramphenicol, oral estrogen are secreted into bile and largely reabsorbed and have long duration of action. Tetracylines which are excreted by biliary tract can be used for treatment of biliary tract infection.

c) **Gastrointestinal excretion:** When a drug is administered orally, a part of the drug is not absorbed and excreted in the faeces. The drugs which do not undergo enterohepatic cycle after excretion into the bile are subsequently passed with stool e.g. aluminium hydroxide changes the stool into white colour, ferrous sulfate changes the stool into black and rifampicin into orange red.

d) **Pulmonary excretion:** Drugs that are readily vaporized, such as many inhalation anaesthetics and alcohols are excreted through lungs. The rate of drug excretion through lung depends on the volume of air exchange, depth of respiration, rate of pulmonary blood flow and the drug concentration gradient.

e) **Sweat**: A number of drugs are excreted into the sweat either by simple diffusion or active secretion e.g. rifampicin, metalloids like arsenic and other heavy metals.

f) **Mammary excretion:** Many drugs mostly weak basic drugs are accumulated into the milk. Therefore lactating mothers should be cautious about the intake of these drugs because they may enter into baby through breast milk and produce harmful effects in the baby e.g.

ampicillin, aspirin, chlordiazepoxide, coffee, diazepam, furosemide, morphine, streptomycin etc.

Clearance of a drug:

It is the volume of plasma cleared of the drug by metabolism (hepatic) and excretion (renal) and other organs.

Total clearance will be calculated by $Ct = C_h + C_r + C$ others

C_t = total clearance

C_h = hepatic clearance

C_r = Renal clearance

IV. Theoretical Pharmacokinetics

Information about the time course of drug absorption, distribution and elimination (pharmacokinetics) can be expressed in mathematical terms and has contributed to our understanding and planning of drug regimens. Pharmacokinetic principles aid in the selection and adjustment of drug-dose schedules.

Half life:

Half life ($t_1/_2$) of a drug is the time taken for the concentration of drug in the blood or plasma to decline to half of original value or the amount of drug in the body to be reduced by 50%. It has two phases i.e half-life of distribution and half-life of elimination.

A half-life value can be readily determined for most drugs by administering a dose of the drug to a subject, taking blood samples at various time intervals and then assaying the samples., For example if a blood level of drug A is 8.6 mg/ml at 10 minutes and 4.3 mg/ml at 60 minutes, so the half – life of that drug is 50 minutes.

In most of the cases the rate of disappearance of a drug from the body is reflected in the rate of lowering of its plasma concentration following a single intravenous dose, the plasma concentration of the drug is focused to fall exponentially. With drugs whose elimination is exponential, the biological half – life is independent of the dose, the route of administration and the plasma concentration. It depends on VD as well as on the metabolism and renal excretion of the drug.

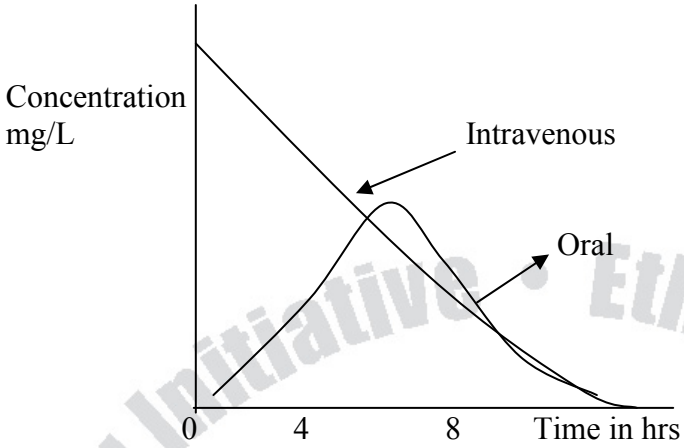


Fig 1.4: Exponential curves of plasma concentration following oral and intravenous drug administration.

Order of kinetics

Drugs are used for the treatment of diseases but the modes of administration of drugs are different. For example atenolol is administered once daily where as paracetamol needs 3-4 times administration daily. Morphine is more effective in intramuscular route, and insulin is in subcutaneous route. The mode of administration is designed on the basis of absorption, distribution, metabolism and excretion (ADME) of drugs. Drugs usually follow two processes for their phamacokinetic behaviour in the body. These are first order and zero order process.

First order:

This is the most common process for many drugs. The rate at which absorption, distribution, metabolism and excretion occur are proportional to the concentration of drugs i.e. constant fraction of this drug in the body disappears in each equal interval of time.

Zero order kinetic:

It is independent of the amount of drug present at the particular sites of drug absorption or elimination. Few drugs follow this process e.g. ethanol, phenytoin. Here constant amount of the drug is eliminated in each equal interval of time. On repeated administration of drug after certain stage it goes on accumulating in the body and leads to toxic reactions.

Steady state plasma concentration:

When a drug dose is given repeatedly over a given period, a steady state is eventually reached, at which point the amount of drug absorbed is in equilibrium with that eliminated from the body.

Steady state is achieved after 4 to 5 half –lives for most of the drugs which follow first order kinetics. For example a drug with half life of 6 hours will be expected to be at steady state after more than 24 hours of administration. The pattern of drug accumulation during repeated administration of drug at intervals equal to its elimination half-life.

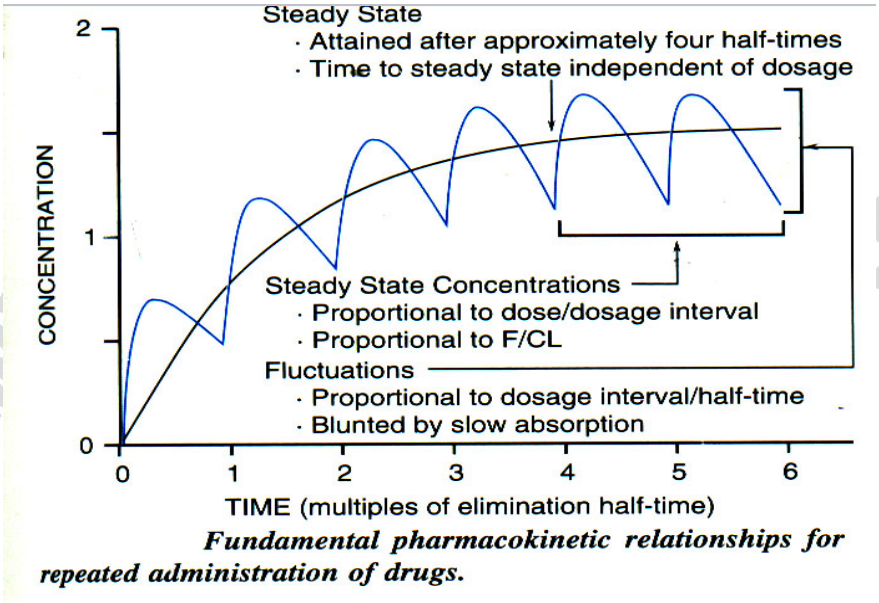


Fig 1.5: Steady state plasma concentration of a drug after repeated administrations.

For some drugs, the effects are difficult to measure, toxicity and lack of efficacy are both potential dangers, and/or the therapeutic window is narrow. In these circumstances doses must be adjusted carefully to a desired steady- state concentration by giving loading and maintenance doses.

Loading dose: The loading dose is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly.

Maintenance dose: To maintain the chosen steady-state or target concentration, the rate of drug administration is adjusted such that the rate of input equals to rate of loss.

V. Drug safety and effectiveness

A. Factors modifying the dosage and action of drugs :

Individuals differ both in the degree and the character of the response that a drug may elicit and therefore the optimum dose of a drug which produces the desired therapeutic effect varies from person to person. The important factors which influence the effect of a drug are:

1**. Drug intolerance:** It is a quantitative deviation from the anticipated response to a given dose of a drug. Thus drug intolerance is inability of the individual to tolerate a drug. It is also called as hypersusceptibility.

2. **Sex difference:** Special care should be exercised when drugs are administrated during menstruation, pregnancy and lactation.

   a) **Menstruation**: Drugs producing pelvic congestion should be avoided during menstruation e.g. drastic purgatives.

   b) **Pregnancy:** During pregnancy, the use of all drugs except those essential to maintain pregnancy should be used with caution. Drugs which may stimulate the uterine smooth muscle, are contraindicated during pregnancy. Further, many drugs administered to mother are capable of crossing the placenta and affecting the foetus. Most of drugs can produce teratogenicity when they are used in pregnancy. Teratogenicity means congenital malformation i) Drugs known to produce teratogenicity e.g thalidomide, cyclophosphamide, methotexate, tetracyclines, phenytoin, carbamazepine and progestogens. ii) drugs may be teratogenic e.g Warfarin, lithium, quinine, primaquine, trimethoprim, rifampicin, anaesthetic agents.

   c) **Breast feeding**: Nearly all agents received by mother are likely to be found in her milk and could theoretically harm the infant. Most of the lipid soluble drugs get into breast milk. Therefore the drugs, which are excreted in the milk and harm the infant health should be, avoided by breast-feeding mothers e.g. sulphonamides, tetracyclines, nalidixic acid, isoniazid, diazepam, lithium, Indomethacin, aspirin, etc.

3. **Body Weight:** The average dose is mentioned either in terms of mg per kg body weight or as the total single dose for an adult weighing between 50-100kg. However, dose expressed in this fashion may not apply in cases of excessively obese individuals or those suffering from edema, or dehydration nutritional factors can sometimes alter drug metabolizing capacity and this should be kept in mind in malnourished patients.

4**. Age:** The pharmacokinetics of many drugs changes with age. Thus gastric emptying is prolonged and the gastric pH fluctuates in neonates and infant, further the liver capacity to metabolize drugs is low, renal function is less developed and the proportion of body water is higher in the newborn and the neonates. Hence children may not react to all drugs in the same fashion as young adults. With a few exceptions, drugs are more active and more toxic in the new born than the adults.

The paediatric doses are expressed in terms of body weight (mg/kg per dose or day) or in terms of body surface area (mg/m^2per day). The body surface area can be calculated from the height and weight of the child.

Like children, old people also present problems in dosage adjustment and this may vary widely with different people. The metabolism of drugs may diminish in the elderly and the renal function declines with age. Elderly are sensitive to the drugs like hypnotics, tranquilizers, phenylbutazone, diazepam, pethidine, etc.

i) Dose adjustment on the basis of age (young's formula)

$$\frac{\text{Age in years}}{\text{Age in years} + 12} \times \text{adult dose}$$

ii) Dose adjustment on the basis of body weight (Clark s formula) (1 Kg=2.2 pounds)

$$\frac{\text{Weight of child in pound}}{150} \times \text{Adult dose}$$

e.g. A 3 year old child having body weight of 30 pound requires to administer drug X. The adult dose is 100mg. So

a) Using age of the child the dose will be

$$\frac{3}{3+12} \times 10 = \frac{3}{15} \times 100 = 20\text{mg}$$

b) Using body weight of the child it will be

$$\frac{30}{150} \times 100 = \frac{1}{5} \times 100 = 20\text{mg}$$

5. **Disease state:** Some antimicrobial agents penetrate the cerebrospinal fluid well across the normal meninges while other antimicrobials penetrate well only when the meninges are inflammed (meningitis) e.g. sulphonamides, metronidazole, chloramphenicol, isoniazid and rifampicin penetrate well through the normal meninges and other antimicrobial agents like benzyl penicillin, ampicillin, tetracycline, streptomycin, gentamicin and cephalosporin penetrate only when the meninges are inflammed.

Acute or chronic liver diseases markedly modify the rate and extent of biotransformation of drugs. The t1/2 of chlordiazepoxide and diazepam in patients with liver cirrhosis is greatly increased with corresponding prolongation of their effects.

Cardiac disease by limiting blood flow to the liver may impair disposition of those drugs whose biotransformation is flow limited e.g. imipramine, isoniazid, lignocaine, morphine and propranolol.

Similarly renal and pulmonary diseases may modify the biotransformation of drugs like insulin or isoprenaline. Excretion of drug is impaired in chronic renal disease.

6. **Pharmacogenetics:** The science pharmacogenetics is concerned with the genetically-mediated variations in drug responses. Some examples of genetically mediated variations are:

Acetylation and hydroxylation of drugs: The rate of acetylation of INH, dapsone, hydralazine procainamide and some sulfonamides is controlled by an autosomal recessive gene and the dosage of these drugs depends up on the acetylator status of individuals.

7) Drug interactions:

It is usual for patients to receive a number of drugs at the same time.

It is a phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another drug(s). A drug interaction may result in beneficial or harmful effects and may be classified into:

a) Pharmaceutical drug interactions:

Serious loss of potency can occur from incompatibility between an infusion fluid and a drug that is added to it.

For example diazepam if added to infusion fluid there will be a precipitate formation $\rightarrow$ loss of therapeutic effect.

b) Pharmacokinetic drug interactions:

1) **Interaction during absorption:** Drugs may interact in the gastrointestinal tract resulting in either decreased or increased absorption.
   e.g. Tetracycline + Calcium $\rightarrow$ Decreased absorption of tetracycline.

2) **Interaction during distribution:** A drug which is extensively bound to plasma protein can be displaced from its binding sites by another drug or displacement from other tissue binding sites.
   e.g. (i) Sulfonamide can be displaced by salicylates from plasma proteins and it leads to sulfonamide toxicity.
   (ii) Quinidine displaces digoxin from binding sites in tissues and plasma and leads to digoxin toxicity.

3) **Interactions during biotransformation:** This can be explained by two mechanisms:

(i) Enzyme induction.

(ii) Enzyme inhibition.

(i) **Enzyme induction:** By this the biotransformation of drugs is accelerated and is a cause of therapeutic failure. If the drug A is metabolized by the microsomal enzymes, then concurrent administration with a microsomal inducer (drug B) will result in enhanced metabolism of drug A.

e.g. Warfarin (anticoagulant) + Barbiturate (enzyme inducer) → decreased anticoagulation.

Enzyme inducers: Rifampicine, phenytoin, sulfonamides, etc.

(ii) **Enzyme inhibition:** By this the biotransformation of drugs is delayed and is a cause of increased intensity, duration of action and some times toxicity.

e.g. Warfarin + Metronidazole (enzyme inhibitor) → Haemorrhage.

Enzyme inhibitors: Disulfiram, isoniazid, allopurinol, cimetidine, etc.

e) **Interactions during excretion:** Some drugs interacts with others at the site of excretion i.e. in kidneys.

e.g. Penicillin (antibiotic) + Probenecid (antigout drug) → Increases the duration of action of penicillin (Both drugs excreted through tubular secretion).

C. Pharmacodynamic interactions:

(i) **Drug Synergism:** When the therapeutic effect of two drugs are greater than the effect of individual drugs, it is said to be drug synergism.It is of two types.

(a) Additive effect: When the total pharmacological action of two or more drugs administered together is equivalent to the summation of their individual pharmacological actions is called additive effect.

i.e A + B = AB

e.g. Combination of ephedrine and aminophyllin in the treatment of bronchial asthma.

(b) Potentiation effect: When the net effect of two drugs used together is greater than the sum of individual effects, the drugs are said to have potentiation effect.

i.e AB > A + B

e.g. Trimethoprim+sulfamethoxazole

(iii) **Drug Antagonism:** The phenomenon of opposing actions of two drugs on the same physiological system is called drug antagonism.

a) **Chemical antagonism:** In this the biological activity of a drug can be reduced or abolished by a chemical reaction with another agent.

e.g. Antagonism between acids and alkalis.

b) **Competitive or reversible antagonism:** In this the agonist and antagonist compete for the same receptors and the extent to which the antagonist opposes the pharmacological action of the agonist. Competitive antagonism can be overcome by increasing the concentration of the agonist at the receptor site.

e.g. Acetylcholine and atropine antagonism at muscarinic receptors.

c) **Non competitive antagonism:** In this type of the antagonism an antagonist inactivates the receptor (R) so that the effective complex with the agonist cannot be formed, irrespective of the agonist concentration.

e.g. Acetylcholine and papaverine on smooth muscle.

Acetyl choline and decamethonium on neuromuscular junction.

d) **Physiological antagonism:** When the physiological effect of a drug is antagonized by another drug by acting on two different types of receptors

e.g. Acetyl choline causes constriction where as adrenaline causes dilatation of pupil.

Importance of drug antagonism

(i) Correcting adverse effects of drugs

(ii) Treating drug poisoning.

e.g. Morphine with naloxone, organophosphate compounds with atropine.

(iii) Predicting drug combinations which would reduce drug efficacy.

8) Repeated administration and drug cumulation:

If a drug is excreted slowly, its administration may build up a sufficiently high concentration in the body to produce toxicity. e.g. digitalis, emetine.

To avoid cumulation. a) One must know if a drug is eliminated slowly or rapidly, b) Stop the drug administration at the appearance of the first warning symptoms c) Carefully select the form in which the drug is to be administered.

d) Check liver and kidney function before and during drug administration, as even an otherwise non-cumulative drug would produce cumulation in the presence of hepatic and renal damage.

9) Drug tolerance:

When an unusually large dose of a drug is required to elicit an effect ordinarily produced by the normal therapeutic dose of the drug, the phenomenon is termed as drug tolerance.

Tachyphylaxis: Rapid development of tolerance on repeated administration is called tachyphylaxis

e.g. Ephedrine, amphetamine and nitroglycerine which produce tachyphylaxis on repeated administration.

10) Emotional factors.

eg. Placebo response.

Placebo: It is a Latin word meaning" I shall please" and it is a tablet looking exactly like the active treatment but containing no active component. It refers originally to substances merely to please the patient when no specific treatment was available.

B. Adverse drug reactions:

The drugs that produce useful therapeutic effect may also produce unwanted or toxic effects. It has been estimated that about 0.5% of patients who die in hospitals do so as a result of their treatment rather than the condition for which they were treated. Serious systemic drug toxicity may result from overdoses. If is always an exaggeration of its pharmacological actions and some times it is predictable.

e.g. Hypotension following antihypertensive drugs. Hypoglycaemia following insulin.

An adverse drug reaction is defined as any response to a drug that is noxious and unintended and that occurs at doses used in man for prophylaxis, diagnosis or therapy (WHO).

The adverse effects are 1)Side effects 2)untoward effects 3)allergic reactions 4)idiosyncratic reactions and 5)teratogenic effects.

1) **Side effects:** Side effects are infact pharmacological effects produced with therapeutic dose of the drug.

e.g: Dryness of mouth with atropine which is troublesome in peptic ulcer patients and useful when used as a preanaesthetic medication.

2) **Untoward effects:** Untoward effects develop with therapeutic dose of a drug. They are undesirable and if very severe, may necessitate the cessation of treatment.

e.g: Diarrhoea with ampicillin and potassium loss with diuretics.

3) **Allergic reactions**: Most of the drugs and sera used in therapeutics are capable of causing allergic or hypersensitive reactions. These reactions may be mild or very severe like anaphylaxis. When an individual has been sensitized to an antigen (allergen) further contact with that antigen can some times lead to tissue damaging reactions. These allergic reactions are 4 types.

- Type-I reactions or anaphylactic reactions (Immediate hypersensitive reaction).
- Type-II reactions or cytotoxic reactions.
- Type-III reactions or immune complex mediated reactions.
- Type-IV reactions or cell mediated reactions (Delayed hypersensitive reactions).

4) **Idiosyncratic reactions:** The term idiosyncrasy means one's peculiar response to drugs. With the increasing knowledge of pharmacogenetics, many idiosyncratic reactions have been found to be genetically determined.

e.g: Drugs like primaquine, sulfonamides and dapsone may cause haemolysis in patients with glucose -6 phosphate dehydrogenase defeciency.

5) **Teratogenic effect:** Some drugs given in the first three months of pregnancy may cause congenital abnormalities and are said to be teratogenic. The best known example is thalidomide which results in early easily recognizable abnormalities such as absent or grossly abnormal limbs.

Other drugs with teratogenic potential are androgens, steroids, anti convulsants, anti neoplastic drugs, cortisone, lithium, pencillamine, tricyclic antidepressants and warfarin.

V) Development and evaluation of new drugs:

The ultimate aim of pharmacological studies in animals is to find out a therapeutic agent suitable for clinical evaluation in man. No doubt, animal studies provide analogies and serve as useful models. The administration of biologically active agent to human beings is associated with an element of risk, which cannot be predicted by even the most careful and exhaustive animal experiments.

Scientists all over the world are in a continuous effort to develop new drugs although drug development is an extremely technical and enormously expensive operation. Among the

contributors to new drug development, pharmacologists are more concerned in evaluating “new chemical entities” (NCE). Synthesis and evaluation of thousands of NCEs are usually necessary for new drugs to be introduced in the market. Research and development of new drugs have been done under strict government regulations which have greatly increased over the past couple of decades.

Drug development comprises of two steps.

a) Preclinical development and
b) Clinical development

A) **Preclinical development**: Synthesis of new chemical entities is done as per research policy decision which is based on:

(i) Random synthesis

(ii) Structure activity relationship (SAR)

(iii) Biochemical and pharmacological insight and

(iv) Chance finding.

The aim of the preclinical development phase for a potential new medicine is to explore the drug’s efficacy and safety before it is administrated to patients. In this preclinical phase, varying drug doses are tested on animals and/or in vitro systems.

If active compounds are found, then studies on animals are done which include pharmacodynamics, pharmacokinetics, toxicology and special toxicological studies (mutagenicity and carcinogenicity) have to be done. In this study single dose is used for acute toxicity and repeated doses for sub chronic and chronic toxicity studies. Most of the preclinical tests have to be conducted in accordance with the standards prescribed.

B) **Clinical development**: About one in 1000 NCEs reach this stage. The steps to be studied in this stage include:

a) Pharmaceutical study
b) Pharmacological study
c) Clinical trial.

a) Pharmaceutical study covers stability of formulation and compatibility of the NCEs with other tablet or infusion ingredients.

b) Pharmacological study includes further chronic toxicological study in animal, initially animal metabolic and pharmacokinetic study. When studies in animals predict that a NCE may be useful medicine i.e. effective and safe in relation to its benefits, then the time has come to put it to the test in man i.e. clinical trial.

c) Studies on human or Clinical Trial:

Clinical trial is a means by which the efficacy of drug is tested on human being. It may also give some idea about the risk involved. It is divided into 4 phases. With each phase, the safety and efficacy of the compound are tested progressively.

Phase - I: This is the first exposure of the new drug on man which is usually conducted in healthy volunteers and which is designed to test the tolerable dose, duration of action. This phase is usually carried out in only one centre on 20 to 50 subjects.

Phase - II: This phase comprises small scale trials on patients used to determine dose level and establish that the treatment offers some benefit. It usually involves 100-500 patients and is usually conducted in several centres.

Phase - III: Full scale evaluation of treatment comparing it with standard treatment is done in this phase. It involves randomised control trials on 250 to 2000 patients and is done in multiple centres. Information from all studies are received by the "Committee of safety of medicines" (CSM). If the drug is satisfied by the CSM, the product license is issued then the drug is marketed.

Phase - IV: It is also called as phase of post marketing surveillance. Reports about efficacy and toxicity are received from the medical practitioners and reviewed by the committee of review of medicines. Renewal or cancellation of the product license depends on the comment of the review committee.

Exercise

1) What are different routes of drug administration and write about advantages and disadvantages of parenteral route of administration.

2) Define bio-availability and describe the factors affecting drug absorption.

3) Define the following:

   a) Half-life of a drug

   b) Steady state plasma concentration

   c) Adverse drug reactions

4) Write about the factors modifying drug action.

5) Write about different types of drug interactions.

CHAPTER TWO

DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM

Objectives

After reading this chapter the students is expected to:

- Correctly identify the different classes of drugs affecting the autonomic nervous system(autonomic drugs)
- Discuss the effects and therapeutic uses of various drugs
- Identify side effects and contraindications of commonly used autonomic drugs.
- Prescribe autonomic drugs in clinical practice rationally.

INTRODUCTION

The nervous system controls all the major functions of the body. It is divided into central and peripheral nervous systems. The peripheral nervous system includes the somatic and autonomic nervous systems which control voluntary and involuntary functions respectively.

The ANS controls the vegetative functions of the body. These include functions like circulation, respiration, digestion and the maintenance of body temperature.

The ANS is subdivided into two major sub-divisions; this classification is based on both anatomic and physiologic grounds; the two subdivisions are sympathetic (thoracolumbar) and parasympathetic (craniosacral). Autonomic nerves are actually composed of two neuron systems, termed preganglionic and postganglionic, based on anatomical location relative to the ganglia. A preganglionic neuron has its cell body in the spinal cord or brain.

The sympathetic nervous system arises from the thoracic and lumbar areas of the spinal cord and the preganglionic fibers for the parasympathetic nervous system arise from the cranial and sacral nerves. The postganglionic neurons send their axons directly to the effector organs (peripheral involuntary visceral organs). Autonomic innervation, irrespective of whether it belongs to the parasympathetic or the sympathetic nervous system, consists of a myelinated preganglionic fiber which forms a synapse with the cell body of a non-myelinated second neuron termed post-ganglionic fiber. The synapse is defined as a structure formed by the close apposition of a neuron either with another neuron or with effector cells.

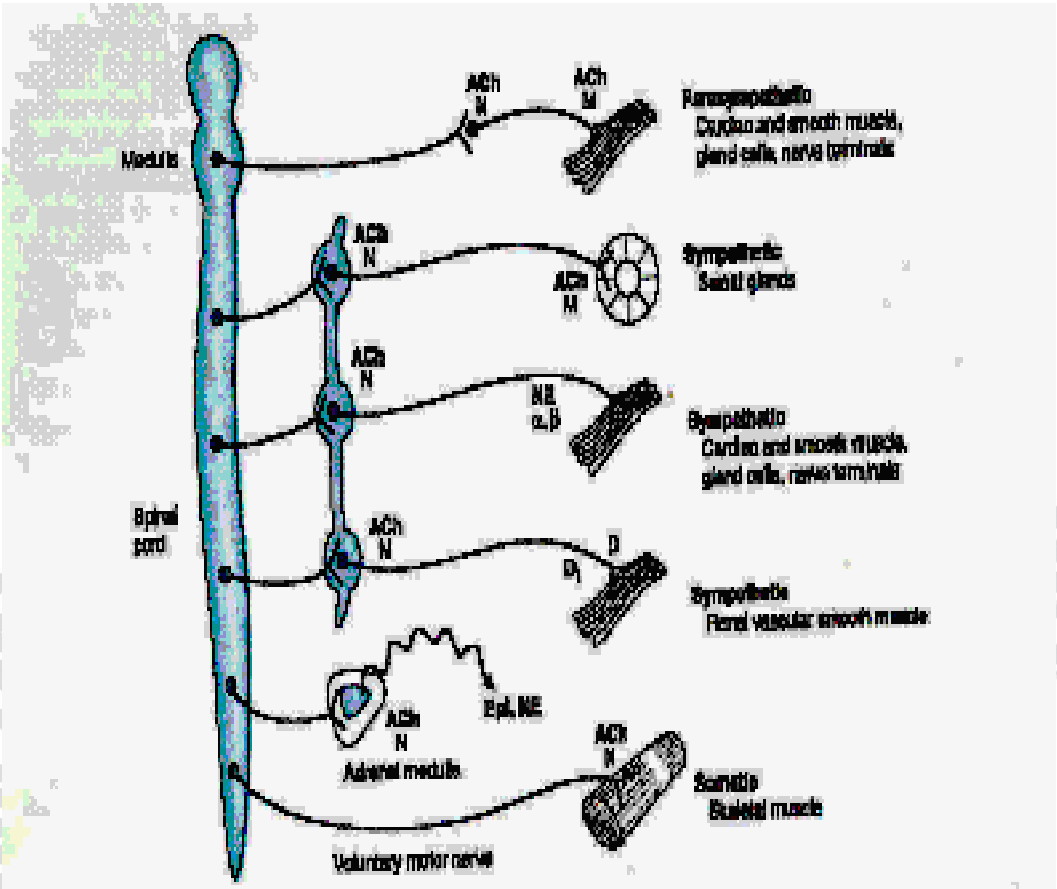


Figure Schematic diagram comparing some anatomic and neurotransmitter features of autonomic and somatic motor nerves. Only the primary transmitter substances are shown. Parasympathetic ganglia are not shown because most are in or near the wall of the organ innervated. Note that some sympathetic postganglionic fibers release acetylcholine or dopamine rather than norepinephrine. The adrenal medulla, a modified sympathetic ganglion, receives sympathetic preganglionic fibers and releases epinephrine and norepinephrine into the blood. (ACh, acetylcholine; D, dopamine; Epi, epinephrine; NE, norepinephrine; N, nicotinic receptors; M, muscarinic receptors.)

In terms of function, the parasympathetic nervous system is concerned primarily with conservation and restoration of function.

In contrast, the sympathetic nervous system is concerned with the expenditure of energy, i.e., it has almost opposite functions with parasympathetic nerve stimulation and it is usually associated with arousal or in emergency situations, i.e., prepares the body for fight-or-flight responses.

To understand autonomic nervous system pharmacology, it is very important to know how the system works and clearly identify the mechanisms behind the functions, i.e., nerve transmission.

There are two important neurotransmitters in the autonomic nervous system. These are acetylcholine and noradrenaline (norepinephrine)

Acetylcholine is a neurotransmitter which is released after stimulation of the parasympathetic nervous system to act on effector organs (cells) to elicit their response, but it also acts as a neurotransmitter:

- At the ganglia of both sympathetic and parasympathetic nervous system,
- At postganlionic sympathetic nerve endings to blood vessels of skeletal muscles and sweat glands(eccrine),
- At the neuromuscular junction of skeletal muscles (somatic motor fibers to skeletal muscle),
- Between some neurons in the CNS, and
- At preganglionic nerve endings to the adrenal medulla.

The process of neurotransmission involves passage of an impulse across a synapse.

Acetylcholine is synthesized inside the cytoplasm of nerve fibers from acetyl coenzyme A and choline through the catalytic action of the enzyme choline acetyltransferase. Once synthesized, it is transported form the cytoplasm into the vesicles to be stored; when action potential reaches the terminal and the latter undergoes stimulation, acetylcholine is released to the synaptic cleft. After release from the presynaptic terminal the molecule binds to and activates an acetylcholine receptor (cholinergic receptor) located on effector cell. Finally, it is hydrolyzed into choline and acetate by acetyl cholinesterase enzyme and thereby the action of the transmitter is terminated.

Cholinergic receptors are classified into muscarinic and nicotinic cholinergic receptors.

The response of most autonomic effector cells in peripheral visceral organs is typically muscarinic, whereas the responses in parasympathetic and sympathetic ganglia, as well as responses of skeletal muscle are nicotinic.

The effect of parasympathetic nervous system activity in an organ may be produced either by stimulation of a parasympathetic nerve fibers supplying the organ or by the application of acetylcholine or other parasympathomimetics to the effector cells. This is known as ***cholinergic activity.***

Noradrenaline is the neurotransmitter released by post ganglionic sympathetic nerves to elicit its effect on effectors cells. The post-ganglionic sympathetic fibers are called noradrenergic or adrenergic. Sympathetic nerve activity may be demonstrated by sympathetic nerve stimulation or by application of noradrenaline or adrenaline or other sympathomimetics, i.e. '***adrenergic***

activity', except in the case of sweat glands and blood vessels to skeletal muscles where acetylcholine is released as a neurotransmitter.

Adrenergic neuron terminals synthesize noradrenaline, store it in vesicles and release it to effector cells upon stimulation of the nerve. The transmitter is synthesized from precursor tyrosine (amino acid) through several processes which are potential sites of drug action. After release to receptor sites noradrenaline produces its effects. Termination of noradrenergic transmission results from several processes such as reuptake into the nerve terminal (reuptake1), diffusion away from the synaptic cleft and subsequent reuptake into the perisynaptic glia or smooth muscle (reuptake2) or degradation by enzymes. Reuptake into the nerve terminal is the most important mechanism for termination of the effects of noradrenaline.

Receptors that respond to adrenergic nerve transmitter are termed adrenergic receptors. These receptors are subdivided into alpha and beta adrenoreceptor types on the basis of both agonist and antagonist selectivity. The receptors have subclasses depending on drug selectivity. These are alpha 1 and 2 and beta 1, 2 and 3.

Table 2.1: Distribution of adrenoceptor subtypes and their actions

Type	**Tissue**	**Actions**
Alpha$_1$	Most vascular smooth muscles	Contraction
	Pupillary dilator muscle	Mydriasis
	Heart	Increase force of contraction
Alpha$_2$	Adrenergic nerve terminals	Inhibition of transmitter release
	Platelets	Aggregation
Beta$_1$	Heart	Increased rate and force of contraction
Beta2	Respiratory, uterine, and vascular smooth muscle	Relaxation
	Human liver	Glycogenolysis
Beta$_3$	Fat cells	Lipolysis

There are five key features of neurotransmitter function representing potential targets of pharmacologic therapy. These are synthesis, storage, release, activation of receptors and termination of the action of the transmitter.

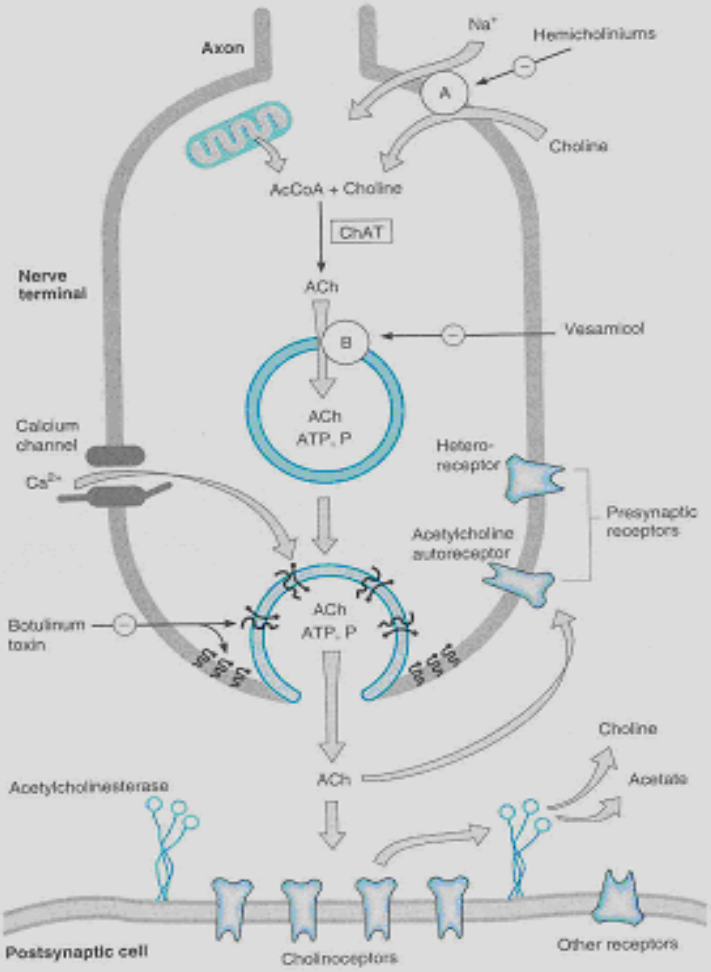


Figure Schematic illustration of a generalized cholinergic junction (not to scale). Choline is transported into the presynaptic nerve terminal by a sodium-dependent carrier *(A)*. This transport can be inhibited by hemicholinium drugs. ACh is transported into the storage vesicle by a second carrier *(B)* that can be inhibited by vesamicol. Peptides *(P)*, ATP, and proteoglycan are also stored in the vesicle. Release of transmitter occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. The resulting increase in intracellular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of ACh and cotransmitters into the junctional cleft. This step is blocked by botulinum toxin. Acetylcholine's action is terminated by metabolism by the enzyme acetylcholinesterase. Receptors on the presynaptic nerve ending regulate transmitter release.

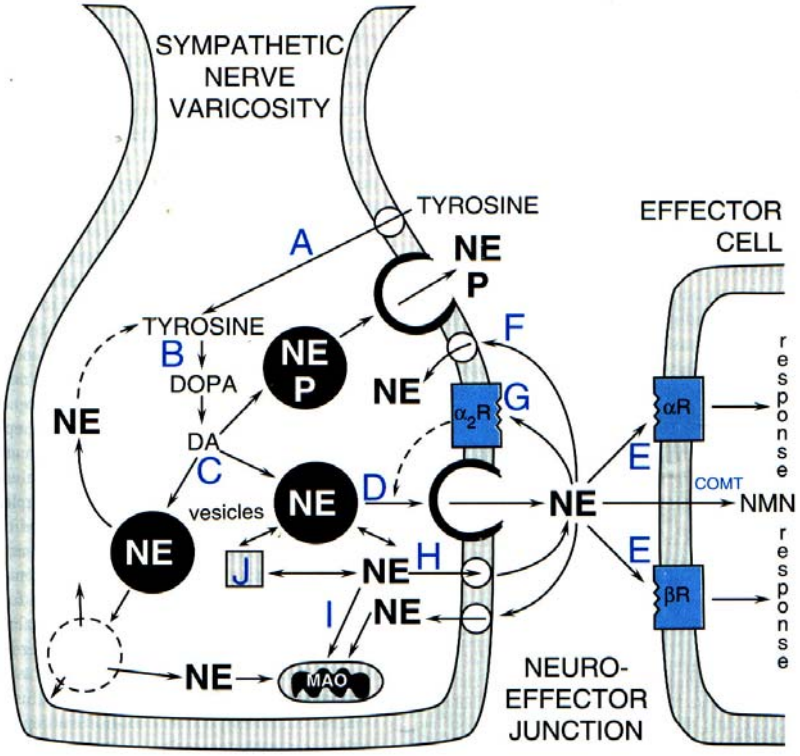


Fig 2.3: Proposed site of action of drugs on the synthesis, action, and fate of norepinephrine at sympathetic neuroeffector junctions

AUTONOMIC DRUGS

There are several drugs affecting the autonomic nervous system which, for a better understanding of specific drugs, are classified into groups.

1. Drugs acting on the sympathetic nervous system

a) Sympathomimetics or adrenergic drugs: are drugs that mimic the effects of sympathetic nerve stimulation.

b) Sympatholytics: are drugs that inhibit the activity of sympathetic nerve or that of sympathomimetics.

2. Drugs acting on the parasympathetic nervous system

a) Parasympathomimetics or cholinergic drugs: are drugs which mimic acetylcholine or the effects of parasympathetic nerve stimulation.

b) Parasympatholytics: are drugs that inhibit parasympathetic nervous system activity or that of cholinergic drugs.

CHOLINERGIC DRUGS

Cholinergic drugs are also called parasympathomimetics because their effect mimics the effect of parasympathetic nerve stimulation. Administration of these drugs will result in an increase in the parasympathetic activities in the systems innervated by cholinergic nerves.

There are two groups of cholinergic drugs:

1. *Direct-acting*: bind to and activate muscarinic or nicotinic receptors (mostly both) and include the following subgroups:
    a. Esters of choline: methacholine, carbachol, betanechol
    b. Cholinergic alkaloids: pilocarpine, muscarine, arecoline, nicotine
2. *Indirect-acting*: inhibit the action of acetylcholinesterase enzyme
    a. Reversible: neostigmine, physostigmine, edrophonium
    b. Irreversible: Organophosphate compounds; echothiophate

The actions of acetylcholine may be divided into two main groups: -

1. Nicotinic actions- those produced by stimulation of all autonomic ganglia and the neuromuscular junction
2. Muscarinic actions- those produced at postganglionic cholinergic nerve endings

ESTERS OF CHOLINE

ACETYLCHOLINE is the prototypical cholinergic agent. It functions as a neurotransmitter at all cholinergic sites in the body; because of its unique pharmacokinetic properties, it has never been used in medical therapeutics; the discussion which follows is for academic exercise.

Pharmacokinetics

Acetylcholine is poorly absorbed from the gastric mucosa; therefore it is ineffective if given orally. The recommended way of administration is parenteral. In the blood it is rapidly hydrolyzed by the enzyme cholinesterase into acetic acid and choline; this makes its duration of action very short and unreliable for therapeutic purposes.

Pharmacodynamics

As mentioned earlier it has two types of actions: nicotinic and muscarinic; the muscarinic actions are of main interest and are discussed below.

- *Cardiovascular system*

Heart→ slow heart rate

Blood vessels→ vasodilator

Blood pressure→ falls because of the effect on the heart and blood revels

i) Gastrointestinal tract

It stimulates the tone and motility of the GI tract but the sphincters will be relaxed

ii) Urinary tract

It stimulates the detrusor muscle and relaxes the internal urethral sphincter resulting in evacuation of bladder

iii) Bronchioles

It increase bronchial secretion and brings about bronchoconstriction

iv) *Eye*- It has two effects- miosis and accommodation for near objects because of stimulation of the constrictor pupillae and ciliary muscles respectively.

v) *Exocrine glands*- it stimulates salivary, gastric, bronchial, lachrymal and sweat gland secretions.

SYNTHETIC CHOLINE ESTERS. These are synthetic derivatives of choline and include metacholine, carbachol and betanechol. These drugs have the following advantages over acetylcholine:

- They have longer duration of action,
- They are effective orally as well as parenterally, and
- They are relatively more selective in their actions.

CARBACHOL

Pharmacokinetics

It is completely absorbed from the gastro intestinal tract and is stable towards hydrolysis by cholinesterase enzyme; therefore it can be given both orally and parenteraly with almost similar dosage.

Pharmacodynamics

It has similar actions to those of acetylcholine with pronounced effects on the gastro intestinal tract and the urinary bladder

Indications

- Glaucoma
- Retention of urine (postoperative)

- Paralytic ileus

BETANECHOL

This drug is similar to carbachol in all parameters, i.e., pharmacokinetics, pharmacodynamics and clinical indications; it has a better advantage over carbachol because it has fewer side effects as a result as lack of nicotinic actions.

Contra indications to the use of choline esters

1. Bronchial asthma because they may induce bronchial constriction and increase bronchial secretions
2. Hyperthyroidism because of the danger of inducing atrial fibrillation
3. Peptic ulcer disease because of the increase in gastric acid secretion
4. Coronary insufficiency because the hypertension produced will further compromise coronary blood flow
5. Mechanical intestinal and urinary outlet obstruction

CHOLINERGIC ALKALOIDS

1. Those with chiefly nicotinic actions include nicotine, lobeline etc.

2. Those with chiefly muscarinic actions include muscarine, pilocarpine, etc.

PILOCARPINE

Pharmacokinetics

This drug is readily absorbed from the gastrointestinal tract and it is not hydrolyzed by cholinesterase enzyme. It is excreted partly destroyed and partly unchanged in the urine.

Pharmacodynamics

The drug directly stimulates the muscarinic receptors to bring about all the muscarinic effects of acetylcholine.

Indications

- Glaucoma

ANTICHOLINESTERASE DRUGS

The commonly used cholinesterase inhibitors fall into three chemical groups:

1. Simple alcohols bearing quaternary amines, e.g., edrophonium
2. Carbamate and related quaternary or tertiary amines, e.g., neostigmine, physostigmine
3. Organic derivatives of phosphates, e.g., isofluorophate, echothiophate

PHYSOSTIGMINE

Pharmacokinetics

This drug is completely absorbed from the gastrointestinal and is highly distributed throughout the body; it can pass the blood brain barrier.

Pharmacodynamics

Inhibits the enzyme cholinesterase; therefore, it increases and prolongs the effect of endogenous acetylcholine at the different sites.It has no direct effect on cholinergic receptors.

Indications

- Glaucoma
- Atropine over dosage

NEOSTIGMINE

Pharmacokinetics

This drug is poorly absorbed from the gastro intestinal tract and is poorly distributed throughout the body; it cannot pass the blood brain barrier.

Pharmacodynamics

Just like physostigmine, it inhibits cholinesterase enzyme; but unlike physostigmine, it has a direct nicotinic action on skeletal muscles.

Indications

- Myasthenia gravis
- Paralytic Ileus
- Reversal of effect of muscle relaxants, e.g. tubocurarine
- Post operative urine retention

Organophosphates such as echothiophate, isofluorophate, etc. combine with cholinesterase irreversibly and thus hydrolysis is very slow.

They may be used in glaucoma. Other organophosphates like parathion and malathion are used as insecticides. Poisoning with organophosphates is an important cause of morbidity and mortality all over the world. It usually results from:

- Occupational exposure as in persons engaged in spraying insecticides,
- Accidental exposure, and

- Ingestion of any of these compounds with suicidal intent.

ANTICHOLINERGICS

Anticholinergics block the effects of acetylcholine and other cholinergic drugs at cholinergic receptors of effector cells. Anticholinergics fall into two major families:

1. Antinicotinics which include ganglion blockers such as hexamethonium, trimethaphan, etc., and neuromuscular blockers such as gallamine, tubocurarine, pancuronium, etc.
2. Antimuscarinics include tertiary amines such as atropine, scopolamine, tropicamide, etc, andquaternary amines such as propantheline, ipratropium, benztropine, etc.

ATROPINE

Atropine is found in the plant *Atropa belladonna and it is the prototype of muscarinic antagonists.*

Pharmacokinetics

Atropine is absorbed completely from all sites of administration except from the skin wall, where absorption is for limited extent; it has good distribution. About 60% of the drug is excreted unchanged in urine.

Pharmacodynamics

Atropine antagonizes the effect of acetylcholine by competing for the muscarinic receptors peripherally and in the CNS; therefore the effects of atropine are opposite to the acetylcholine effects.

Organ-system Effects:

CNS: - lower doses produce sedation
- higher doses produce excitation, agitation and hallucination

Eyes: - relaxation of constrictor pupillae (mydriasis)
- relaxation or weakening of ciliary muscle (cycloplegia-loss of the ability to accommodate)

CVS: - blocks vagal parasympathetic stimulation (tachycardia)
- vasoconstriction

Respiratory: - bronchodilatation and reduction of secretion

GIT: - decreased motility and secretions

GUS: - Relaxes smooth muscle of ureter and bladder wall; voiding is slowed.

Sweat Glands: - suppresses sweating

Clinical Indications

Pre anesthetic medication -to reduce the amount of secretion and to prevent excessive vagal tone due to anesthesia.

As antispasmodic in cases of intestinal, biliary, and renal colic

Heart block

Hyperhidrosis

Organophosphate poisonings

Side effects

- Dryness of the mouth, tachycardia and blurred vision
- Retention of urine

Contraindications

Glaucoma

Bladder outlet obstruction.

HYOSCINE (SCOPOLAMINE)

This drug has the same effect as atropine except for some differences which includes:-

- It has shorter duration of action
- It is more depressant to the CNS.
- All other properties are similar to atropine. It has certain advantage over atropine. These include:

3. Better for preanesthetic medication because of strong antisecretory and antiemetic action and also brings about amnesia
4. Can be used for short- travel motion sickness

SYNTHETIC ATROPINE DERIVATIVES

There are a number of synthetic atropine derivatives, which are used in the treatment of various conditions, their actions are similar to that of atropine but have fewer side effects. These groups of drugs include

1. Mydriatic atropine substitutes, this group of drugs have shorter duration of action than atropine and are used locally in the eye; drugs included: Homatropine, Eucatropine etc.
2. Antiseccretory antispasmodic atropine substitutes:
   - Effective more localized to the GI. Drugs include: propantheline and hyoscine

3. Antiparkinsonian atropine substitute: - drugs like Benztropine, Trihexyphenidyl
4. Atropine substitutes which decrease urinary bladder activity like oxybutynin
5. Atropine substitutes used in bronchial asthma drugs like ipratropium

ADRENERGIC DRUGS

As their name suggests, these drugs resemble sympathetic nerve stimulation in their effects; they may be divided into two groups on the basics of their chemical structure.

1**. Catecholamines**: -these are compounds which have the catechol nucleus.

Catecholamines have a direct action on sympathetic effectors cells through interactions with receptor sites on the cell membrane.

The group includes adrenaline, noradrenaline, dopamine, isoprenaline, and dobutamine.

- *Noncatecholmines:* - lack the catechol nucleus.

They may directly act on the receptors or may indirectly release the physiologic catecholamines- e.g. ephedrine, phenylephrine, amphetamine

Adrenergic drugs, like cholinergic drugs, can be grouped by mode of action and by the spectrum of receptors that they affect.

a. *Direct mode of action:* directly interact with and activate adrenoreceptors, e.g., adrenaline and noradrenaline
b. *Indirect mode of action:* their actions are dependent on the release of endogenous catecholamines. This may be
   i. Displacement of stored catecholamies from the adrenergic nerve endings, e.g., amphetamine, tyramine
   ii. Inhibition of reuptake of catecholamines already released, e.g. cocaine, tricyclic antidepressants

Both types of sympathomimetics, direct and indirect, ultimately cause activation of adrenoreceptors leading to some or all characteristic effects of the catecholamines.

Organ-system Effects of Activation of the Adrenergic System

1. *CVS:*
   a. *Heart:* increased rate and force of contraction, increased cardiac output, myocardial demand, and AV conduction
   b. *Blood Vessels and Blood pressure*: constriction of blood vessels in the skin and mucous membranes

- Dilatation of skeletal muscle vessels
- Adrenaline increases systolic and decreases diastolic blood pressure at low doses but increases both at higher doses
- Noradrenaline increases both systolic and diastolic blood pressure

2. *Smooth Muscle:*
   a. Bronchi: relaxation.
   b. Uterus: relaxation of the pregnant uterus
   c. GIT: relaxation of wall muscles and contraction of sphincters
   d. Bladder: relaxation of detrusor muscle; contraction of sphincter and trigone muscle
3. *Eye:* mydriasis; reduction of intraocular pressure in normal and glacucomatous eyes
4. *Respiration:* Bronchodilatation; relief of congestion; mild stimulation of respiration
5. *Metabolic:* Increased hepatic glycogenolysis; decreased peripheral glucose intake; increased free fatty acids in the blood (lipolysis)
6. *CNS:* excitement, vomting, restlessness
7. *Skeletal muscle*: facilitation of neuromuscular transmission and vasodilatation

Drugs Acting on the Adrenergic Receptor Subtypes

	α_1	α_2	β_1	β_2
Agonist	Phenylephrine Methoxamine	Clonidine Oxymetazoline	Dobutamine Isoproterenol Terbutaline	Salbutamol Terbutaline Isoetharine
Antagonist	Prazosin Phentolamine Phenoxybenzamine	Yohimbine Phentolamine Phenoxybenzamine	Propranolol Pindolol Atenolol Metoprolol Timolol	Propranolol Pindolol Butoxamine Timolol

Adrenaline stimulates all the four receptor subtypes.

Noradrenaline stimulates both alpha receptors and $beta_1$ but has very poor affinity for $beta_2$ receptors. Labetalol blocks all beta receptors as well as some alpha receptors.

ADRENALINE

This is the prototype of adrenergic drugs and is produced in the body by the cells of the Adrenal medulla and by chromaffin tissues.

Pharmacokinetics

Adrenaline is rapidly destroyed in the gastrointestinal tract, conjugated, and oxidized in the liver. It is therefore ineffective when given orally and should be given intramuscularly or subcutaneous. Intravenous injection is highly dangerous and is likely to precipitate ventricular fibrillation. The drug may how ever, be given by nebulizer for inhalation when its relaxing effect on the bronchi is desired or it may be applied topically to mucus membranes to produce vasoconstriction. Because of the extensive metabolism of the drug in liver, little is excreted unchanged in the urine.

Pharmacodynamics

Adrenaline directly stimulates all the adrenergic receptors both and brings about effects of sympathetic nerve stimulation. Its action may be divided in to two, depending on the type of receptor stimulated.

The α effects consist of vasoconstriction in skin and viscera, mydriasis, platelet aggregation and some increase in blood glucose. The ß effects consists of increased contractility and rate of heart with a decreased refractory period (ß1), vasodilatation in muscles and coronary vessels (ß2), bronchial relaxation (ß2) uterine relaxation (ß2), hyperglycemia, lactic acidemia and increased circulating free fatty acids.

Indications

1. Acute bronchial asthma
2. Anaphylaxis
3. Local haemostatic to stop bleeding in epistaxis
4. With local anesthesia to prolong the action
5. Cardiac arrest

Adverse reactions

1. Anxiety, restlessness, headache tremor
2. Anginal pain
3. Cardiac arrhythmias and palpitations
4. Sharp rise in blood pressure
5. Sever vasoconstriction resulting in gangrene of extremities
6. Tearing, conjunctival hyperemia

Contra indications

1. Coronary diseases
2. Hyperthyroidism
3. Hypertension
4. Digitalis therapy
5. Injection around end arteries

NOR ADRENALINE

Nor adrenaline is the neurochemical mediator released by nerve impulses and various drugs from the postganglionic adrenergic nerves. It also constitutes 20% of the adrenal medulla catecholamine out put.

Pharmacokinetics

Like adrenaline, noradrenaline is ineffective orally so it has to be given intravenously with caution. It is not given subcutaneous or intramuscularly because of its strong vasoconstrictor effect producing necrosis and sloughing. The metabolism is similar to adrenaline; only a little is excreted unchanged in urine.

Pharmacodynamics

Nor adrenaline is a predominantly α receptor agonist with relatively less β agonist action when compared to adrenaline.

Indication

Nor adrenalines is used as hypertensive agent in hypotensive states

E.g. During spinal anesthesia or after sympathectomy.

Adverse effects include:

- Anxiety, headache, bradycardia are common side effects
- Severe Hypertension in sensitive individuals
- Extravasation of the drug causes necrosis and sloughing.

ISOPRENALINE DOPAMINE, DOBUTAMINE. These are the other catecholamines which have similar properties to adrenaline and noradrenaline.

Dopamine is naturally occurring and is a precursor of noradrenaline. The other two-isoprenaline and dobutamine- are synthetic. These drugs have advantage over the others because they are

more selective in their action so that they have fewer side effects than adrenaline and nor adrenaline. Dopamine and dobutamine are very useful drugs for the treatment of shock.

NON- CATECHOLAMINES

Most of the non- catecholamines function by releasing the physiologic catecholamines from the postganglionic nerve endings

EPHEDRINE

Pharmacokinetics

Ephedrine in absorbed from the gastrointestinal tract and from all parenteral sites. It has a good distribution through out the body and is resistant to hydrolysis by the liver enzymes. Major proportion of the drug is excreted unchanged in the urine. Because of its stability to metabolism it has long duration of action than the catecholamines.

Pharmacodynamics

Ephedrine stimulates both α and β receptors. This effect is partly by a direct action on the receptors and partly indirectly by releasing noradrenaline from its tissue stores the effect of the drug to various organs and systems is similar to that of adrenaline. It is also a mild CNS stimulant.

Indications:

1. Bronchial asthma: - usually as a prophylactic for prevention of attacks
2. Nasal decongestion
3. Mydriasis
4. Heart block
5. Nocturnal enuresis

Side effects

The side effects are similar to those of adrenaline; but in addition it may produce insomnia and retention of urine.

Contraindications

They are the same as Adrenaline.

Based on their selectivity to specific receptors the rest of the catecholamines, are classified but it is very difficult to exhaust all the drugs. More over their effect and pharmacology is discussed where they are clinically indicated.

ADRENERGIC BLOCKERS

Adrenergic receptor blockers may be considered in two groups:

1. Drugs blocking the ą adrenergic receptor
2. Drugs blocking theβ Adrenergic receptor

These drugs prevent the response of effectors organs to adrenaline, noradrenaline and other sympathomimetic amines whether released in the body or injected. Circulating catecholamines are antagonized more readily than are the effects of sympathetic nerve stimulation. The drugs act by competing with the catechoamines for α or β receptors on the effectors organs. They don't alter the production or release of the substances.

α- Adrenergic blockers

Alpha adrenergic receptor antagonists may be reversible or irreversible. Reversible antagonists dissociate from the receptors e.g. phentolamine, tolazoline, prazosin,yohimbine, etc. Irreversible antagonists tightly bind to the receptor so that their effects may persist long after the drug has been cleared from the plasma e.g. phenoxybenzamine

Pharmacologic Effects:

Alpha receptor antagonist drugs lower peripheral vascular resistance and blood pressure. Hence, postural hypotension and reflex tachycardia are common during the use of these drugs. Other minor effects include miosis, nasal stuffiness, etc.

Prazosin

This is an effective drug for the management of hypertension. It has high affinity for alpha$_1$ receptor and relatively low affinity for the alpha$_2$ receptor. Prazosin leads to relaxation of both arterial and venous smooth muscles due to the blockage of alpha$_1$ receptors. Thus, it lowers blood pressure, reduces venous return and cardiac output. It also reduces the tone of internal sphincter of urinary bladder.

Indications:

- Essential hypertension
- Raynaud's syndrome

Benign prostatic hyperplasia

β - ADRENERGIC BLOCKING DRUGS

The β - adrenergic receptor blocking drugs in use may be classified by their selectivity for receptors in different tissues.

1. Drugs blocking all the β receptor effects of adrenaline (non-selective beta blockers) e.g. propanalol, pinadolol, timolol etc
2. Drugs blocking mainly the β1 effects (those on the heart) with less effect on the bronchi and blood vessels (beta1-selective blockers), e.g. atenolol, practalol acebutalol, etc.

PROPRANOLOL

Propranolol is a non- selective β adrenergic blocker; it has also other actions like membrane stabilization.

Pharmacokinetics

Propranolol is almost completely absorbed following oral administration. How ever, the liver, leaving only 1/3 rd of the dose to reach the systemic circulations, metabolizes most of the administered dose. It is bound to plasma to the extent of 90-95%. It is excreted in the urine.

Pharmacodynamics

The drug has the following main actions.

1. Cardiovascular system
   - Bradycardia
   - Reduces force of contraction
   - Reduces blood pressure
2. Respiratory system
   - Bronchoconstriction
3. Metabolic system
   - Hypoglycemia
4. Central nervous system
   - Anti-anxiety action
5. Eye
   - Decrease the rate of Aqueous humor production
6. Kidneys:
   - Decrease renin secretion

Indications

- Cardiac arrhythmias
- Hypertension
- Prophylaxis against angina
- Myocardial infarction
- Thyrotoxicosis
- Anxiety states (suppression of the physical manifestations of situational anxiety)
- Prophylaxis against migraine attacks
- Glaucoma

Adverse reactions

- GI disturbances like nausea, vomiting
- Heart failure
- Heart block
- Hypotension and severe bradycardia
- Bronchospasm
- Allergic reaction
- Vivid dreams night mare and hallucinations
- Cold hands
- Withdrawal symptoms in case of abrupt discontinuation
- Masking of hypoglycemia in diabetic patients

Contraindications and Precautions:

- Bronchial asthma
- Diabetes mellitus
- Heart failure
- Peripheral vascular disease

Exercice

1. What is the autonomic nervous system?
2. How are drugs affecting the Autonomic nervous system classified?
3. Discuss the effects of Acetylcholine.
4. Discuss the effects and clinical uses of atropine.
5. Discuss the effects of Adrenaline.
6. Discuss the effects and contraindications of propranolol.

CHAPTER THREE

CARDIOVASCULAR AND RENAL DRUGS

Learning objectives

After completing this chapter the student will be able to:

- Describe the different cardiovascular and renal disorders,
- Understand the basic pharmacological principles of cardiovascular and renal drugs,
- Learn the rational use of these drugs,
- Describe the side effects of these drugs,

INTRODUCTION

In the past decades, cardiovascular diseases were considered as major health problems mainly for western countries. However, the problem of cardiovascular disorders is also increasing in developing countries including Ethiopia. The most commonly encountered cardiovascular disorders include hypertension, congestive heart failure, angina pectoris and cardiac arrhythmias. Most drugs available currently are able to reduce the morbidity and mortality due to these disorders, and therefore, this chapter discusses the pharmacology of these drugs.

I. Antihypertensive drugs

a. General consideration:-

Hypertension is defined as an elevation of arterial blood pressure above an arbitrarily defined normal value. The American Heart Association defines hypertension as arterial blood pressure higher than 140/90mmHg (based on three measurements at different times).

Hypertension may be classified in to three categories, according to the level of diastolic blood pressure:

- Mild hypertension with a diastolic blood pressure between 95-105 mmHg
- Moderate hypertension with a diastolic blood pressure between 105 – 115mmHg
- Severe hypertension with a diastolic blood pressure above 115mmHg.

Sustained arterial hypertension damages blood vessels in kidney, heart and brain and leads to an increased incidence of renal failure, cardiac failure, and stroke.

Effective pharmacologic lowering of blood pressure prevents the damage to blood vessels and reduces the morbidity and mortality rate.

In order to understand the pathophysiology of hypertensive states and, in turn, the underlying rationale of drug therapy, an appreciation of the systems normally involved in monitoring and regulating blood pressure is required.

Two factors which determine blood pressure are cardiac out put (stroke volume x heart rate) and total peripheral resistance of the vasculature. Blood pressure is regulated by an interaction between nervous, endocrine and renal systems

Elevated blood pressure is usually caused by a combination of several abnormalities such as psychological stress, genetic inheritance, environmental and dietary factors and others.

Patients in whom no specific cause of hypertension can be found are said to have essential hypertension or primary hypertension (accounts for 80-90 % of cases).

Secondary hypertension arises as a consequence of some other conditions such as, atherosclerosis, renal disease, endocrine diseases and others. The central issue of antihypertensive therapy is to lower arterial blood pressure, irrespective of the cause.

The choice of therapy of a patient with hypertension depends on a variety of factors: age, sex, race, body build, life-style of the patient, cause of the disease, other co-existing disease, rapidity of onset and severity of hypertension, and the presence or absence of other risk factors for cardiovascular disease (e.g. smoking, alcohol consumption, obesity, and personality type).

b. Antihypertensive therapies.

1. Non pharmacological therapy of hypertension

Several non-pharmacological approaches to therapy of hypertension are available. These include:

- Low sodium chloride diet
- Weight reduction
- Exercise
- Cessation of smoking
- Decrease in excessive consumption of alcohol

- Psychological methods (relaxation, meditation …etc)
- Dietary decrease in saturated fats.

The sensitivity of patients differs to these non-pharmacological approaches, but, on the average, only modest reductions (5 to 10 mmHg) in blood pressure can be achieved. This may be sufficient for the treatment of some mild hypertensive cases.

The major advantage of non-pharmacological approaches is the relative safety and freedom from side effects, compared with drug therapy.

2. Pharmacological therapy of hypertension.

Most patients with hypertension require drug treatment to achieve sustained reduction of blood pressure. Currently available drugs lower blood pressure by decreasing either cardiac output (CO) or total peripheral vascular resistance (PVR) or both although changes in one can indirectly affect the other. However, physiological mechanisms tend to oppose a drug – induced reduction of blood pressure.

Anti - hypertensive drugs are classified according to the principal regulatory site or mechanism on which they act. They include:

A) Diuretics, which lower blood pressure by depleting the body sodium and reducing blood volume. Diuretics are effective in lowering blood pressure by 10 – 15 mmHg in most patients.

Diuretics include:

a) Thiazides and related drugs, e.g. hydrochlorthiazide bendrofluazide, chlorthalidone, etc.

Initially, thiazide diuretics reduce blood pressure by reducing blood volume and cardiac out put as a result of a pronounced increase in urinary water and electrolyte particularly sodium excretion.

With chronic administration (6-8weeks), they decrease blood pressure by decreasing peripheral vascular resistance as the cardiac out put and blood volume return gradually to normal values.

Thiazides are appropriate for most patients with mild or moderate hypertension and normal renal and cardiac function.

b) Loop diuretics, e.g. furosemide, ethacrynic acid, etc.

Loop diuretics are more potent than thiazides as diuretics. The antihypertensive effect is mainly due to reduction of blood volume.

Loop diuretics are indicated in cases of severe hypertension which is associated with renal failure, heart failure or liver cirrhosis.

c) Potassium sparing diuretics, e.g. spironolactone

They are used as adjuncts with thiazides or loop diuretics to avoid excessive potassium depletion and to enhance the natriuretic effect of others. The diuretic action of these drugs is weak when administered alone.

B) Sympathoplegic agents (Depressants of sympathetic activity).

Based on the site or mechanism of action sympathoplegic drugs are divided into:

a) Centrally acting antihypertensive agents e.g. methyldopa, clonidine

Centrally acting sympathetic depressants act by stimulating α_2 - receptors located in the vasomotor centre of the medulla. As a result, sympathetic out flow from the medulla is diminished and either total peripheral resistance or cardiac out put decreases. . Methyldopa is useful in the treatment mild to moderately severe hypertension.

Methyldopa is a prodrug and must be converted in the CNS to active α - methylnorepinephrine to exert the effect on blood pressure.

The side effects of methyldopa include sedation, vertigo, dry mouth, nausea, vomiting, diarrhea, postural hypotension, impotence, haemolytic anemia, weight gain and hypersensitivety reactions (fever, liver damage, thrombocytopenia).

b) Adrenoceptor antagonists, e.g propranolol (beta blocker), prazosin (alpha blocker), labetalol (alpha and beta blocker).

β – Blockers antagonize beta, receptors located on the myocardium and prevent the cardio acceleration, which follows sympathetic stimulation.

The rate and force of myocardial contraction is diminished, decreasing cardiac out put and thus, lowering blood pressure. An additional effect which can contribute to a reduction of blood pressure is that renin release is mediated by β receptors. Therefore, receptor blockade prevents angiotensin II formation and associated aldosterone secretion, resulting in a decrease in total peripheral resistance and blood volume.

The principal action of alpha adrenergic blocking drugs is to produce peripheral vasodilation.

Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels. Treatment with prazosin should be initiated with low dose (1mg 3 times daily) to prevent postural hypotension and syncope or be given at bed time.

c) Adrenergic neuron – blocking agents, e.g. guanethidine

Guanethidine is an adrenergic neuron-blocking drug recommended for treatment of severe forms of hypertension.

Guanethidine blocks adrenergic nerve transmission, preventing the release of transmitter. It lowers blood pressure by reducing both cardiac out put and total peripheral resistance.

d) Drugs which deplete catecholamine stores, e.g. reserpine.

Reserpine interferes with the storage of endogenous catecholamines in storage vesicles as a result of which little neurotransmitter is released upon stimulation. It leads to reduction of cardiac out put and peripheral vascular resistance. Reserpine is a second-line drug for treatment of hypertension.

e) Ganglion blockers, e.g. trimethaphan

Trimethaphan is ganglion blocking drug which is reserved for use in hypertensive emergencies only.

C) Direct vasodilators. These include:-

- Arterial vasodilators, e.g. hydralazine
- Arteriovenous vasodilators, e.g. sodium nitroprusside

Hydralazine: It dilates arterioles but not veins. It is used particularly in severe hypertension.

The most common adverse effects are headache, nausea, anorexia, palpitations, sweating and flushing which are typical to vasodilators.

Sodium nitroprusside: It is a powerful vasodilator that is used in treating hypertensive emergencies as well as severe cardiac failure.

It dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return.

Nitroprusside rapidly lowers blood pressure and it is given by intravenous infusion.

The most serious toxicities include metabolic acidosis, arrhythmias, excessive hypotension and death.

D) Angiotensin converting enzyme inhibitors, e.g. captopril, enalapril, etc. The prototype is captopril. Captopril inhibits angiotensin converting enzyme that hydrolyzes angiotensin I (Inactive) to angiotensin II (Active), a potent vasoconstrictor, which additionally stimulates the secretion of aldosterone. It lowers blood pressure principally by decreasing peripheral vascular resistance.

The adverse effects include maculopapular rash, angioedema, cough, granulocytopenia and diminished taste sensation.

Enalapril is a prodrug with effects similar to those of captopril.

E) Calcium channel blockers, e.g. nifedipine, verapamil, nicardipine, etc.

The prototype is verapamil.

The mechanism of action in hypertension is inhibition of calcium influx in to arterial smooth muscle cells, resulting in a decrease in peripheral resistance.

Verapamil has the greatest cardiac depressant effect and may decrease heart rate and cardiac out put as well.

The most important toxic effects for calcium channel blockers are cardiac arrest, bradycardia, atrioventricular block and congestive *heart failure.*

Lines of treatment of primary hypertension

The initial step in treating hypertension may be non-pharmacologic. Dietary salt restriction may be effective treatment for about half of the patients with mild hypertension. Weight reduction even without salt restriction normalizes blood pressure in up to 70% of obese patients with mild to moderate hypertension. Regular exercise may also be helpful in some hypertensive patients.

When non-pharmacologic approaches do not satisfactorily control blood pressure, drug therapy begins in addition to non-pharmacological approaches.

The selection of drug(s) depends on various factors such as the severity of hypertension, patient factors (age, race, coexisting diseases, etc.).

For most patients with mild hypertension and some patients with moderate hypertension mono-therapy with either of the following drugs can be sufficient.

- Thiazide diuretics
- Beta blockers
- Calcium channel blockers

- Angiotensin converting enzyme inhibitors
- Central sympathoplegic agents

Beta-blockers are preferred in young patients, high renin hypertension and patients with tachycardia or angina and hypertension. Black patients respond well to diuretics and calcium channel blockers than to beta-blockers and ACE inhibitors.

If mono-therapy is unsuccessful, combination of two drugs with different sites of action may be used. Thiazide diuretics may be used in conjunction with a beta-blocker, calcium channel blocker or an angiotensin converting enzyme inhibitor.

If hypertension is still not under control, a third drug e.g. vasodilator such as hydralazine may be combined.

When three drugs are required, combining a diuretic, a sympathoplegic agents or an ACE inhibitor, and a direct vasodilator or calcium channel block is effective.

The treatment of hypertensive emergencies is usually started with furosemide given by parenteral route at dose of 20-40mg. In addition, parenteral use of diazoxide, sodium nitroprusside, hydralazine, trimethaphan, labetalol can be indicated.

II. Drug used in heart failure

Congestive heart failure occurs when there is an inability of the heart to maintain a cardiac out put sufficient to meet the requirements of the metabolising tissues.

Heart failure is usually caused by one of the following:

- Ischaemic heart disease,
- Hypertension,
- Heart muscle disorders, and
- Valvular heart disease.

Drugs used to treat heart failure can be broadly divided into:

A. *Drugs with positive inotropic effect.*
B. *Drugs without positive inotropic effect.*

A. Drugs with positive inotropic effect:-

Drugs with positive inotropic effect increase the force of contraction of the heart muscle. These include:

- Cardiac glycosides,

- Bipyridine derivatives,
- Sympathomimetics, and
- Methylxanthines

1. Cardiac glycosides.

Cardiac glycosides comprise a group of steroid compounds that can increase cardiac out put and alter the electrical functions. Commonly used cardiac glycosides are digoxin and digitoxin.

The mechanism of inotropic action of cardiac glycosides is inhibition of the membrane-bound Na^+/K^+ ATPase often called the "*Sodium Pump*". This results in an increased intracellular movement of sodium and accumulation of sodium in the cells. As a consequence of the higher intracellular sodium, decreased transmembrane exchange of sodium and calcium will take place leading to an increase in the intracellular calcium that acts on contractile proteins.

All cardiac glycosides exhibit similar pharmacodynamic properties but do differ in their pharmacokinetic properties. For example, digitoxin is more lipid soluble and has long half-life than digoxin.

Therapeutic uses of cardiac glycosides include:

- Congestive heart failure
- Atrial fibrillation,
- Atrial flutter, and
- Paroxysmal atrial tachycardia.

Toxicity of cardiac glycosides include:

- Gastrointestinal effects such as anorexia, nausea, vomiting, diarrhoea
- Cardiac effects such as bradycardia, heart block, arrhythmias
- CNS effects such as headache, malaise, hallucinations, delirium, visual disturbances (yellow vision)

Mild toxicities such as gastrointestinal and visual disturbance can be managed by reducing the dose of the drug.

For the management of arrhythmias or serious toxicity, potassium supplementation, administration of anti-arrhythmic drugs (e.g. lidocaine), and use of digoxin antibodies can be helpful.

2. Bipyridine derivatives, e.g. amrinone, milrinone.

These drugs possess both positive inotropic effect and vasodilator effects.

The suggested mechanism of action is inhibition of an enzyme known as phophodiesterase, which is responsible for the inactivation of cyclic AMP. Inhibition of this enzymes result in an increase in cAMP.

Bipyridine derivatives are used in cases of heart failure resistant to treatment with cardiac glycosides and vasodilators.

3. *Beta - adrenergic stimulants* e.g. dobutamine, dopamine

The increase in myocardial contractility by beta stimulants increase the cardiac out put. However, positive chronotropic effect of these agents minimizes the benefit particularly in patients with ischaemic heart disease. The positive inotropic effect of dobutamine is proportionally greater than its effect on heart rate.

It is reserved for management of acute failure or failure refractory to other oral agents.

4. Methylxanthines, e.g. theophylline in the form of aminophylline

Aminophylline has a positive inotropic effect, bronchodilating effect and a modest effect on renal blood flow.

It is used for management of acute left ventricular failure or pulmonary edema.

B. Drugs without positive inotropic effect. These include:

- Diuretics, e.g. hydrochlorothiazide, furosemide
- Vasodilators, e.g. hydralazine, sodium nitroprusside
- Angiotensin converting enzyme inhibitors e.g. captopril, enalapril

1. Diuretics

Diuretics are first – line drugs for treatment of patients with heart failure. In mild failure, a thiazide may be sufficient but are ineffective at low glomerular filtration rates. Moderate or severe failure requires a loop diuretic.

In acute failure, diuretics play important role by reducing ventricular preload. The reduction in venous pressure causes reduction of edema and its symptoms and reduction of cardiac size which leads to improved efficiency of pump function.

2. Vasodilators.

The vasodilators are effective in acute heart failure because they provide a reduction in preload (through venous dilation), or reduction in after-load (through arteriolar dilation), or both.

Hydralazine has a direct vasodilator effect confined to arterial bed. Reduction in systemic vascular resistance leads to a considerable rise in cardiac out put.

Sodium nitroprusside is a mixed venous and arteriolar dilator used also for acute reduction of blood pressure.

Vasodilator agents are generally reserved for patients who are intolerant of or who have contraindications to ACE inhibitors.

3. ***Angiotensin c*onverting enzyme (ACE) inhibitors.** Because of the pervasive involvement of angiotensin II in the undesirable compensatory responses to heart failure, reduction of this peptide has positive effects on the course of the disease.

These drugs reduce after load by reducing peripheral resistance and also reduce preload by reducing salt and water retention by way of reduction in aldosterone secretion.

They are nowadays considered a head of cardiac glycosides in the treatment of chronic heart failure.

The following are essential for long-term management of chronic heart failure:

Modify cardiovascular risk factor profile, e.g. cigarette smoking, obesity, salt intake Underlying causes should be treated, e.g. anemia, hypertension, valvular disease If this proves inadequate, diuretic should be given.

Give ACE inhibitor and digitalis (ACE inhibitors may be used before digitalis). In patients with persisting symptoms give vasodilators besides increasing the dose of diuretic and ACE inhibitors.

III) Pharmacotherapy of Angina pectoris

Angina pectoris develops as a result of an imbalance between the oxygen supply and the oxygen demand of the myocardium. It is a symptom of myocardial ischemia. When the increase in coronary blood flow is unable to match the increased oxygen demand, angina develops. It has become apparent that spasm of the coronary arteries is important in the production of angina.

Drugs used in angina pectoris

Organic nitrates e.g. nitro-glycerine, isosorbide dinitrate, etc.

Beta adrenergic blocking agents e.g. propranolol, atenolol, etc.

Calcium channel blocking agents e.g. verapamil, nifedipine, etc.

Miscellaneous drugs e.g. aspirin, heparin, dipyridamole.

1. Organic nitrates: organic nitrates are potent vasodilators and successfully used in therapy of angina pectoris for over 100 years.

The effects of nitrates are mediated through the direct relaxant action on smooth muscles. Nitrates are believed to act by mimicking the vasodilator action of endothelium derived relaxing factor (EDRF) identified as nitric oxide. Vasodilating organic nitrates are reduced to organic nitrites, which is then converted to nitric oxide.

The action of nitrates begins after 2-3 minutes when chewed or held under tongue and action lasts for 2 hours. The onset of action and duration of action differs for different nitrates and varying pharmaceutical preparations.

Adverse effects include flushing, weakness, dizziness, tachycardia, palpitation, vertigo, sweating, syncope localized burning with sublingual preparation and contact dermatitis with ointment.

Therapeutic uses: prophylaxis and treatment of angina pectoris, post myocardial infarction, coronary insufficiency, acute LVF (left ventricle failure)

2. Adrenergic blocking agents

Exercise and emotional excitement induce angina in susceptible subject by the increase in heart rate, blood pressure and myocardial contractility through increased sympathetic activity.

Beta receptor blocking agents prevent angina by blocking all these effects. In most patients the net effect is a beneficial reduction in cardiac workload and myocardial oxygen consumption e.g. atenolol, propranolol metoprolol, labetolol.

Adverse effects: Lethargy, fatigue, rash, cold hands and feet, nausea, breathlessness, nightmares and bronchospasm. Selective beta blockers have relatively lesser adverse effects.

Therapeutic uses other than angina include hypertension, Cardiac arrhythmias, post myocardial infarction and pheochromocytoma.

3. Calcium channel blockers: calcium is necessary for the excitation contraction coupling in both the cardiac and smooth muscles. Calcium channel blockers appear to involve their interference with the calcium entry into the myocardial and vascular smooth muscle, thus decreasing the availability of the intracellular calcium e.g. nifedipine, felodipine, verapamil and diltiazem.

Other therapeutic uses: hypertension, acute coronary insufficiency, tachycardia,

Adverse effects: flushing nausea/vomiting, headache, Ankle swelling, dizziness, constipation, etc.

4. Miscellaneous drugs,e.g. Acetylsalicylic acid

Acetylsalicylic acid (aspirin) at low doses given intermittently decreases the synthesis of thromboxne A_2 without drastically reducing prostacylin synthesis. Thus, at the doses of 75 mg per day it can produce antiplatelet activity and reduce the risk of myocardial infarction in anginal patients.

IV) Anti - arrhythmics

Electrophysiology of cardiac muscle: the pathophysiological mechanisms responsible for the genesis of cardiac arrhythmias are not clearly understood. However, it is generally accepted that cardiac arrhythmias arise as the result of either of

a) Disorders of impulse formation and/ or

b) Disorders of impulse conduction.

Pharmacotherapy of cardiac arrhythmias

Antiarrhythmic drugs are used to prevent or correct cardiac arrhythmias (tachyarrhythmias).

Drugs used in the treatment of cardiac arrhythmias are traditionally classified into:

Class (I): Sodium channel blockers which include quinidine, lidocaine, phenytion, flecainide, etc.

Class (II): Beta adrenergic blockers which include propranolol, atenolol, etc.

Class (III): Potassium channel blockers e.g. amiodarone, bretylium.

Class (IV): Calcium channel blockers e.g. verapamil, etc.

Class (V): Digitalis e.g.digoxin.

Class – I drugs

Quinidine: It blocks sodium channel so that there is an increase in threshold for excitability. It is well absorbed orally

Adverse effects: It has low therapeutic ratio. Main adverse effects are SA block, cinchonism, severe headache, diplopia and photophobia.

Lidocaine, which is used commonly as a local anaesthetic blocks both open and inactivated sodium channel and decreases automaticity. It is given parenterally.

Adverse effects: excessive dose cause massive cardiac arrest, dizziness, drowsiness, seizures, etc.

Flecainide: It is a procainamide analogue and well absorbed orally. It is used in ventricular ectopic beats in patients with normal left ventricular function.

Class –II drugs: Beta-adrenergic receptor blockers

Propranolol: Myocardiac sympathetic beta receptor stimulation increases automaticity, enhances A.V. conduction velocity and shortens the refractory period. Propranolol can reverse these effects. Beta blockers may potentiate the negative inotropic action of other antiarrhythmics.

Therapeutic uses: This is useful in tachyarrhythmias, in pheochromocytoma and in thyrotoxicosis crisis. It is also useful in patients with atrial fibrillation and flutter refractory to digitalis.

Class – III: Potassium channel blockers

AMIODARONE: This drug is used in the treatment of refractory supraventriculat tachyarrhythmias and ventricular tachyarrhythmias. It depresses sinus, atrial and A.V nodal function.

The main adverse effects of this drug are anorexia, nausea, abdominal pain, tremor, hallucinations, peripheral neuropathy, A.V. block

Class IV drugs: Calcium channel blockers

Verapamil: this drug acts by blocking the movement of calcium ions through the channels. It is absolutely contraindicated in patients on beta blockers, quinidine or disopyramide.

It is the drug of choice in case of paroxysmal supraventricular tachycardia for rapid conversion to sinus rhythm.

Class - V drugs:

Digoxin causes shortening of the atrial refractory period with small doses (vagal action) and a prolongation with the larger doses (direct action). It prolongs the effective refractory period of A.V node directly and through the vagus. This action is of major importance in slowing the rapid ventricular rate in patients with atrial fibrillation

Diuretics

Diuretics are drugs, which increase renal excretion of salt and water: are principally used to remove excessive extracellular fluid from the body.

In order to understand the action of diuretics it is important to have some knowledge of the basic processes that take place in the nephron (unit structure of kidney.

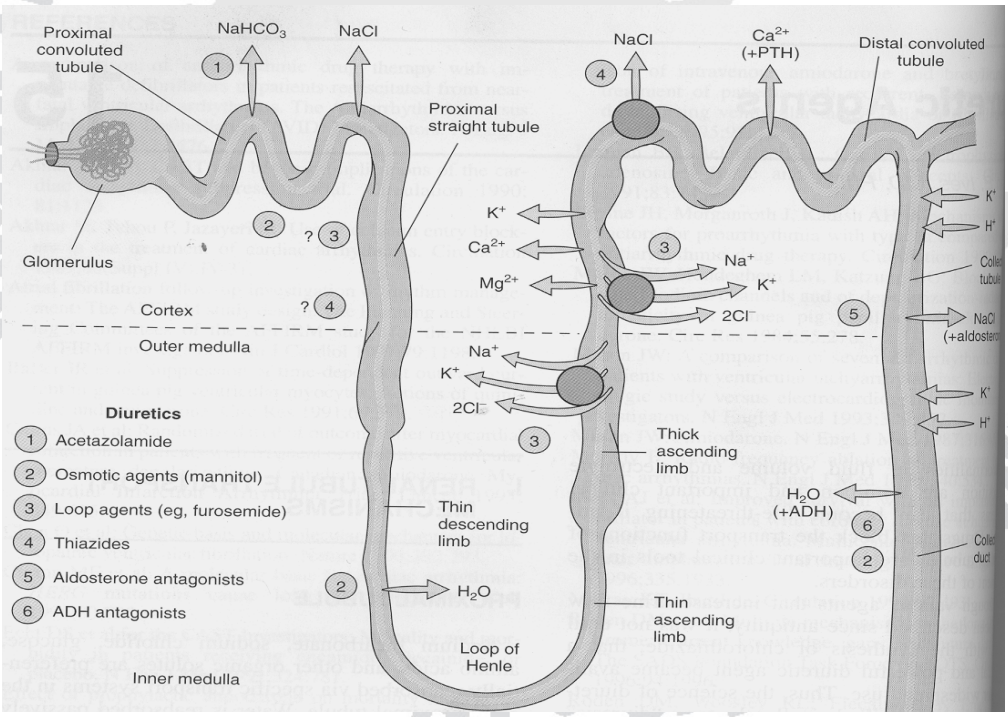


Fig 3.1 Sites of action of diuretics on renal tubule.

Approximately 180 liters of fluid is filtered from the glomerulus into the nephron per day. The normal urine out put is 1-5 liters per day. The remaining is reabsorbed in different areas of nephron. There are three mechanisms involved in urine formation

a) glomerular filtration
b) tubular reabsorption
c) Tubular secretion. These processes normally maintain the fluid volume, electrolyte concentration and PH of the body fluids.

Classification of diuretics:-

Most of the diuretics used therapeutically act by interfering with sodium reabsorption by the tubules. The major groups are:

I. Thiazides and related diuretics: e.g. Hydrochlorothiazide chlorthalidone, bendrofluazide, etc.
II. Loop diuretics: e.g. furosemide, ethacrynic acid, etc.
III. Potassium sparing diuretics e.g. triamterene, amiloride, spironolactone, etc.
IV. Carbonic anhydrase inhibitors e.g. acetazolamide
V. Osmotic diuretics e.g. mannitol, glycerol

I. Thiazide diuretics act by inhibiting NaCl symport at the distal convoluted tubule. They are used in hypertension, edema of hepatic, renal and cardiac origin.

Adverse effects: epigastric distress, nausea, vomiting, weakness, fatigue, dizziness, impotence, jaundice, skin rash, hypokalemia, hyperuricemia, hyperglycaemia and visual disturbance.

II. Loop diuretics: Loop diuretics like frusemde inhibit Na^+- K – 2Cl symporter in the ascending limb.

Adverse effects: Hypokalemia, nausea, anorexia, vomiting epigastric distress, fatigue weakness muscle cramps, drowsiness. Dizziness, hearing impairment and deafness are usually reversible. Therapeutic uses: acute pulmonary edema, edema of cardiac, hepatic and renal disease. Hypertension, cerebral edema, in drug overdose it can be used to produce forced diuresis to facilitate more rapid elimination of drug.

III. Potassium sparing diuretics mechanism of action: Potassium sparing diuretics (spironolactone, triamterene, amiloride) are mild diuretics causing diuresis by increasing the excretion of sodium, calcium and bicarbonate but decrease the excretion of potassium.

Adverse effects: G.I. disturbances, dry mouth, rashes confusion, orthostatic hypotension, hyperkalaemia. Hyponatraemia

Therapeutic uses: used with conjunction with thiazides or loop diuretics in edema due to, cardiac failure nephrotic syndrome and hepatic disease.

IV. Carbonic anhydrase inhibitors: these drugs like acetazolamide inhibit the enzyme carbonic anhydrase in renal tubular cells and lead to increased excretion of bicarbonate, sodium and potassium ions in urine. In eye it results in decrease information of aqueous humor. Therefore these are used in treatment of acute angle glaucoma. Main adverse effects of these agents are drowsiness, hypokalemia, metabolic acidosis and epigastric distress.

V. Osmotic diuretics: these drugs like mannitol and glycerine (glycerol) are freely filtered at the glomerulus and are relatively inert pharmacologically and undergo limited reabsorption by renal tubule. These are administered to increase significantly the osmolality of plasma and tubular fluid. Some times they produce nausea, vomiting, electrolyte imbalances. They are used in cerebral edema and management of poisoning.

Drugs used in hypotensive states and shock

Antihypotensive drugs or agents are used to elevate a low blood pressure and may be classified as follows:

I. ***Agents intended to increase the volume of blood in active circulation***. These include intravenous fluids such as whole blood, plasma, plasma components, plasma substitutes and solution of crystalloids

II. ***Vasoconstrictor drugs*** these include:

- Peripherally acting vasoconstrictors which are further divided into sympathomimetic drugs and direct vasoconstrictors.

Sympathomimetics used to elevate the blood pressure include adrenaline, noradrenaline, methoxamine, phenylephrine, mephentermine and ephedrine.

Direct vasoconstrictors include vasopressin and angiotensin.

Treatment of shock

Shock is a clinical syndrome characterized by decreased blood supply to tissues. Common signs and symptoms include oliguria, heart failure, disorientation, mental confusion, seizures, cold extremities, and comma.

Most, but not all people in shock are hypotensive. The treatment varies with type of shock.

The choice of drug depends primarily on the *patho-physiology involved.*

- For cardiogenic shock and decreased cardiac out put, ***dopamine*** or other ***cardiotonic*** drug is indicated. With severe CHF characterized by decreased CO and high PVR, ***vasodilator drugs*** (nitropruside, nitroglycerine) may be given along with the cardiotonic drug. ***Diuretics*** may also be indicated to treat pulmonary congestion if it occurs.
- For anaphylactic shock or neurogenic shock characterized by ***severe vasodilation*** and decreased PVR, a ***vasoconstrictor*** drug (e.g. levarterenol) is the first drug of choice
- For hypovolemic shock, intravenous fluids that replace the type of fluid lost should be given
- For septic shock, appropriate ***antibiotic therapy*** in addition to other ***treatment measures***.

Exercises

1. Discuss briefly the different groups of antihypertensive drugs.

2. Which of the antihypertensive drugs can also be used in angina pectoris?

3. What are the common adverse effects of vasodilators?

4. Discuss how digitalis and loop diuretics interact.

5. Describe the pharmacological approaches used in the management of shock.

CHAPTER FOUR

AUTACOIDS

Learning Objectives:

After going through this unit, the student will be able to:

1. Explain the role of histamine in anaphylactic reactions
2. List some of the therapeutic uses and adverse effects of H_1 antagonists
3. Describe the major pharmacological actions of prostaglandins E and F

INTRODUCTION

"Autacoids" (Greek "self-remedy") is a collective term for various endogenous peptides, prostaglandins, leukotrienes, and cytokines. These are sometimes also called local hormones. They play important roles in physiologic processes and also have several pharmacological significances.

1. Histamine

It is a potent tissue amine widely distributed in plant and animal tissues and in the venoms of bees. In man, it is formed by decarboxylation of histidine and major portion is stored in mast cells and basophils.

Mechanisms of Action: It acts on 2 major types of receptors

a. Stimulation of H_1 receptors results in smooth muscle contraction, increased vascular permeability, and mucus production. These effects are blocked competitively by H_1 antagonists.
b. Activation of H_2 receptors increases gastric acid production, and this effect is blocked by H_2 blockers such as cimetidine.

Both types of receptors are involved in vascular dilatation and edema formation.

Pharmacological Actions:

1. ***Cardiovascular system***

Histamine produces dilatation of capillaries and venules accompanied by a fall in blood pressure. The mechanism is direct relaxation of the smooth muscles of blood vessels. This effect cannot be adequately reversed by antihistaminic agents but by adrenaline.

It also has positive inotropic and chronotropic actions on the heart, impairs AV conduction, and increases coronary blood flow.

2. ***Smooth Muscles***:

Histamine directly stimulates the smooth muscles of various tissues including the bronchi and uterus. Histamine-induced bronchospasm is effectively antagonized by adrenaline.

3. ***Exocrine Glands***:

It is a powerful stimulant of HCl secretion by the gastric mucosa.

4. ***CNS***: Histamine is formed locally in the brain and is believed to be a "waking amine", acting by "increasing the sensitivity of large cerebral areas to excitation inputs"

5. ***Miscellaneous*** actions include induction of itching and pain.

Histamine has no valid therapeutic use currently. But it plays very important role in anaphylaxis and other forms of allergic reactions. Its release may be induced by various agents including certain venoms, drugs, trauma (thermal, chemical, radiation), and antigen-antibody reactions.

Treatment of Anaphylaxis

1. Exposure to the offending agent should be terminated.
2. Adrenaline has actions opposite to those of histamine and thus acts as a physiological antagonist. It may be given by SC or IM route.
3. Hypotension should be corrected with the infusion of intravenous fluids.
4. Corticosteroids are occasionally used.
5. Other supportive measures include administration of oxygen and artificial respiration if necessary.

N.B. Antihistaminic drugs are not able to counteract the hypotension and brochospasm characteristic of anaphylactic shock.

Antihistaminc Drugs

These drugs competitively block histamine receptors and are of two types:

1. H_1 receptor antagonists
2. H_2 receptor antagonists (used in the treatment of acid-peptic disease)

H_1 Receptor Antagonists

Classification of H1 recepror antagonists:

1. Potent and sedative: such as diphenhydramine and promethazine.
2. Potent but less sedative: such as cyclizine and chlorpheniramine

3. Less potent and less sedative: such as pheniramine
4. Non-sedative: such as terfenadine, loratadine, and cetrizine.

The newer generation agents are relatively free of central depressant effects.

These agents may also possess anti-emetic effects.

Pharmacological Actions:

1. Antihistaminic Actions:-they block histamine effects at various sites.
2. Other Effects: are independent of the antihistaminic effects and vary widely according to the drug used.

Most of them produce CNS depression resulting in sedation, drowsiness, inability to concentrate, and disturbances of coordination. But very few agents such as phenindamine may produce stimulation.Anti-motion sickness effects are exhibited by promethazine, diphenhydramine, and dimenhydinate.Promethazine and mepyramine have significant local anesthetic effect.Majority possess atropine-like effects.Some have central antimuscarinic actions which is useful in the treatment of Parkinsonism.

Pharmacokinetics:

They are well-absorbed following oral and parenteral administration. And are mainly metabolized by the liver; degradation products are removed in the urine.

Therapeutic Uses:

1. ***Allergic Disorders***:-Including urticaria, seasonal hay fever, atopic and contact dermatitis, mild blood transfusion reactions.

N.B. Their topical use is not recommended because of the risk of sensitization and a high tendency to cause eczematous reactions.

They are not effective in bronchial asthma and common cold.

2. ***Other uses:***

Diphehydramine and promethazine are used as hypnotics. Diphenhydramine and orphenadrine are effective in the treatment of Parkinsonism .Dimehydrinate and promethazine are employed in the prevention and treatment of motion sickness, other vomiting disorders associated with labyrinthine dysfunction as well as nausea and vomiting associated with pregnancy. Diphenhydramine is frequently used in the treatment of cough as combination preparation with other agents.

Adverse Effects:

- Are usually mild. Most common is sedation. The most common anticholinergic adverse effect is dryness of the mouth. They may themselves occasionally cause allergic reactions.

2. 5-Hydroxytreptamine (Serotonin)

It is widely distributed in plants and animals. Highest concentration in mammals is found in the pineal gland, acting as a precursor for melatonin. It is synthesized from the amino acid tryptophan and acts on several types of receptors.

Pharmacolocial Actions:

5-HT causes constriction of renal, splanchnic, meningeal, and pulmonary arteries and veins and venules, but dilatation of the blood vessels of skeletal musles, coronaries, and skin capillaries. It has weak direct ino-chronotropic effect on the myocardium. It also stimulates smooth muscles, especially of the intestines. Serotonin is widely distributed in the CNS, serving as a neurotransmitter. Altered functions may be responsible for disturbances in sleep, mood, sexual behavior, motor activity, pain perception, migraine, temperature regulation, endocrine control, psychiatric disorders and extra-pyramidal activity.

Serotonin Agonists:

Sumatriptan is a selective agonist of 5-HT_1 receptors and is highly effective in treating acute attacks of migraine, but is not useful in the prevention. It relieves the nausea and vomiting, but the headache may recur, necessitating repeated administrations.

It is administered orally or by the subcutaneous route. The bioavailability of oral dose is only 14 %; thus, the oral dose is several times larger than the subcutaneous dose.

Adverse effects include flushing and heat at the injection site, neck pain, dizziness, and tingling of the hands.

The drug is contraindicated with symptomatic ischemic heart diseases, angina, and hypertension as it may cause coronary vasoconstriction.

Buspirone, another serotonin agonist, is a useful effective anxiolytic agent.

Serotonin Antagonists:

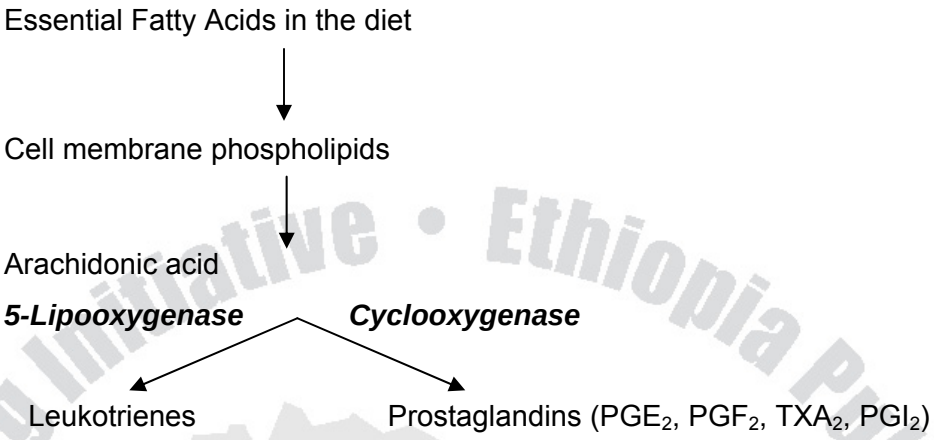
a. ***Methysergide:*** blocks the actions of 5-HT on a variety of smooth muscles. It also has a weak direct vasoconstrictor effect. It is an effective prophylactic agent for migrainous headaches. But has no effect in treating acute attacks, even may worsen the condition.
   Adverse reactions include gastrointestinal irritation, drowsiness, vertigo, and psychic disturbances.
b. ***Cyproheptadine:*** is a potent antagonist of 5-HT and to a smaller extent of histamine and acetylcholine. It stimulates appetite probably by acting directly on the hypothalamus. It can block the release of hydrocortisone, and the production of aldosterone. It is mainly used to relieve the itching associated with skin disorders such as allergic dermatitis. The common adverse reaction is drowsiness.
c. ***Ondansetron***: is specific 5-HT_3 receptor antagonist. Given orally or intravenously, it is useful in the management of nausea and vomiting associated with cytotoxic therapy. Adverse reactions include headache, constipation, and allergic reactions.
d. Prochlorperazine and haloperidol have anti-5-HT activity and are sometimes used for resistant acute attacks.

3. Prostaglandins:

They were named so because of their presumed origin from the prostate gland. Human seminal fluid is the richest known source, but they are also present in various tissues. The prostaglandins are synthesized from polyunsaturated fatty acids at their sites of action. PG E_2 and PG F_2 are the two main prostaglandins. They are released in the body by mechanical, chemical, and infectious insults.

They play an important role in the development of the inflammatory response in association with other mediators.

Synthesis of important prostaglndins and leukotriens:



Pharmacological Actions:

a. Smooth muscle: most stimulate myometrium and are known to be important in the initiation and maintenance of labor. Prostaglandin E has bronchodilator action.
b. GIT: they increase intestinal motility. PG E inhibits gastric acid secretion and has cytoprotective action on the gastroduodenal mucosa. Both PG E and F produce contraction of the longitudinal muscle of the gut. They also stimulate intestinal fluid secretion, resulting in diarrhea.
c. CVS: PGE is peripheral vasodilator and powerful natriuretic. PGF constricts arterioles and veins.
d. Platelets: Thromobxane causes platelet aggregation and vasoconstriction. PG I (prostacycline) is found in the vascular endothelium and is a potent inhibitor of platelet aggregation and is a vasodilator.
e. Miscellaneous: Prostaglandins are important in pain generation and perception. PGE and PGI produce hyperalgesia associated with inflammation. In addition, PG E is a potent pyrogenic substance.

Natural prostaglandins have no therapeutic application because of short duration of action, but their derivatives such as carboprost, dinoprostone and misoprostol find clinical application.

Therapeutic uses include cervical ripening and labor induction, control of postpartum hemorrhage, induction of abortion, and prophylaxis of NSAID-induced peptic ulcers. They are also finding several other uses more recently such as erectile dysfunction, glaucoma, etc.

Adverse Effects include fever, diarrhea, abdominal cramps, headache, nausea, and vomiting.

Exercise

1. Explain the antagonistic effects of histamine and adrenaline.

2. Discuss the consequences of inhibition of prostaglandin synthesis.

CHAPTER FIVE

DRUGS ACTING ON THE RESPIRATORY SYSTEM

Learning Objectives

At the end of the chapter the students will be able to learn:

- Detail description of drug used to treat bronchial asthma, cough, nasal congestion as a result of some disorders and allergic condition.
- Broad classification of drugs used to treat bronchial asthma
- The pharmacokinetics, mechanism of action, side effects of each group of drugs used to treat bronchial asthma.

INTRODUCTION

The respiratory system includes the upper airway passages, the nasal cavities, pharynx and trachea as well as the bronchi and bronchioles. Respiration is the exchange of gases between the tissue of the body and to outside environment. It involves breathing in of an air through the respiratory tract, uptake of oxygen from the lungs, transport of oxygen through the body in the blood stream, utilization of oxygen in the metabolic activities (cells and removal of carbon dioxide from the body.

Drug therapy of pulmonary disorders is generally directed towards altering a specific physiologic function. The chapter will focus on drugs used to treat some of the more common disorders affecting the respiratory system particularly bronchial asthma, allergies and congestions associated with certain respiratory disorders.

1.1 Bronchial asthma

Asthma is physiologically characterized by increased responsiveness of the trachea and bronchi to various stimuli and by wide spread narrowing of the airways that changes in severity either spontaneously or as a result of therapy

Impairment of airflow in bronchial asthma is caused by three bronchial abnormalities.

i. Contraction of airway smooth muscles
ii. Thickening of bronchial mucosa from edema and cellular infiltration
iii. Inspissations in the airway lumen of abnormally thick, viscid plugs of excessive mucus.

Pathogenesis

There are two types of bronchial asthma i.e extrinsic and intrinsic.

Extrinsic asthma is associated with history of allergies in childhood, family history of allergies, hay fever, or elevated IgE.

Intrinsic asthma occurs in middle-aged subjects with no family history of allergies, negative skin tests and normal serum IgE.

Immunologic model

Asthma is a disease mediated by reaginic (IgE) antibodies bound to mast cells in the airway mucosa. But not all features of asthma can be accounted for by antigen-challenge model. Non-antigenic stimuli like viral infections, exercise, and cold air stimulate bronchial spasm.

In allergic asthma, the immediate phase, i.e the initial response to allergen provocation, occurs abruptly and is due mainly to spasm of the bronchial muscle.Allergen interaction with mast cell-fixed IgE release histamine, LTC4 and LTD4 which cause bronchial spasm.

PHARMACOTHERAPY OF BRONCHIAL ASTHMA

Drug used in the treatment of bronchia asthma can be grouped into three main categories:

1. Bronchodilators
   a. β- Adrenergic agonists which include:
      - Non selective β-agonists e.g. adrenaline
      - Selective β-agonists e.g. salbutamol
   b. Methylxanthines; theophylline derivatives
   c. Muscranic receptor antagonists e.g. Ipratropium bromide
2. Mast cell stabilizers, e.g. cromolyn sodium, nedocromil, ketotifen
3. Antiinflammatory agents: corticosteroids

1. β- ADRENERGIC AGONISTS (SYMPATHOMIMETIC AGENTS)

a) Non- selective- β-agonists

- Epinephrine, ephedrine, isoprotenerol

b). Selective β-agonists

- Salbutamol, terbutaline, metaproterenol, salmeterol, formaterol and etc

Mechanism of Action

β-Agonists stimulate adenyl cyclase and increase formation of cAMP in the airway tissues.

They have got several pharmacological actions important in the treatment of asthma

- Relax smooth muscles
- Inhibit release of inflammatory mediator or broncho constricting substances from mast cells.
- Inhibit microvasculature leakage
- Increase mucociliary transport

a. Non-selective β- agonists

- Cause more cardiac stimulation (mediated by a β1 receptor), they should be reserved for special situation.
- Epinephrine: very effective, rapidly acting bronchodilator especially preferable for the relief of acute attack of bronchial asthma.
- Administered by inhalation or subcutaneously.

Side effects include arrhythmia and worsening of angina pectoris, increase blood pressure, tremors etc

Contraindication: - hypertension, arrhythmia,

Ephedrine: compared to epinephrine, it has longer duration of action but more pronounced central effect and lower potency. It can be given orally. The drug is currently infrequently used because of development of more efficacious and beta$_2$-selective agents.

b. Selective β_2- selective agonists

Largely replaced non – selective β_2- agonists, are effective after inhaled or oral administration and have got longer duration of action. They are the most widely used sympathomimetics. Commonly used drugs both by oral and inhalation are Salbutamol, terbutaline, metaproterenol, pirbuterol and bitolterol.

Salmeterol and formeterol are new generation, long acting β_2- selective agonists (with duration of action 12 hrs or more). These drugs appear to interact with inhaled corticosteroids to improve asthma control.

Delivery of adrenoreceptor agonists through inhalation results in the greatest local effect on airway smooth muscle with least systemic toxicity.

Side effects

Tremors, anxiety, insomnia, tachycardia, headache, hypertension and etc.

Contraindications: Sympathomimetics are contraindicated in patients with known hypersensitivity to the drugs

Precautions: They should be used cautiously in patients with hypertension, cardiac dysfunction, hyperthyroidism, glaucoma, diabetes, pregnancy.

2. METHYLXANTHINES

- The three important methylxanthines are theophylline, theobromine, and caffeine. The theophylline preparations most commonly used for therapeutic purposes is aminophylline (theophylline plus diethylamine).

Mechanism of Action

i. Competitively inhibit phosphodiesterase (PDE) enzyme leading to increased cAMP level.

ii. They competitively inhibit the action of adenosine on adenosine (A1 and A2) receptors (adenosine has been shown to cause contraction of isolated airway smooth muscle and to provoke histamine release from airway mast cells.

iii. Inhibit the release of histamines and leukotriens from the mast cells

Of the three natural xanthines, agents theophylline is most selective in its smooth muscle effect, while caffeine has the most marked central effect.

Pharmacokinetics

Only slightly soluble in water so has been administered as several salts containing varying amounts of theophylline base. Most preparations are well absorbed from gastro intestinal tract and metabolized by liver. Doses should be decreased in cases of liver disease and heart failure.

Adverse Effects:

Anorexia, nausea vomiting, abdominal discomfort, headache, anxiety, insomnia, seizures, arrhythmias

Theophylline is now largely reserved for patients in whom symptoms remain poorly controlled despite the combination of regular treatment with an inhaled anti- inflammatory agent and as needed use of a ß2 agonist.

3. MUSCRANIC RECEPTOR ANTAGONISTS

Mechanism of Action

Muscarinic antagonist competitively inhibit effect of acetylcholine at muscarinic receptors – hence block the contraction of air way smooth muscle and the increase in secretion of mucus that occurs in response to vagal activity e.g atropine sulfate

Systemic adverse effects as a result of rapid absorption include urinary retention, tachycardia, loss of accommodation and agitation and local effects like excessive dryness of mouth limits the quantity of atropine used. Ipratropium bromide is poorly absorbed and does not readily enter the central nervous system thus permits the delivery of high doses to muscarinic receptor in the airways; hence, it can safely be used for bronchial asthma.

Antimuscranic antagonist drugs appear to be slightly less effective than β- agonists agents in reversing asthmatic bronchospasm, The addition of ipratropium enhances the bronchodilation produced by nebulized albuterol in acute sever asthma. The antimuscarinic agents appear to be of significant value in chronic obstructive pulmonary diseases - perhaps more than asthma. They are useful as alternative therapies for patients intolerant of β - agonists

4. ANTI-INFLAMMATORY AGENTS: CORTICOSTEROIDS

Used both for treatment and prophylactic purposes

Mechanism of action

They are presumed to act by their broad anti inflammatory efficacy mediated in part by inhibition of production of inflammatory mediators. They also potentiate the effects of β- receptor agonists and inhibit the lymphocytic-eosinophilic airway mucosal inflammation

Effects on airway

- decreases bronchial reactivity
- increases airway caliber
- decreases frequency of asthma exacerbation and severity of symptoms

The corticosteroids commonly used are hydrocortisone, predinisolone, beclomethasone, triamcinolone and etc.

The drugs can be taken by inhalation as aerosol, oral, or an IV administration

Because of severe adverse effects when given chronically, oral and parenteral corticosteroids are reserved for patient who need urgent treatment and those who have not improved with

bronchodilator. Aerosol treatment is the most effective way to decrease the systemic adverse effect of corticosteroid therapy. Abrupt discontinuation should be discouraged because of the fear of adrenal insufficiency. Doses should be decreased after improvement. Regular or controlled therapy is better maintained with aerosol corticosteroids.

Clinical uses in bronchial asthma

- Urgent treatment of severe asthma not improved with bronchodilator
    - IV, inhalation or oral.
- Nocturnal asthma prevention
    - oral or inhalation
- Chronic asthma
    - Regular aerosol corticosteroids

Side effects:

- Suppression of the hypothalamic-pituitary-adrenal axis
- Osteoporosis
- Sodium retention and hypertension
- Cataract
- Impairment of growth in children
- Susceptibility to infection like oral candidiasis, tuberculosis

5. MAST CELL STABILIZERS

e.g cromolyn sodium

Mechanism of action

Stabilize the mast cells so that release of histamine and other mediators is inhibited through alteration in the function of delayed chloride channel in cell membrane. It has no role once mediator is released and is used for casual prophylaxis.

Clinical uses

- Exercise and antigen induced asthma
- Occupational asthma

Side effects

Poorly absorbed so minimal side effect

Throat irritation, cough, dryness of mouth, chest tightness and wheezing

TREATMENT OF STATUS ASTHMATICS

Status asthmatics

Very sever and sustained attack of asthma which fails to respond to treatment with usual measures

Management includes:

- Administration of oxygen
- Frequent or continuous administration of aerosolized ß2 agonists like salbutamol
- Systemic corticosteroid like methyl prednisolone or hydrocortisone IV
- Aminophylline IV infusion
- Iv fluid to avoid dehydration
- Antibiotics in the presence of evidence of infection

ANTI-TUSSIVES

Cough is a protective reflex, which serves the purpose of expelling sputum and other irritant materials from the respiratory airway.

Types:

- Useful productive cough
    - Effectively expels secretions and exudates
- Useless cough
    - Non-productive chronic cough
    - Due to smoking and local irritants

Anti-tussives are drugs used to suppress the intensity and frequency of coughing.

Two Types of Anti-tussives:

1. Central anti- tussives
    - Suppress the medullay cough center and may be divided into two groups:
        - Opoid antitussive e.g. codeine, hydrocodeine, etc
        - Non opoid antitussives e.g. dextromethorphan
2. Peripheral antitussives
    - Decrease the input of stimuli from the cough receptor in the respiratory passage.

e.g: Demulcents e.g. liquorices lozenges, honey

Local anesthetics e.g. lidocaine aerosol

Demulcents coat the irritated pharyngeal mucosa and exert a mild analgesic effect locally.

CODEINE

Codeine is a narcotic relatively less addicting drug and central antitussive agen and it's main side effects are dryness of mouth, constipation and dependence.

DEXTROMETROPHAN

Dextromethorphan is an opoid synthetic antitussive, essentially free of analgesic and addictive properties and the main side effects are respiratory depression

Expectorant is a drug that aid in removing thick tenacious mucus from respiratory passages, e.g. Ipecac alkaloid, sodium citrate, saline expectorant, guanfenesin, potassium salts

Mucolytics are agents that liquefy mucus and facilitate expectoration, e.g.acetylcysteine.

DECONGESTANTS

Decongestants are the drugs that reduce congestion of nasal passages, which in turn open clogged nasal passages and enhances drainages of the sinuses.

e.g phenylephrine, oxymetazoline etc.

Mechanism of Action

Mucus membrane decongestants are α_1 agonists, which produce localized vasoconstriction on the small blood vessels of the nasal membrane. Reduce congestion in nasal passages.

Clinical uses:

Used in congestion associated with rhinitis, hay fever, allergic rhinitis and to a lesser extent common cold.

Drugs can be administered nasally or orally for longer duration of action.

Classification:

1. Short acting decongestants administered topically – phenylepherne, phenylpropanolamine
2. Long acting decongestants administered orally - ephedrine, pseudoephedrine, naphazoline
3. Long acting topical decongestants
    - Xylometazoline
    - oxymetazoline

Side effects:

1. Rebound nasal congestion
2. Ischemic changes in mucus membranes
3. Nasal burning, stinging, dryness
4. Tachycardia, arrhythmia, nervousness, restlessness, insomnia, blurred vision

Contraindications

1. Hypertension, severe coronary artery disease

Exercice

1. What are the drugs used to treat bronchial asthma and how are they classified?
2. Explain mechanism of action and pharmacokinetic properties of methylxanthines.
3. What are the side effects and contraindications of glucocorticoids?
4. What are differences between antitussives and expectorants? Give example.
5. Give examples of decongestant drugs and their side effects.

CHAPTER SIX

DRUGS USED IN GASTROINTESTINAL DISEASES

Learning objectives

After completing this chapter the student will be able to:

- Descibe different drugs used for treatment of gastrointestinal diseases,
- Understand the basic pharmacological principles of these drugs,
- Know the adverse effects of these drugs,
- Use the drugs rationally.

INTRODUCTION

The pharmacologically treatable disorders of impairements of normal motility, digestion, absorption, secretions of the gastrointestinal tract include peptic ulcer, reflux esophagitis, Zollinger-Ellison syndrome, gastroparesis, constipation, diarrhea, inflammatory diseases and infections. This chapter discusses different drugs used for treatment of these disorders. However, anti-infective drugs will be discussed in other chapter.

I. Drugs used in Acid-peptic disease:

Acid-peptic disease includes peptic ulcer (gastric and duodenal), gastroesophageal reflux and Zollinger – Ellison syndrome.

Peptic – ulcer disease is thought to result from an imbalance between cell – destructive effects of hydrochloric acid and pepsin and cell-protective effects of mucus and bicarbonate on the other side. Pepsin is a proteolyic enzyme activated in gastric acid, also can digest the stomach wall.

A bacterium, Helicobacter pylori is now accepted to be involved in the pathogenesis of ulcer.

In gastroesophageal reflux, acidic stomach contents enter into the esophagus causing a burning sensation in the region of the heart; hence the common name heartburn, or other names such as indigestion, dyspepsia, pyrosis, etc.

Zollinger-Ellison syndrome is caused a tumor of gastrin secreting cells of pancreas characterized by excessive secretion of gastrin that stimulates gastric acid secretion.

The disorders can be treated by drugs, which are able to:

- Neutralize gastric acid (HCl) e.g. magnesium hydroxide
- Reduce gastric acid secretione.g. cimetidine
- Enhance mucosal defences e.g sucralfate
- Exert antimicrobial action against H.pylori e.g. clarithromycin

The effective therapeutic approach of ucler is based on the adage:

“no acid, no ulcer”

Anti – ulcer drugs: drugs used in the prevention and treatment of peptic ulcer disease act mainly to decrease cell-destructive effects, increase cell – protective effects or both.

A: Gastric acid neutralizers (antacids)

Antacids are alkaline substances (weak bases) that neutralize gastric acid (hydrochloric acid)

They react with hydrochloric acid in the stomach to produce neutral or less acidic or poorly absorbed salts and raise the PH of stomach secretion, and above PH of 4, pepsin is inactive. Antacids are divided into systemic and nonsystemic

Systemic, e.g. sodium bicarbonate are absorbed into body fluids and may alter acid – base balance. It can be used in the treatment of metabolic acidosis.

Non systemic, do not alter acid – base balance significantly. They are used as gastric antacids; and include aluminium, magnesium and calcium compounds e.g. ($Al(OH)_3$, MgS_2O_3 , $Mg(OH)_2$, $CaCO_3$)

- Gastric antacids differ in their potency, in onset of action, duration of action and adverse effects produced.
- Magnesium compounds have a relatively high neutralizing capacity, rapid onset of action, cause diarrhoea and hypermagnesemia.
- Aluminium compounds generally have a low neutralizing capacity, slow onset of action but long duration of action and may cause constipation.

Calcium compounds are effective and have a rapid onset of action but may cause hypersecretion of acid (acid - rebound) and milk-alkali syndrome (hence rarely used in peptic ulcer disease). All gastric antacids act chemically although some like magnesium trisiolicate can also act physically.

The most commonly used antacids, are mixtures of aluminium hydroxide and magnesium hydroxide (e.g. Gelusil, Maalox etc).

Antacids act primarily in the stomach and are used to prevent and treat peptic ulcer. They are also used in the treatment of Reflux esophagitis and Gastritis

B. Gastric acid secretion inhibitors (antisecretory drugs):

HCl is secreted by parietal cells of the gastric mucosa which contain receptors for acetylcholine, histamine and gastrin that stimulate the secretion.

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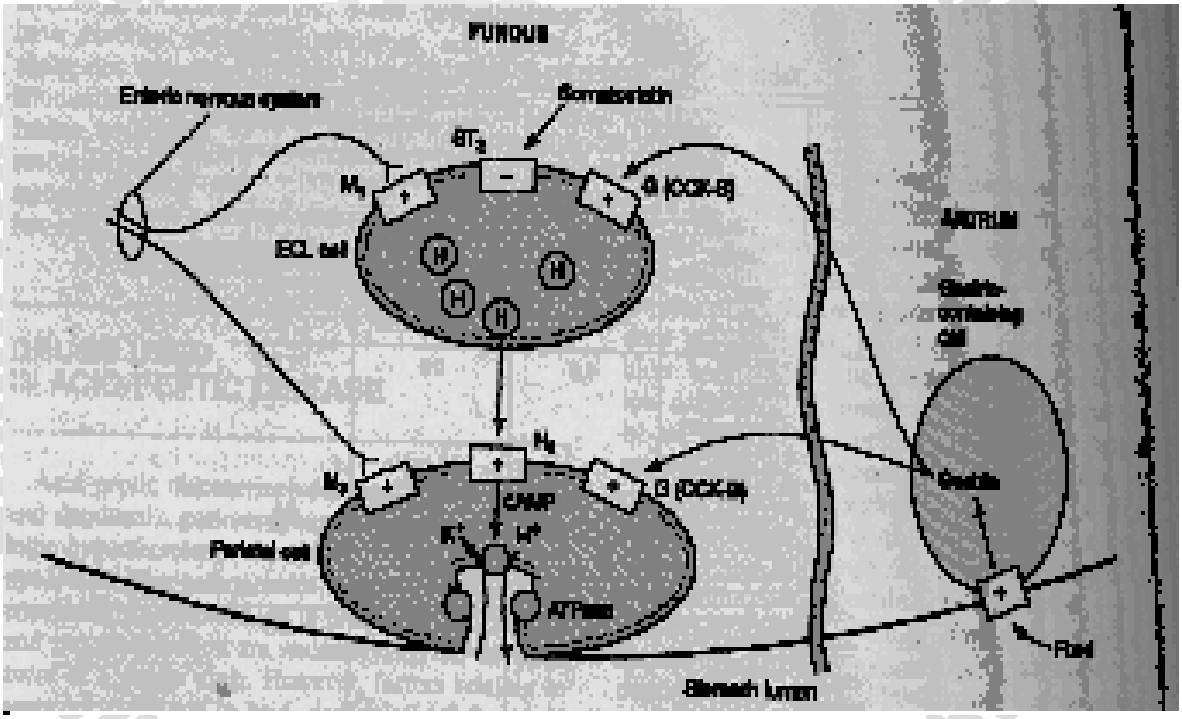

Fig 6.1 Endogenous acid secretagogues.

Antagonists of ***acetylcholine***, ***histamine*** and ***gastrin*** inhibit acid secretion.

Antisecretory drugs include:

- H_2-receptors blocking agents such as ***cimetidine, ranitidine, famotidine, nizatidine.*** *Cimetidine is the proto type of the group.*

Cimetidine dosage: PO 400mg 2 times/day, with meals and at bed time, or 800mg once daily at bed time for 6-8 weeks.

Prophylaxis of recurrent ulcer, PO 400mg at bed time. High doses are used in the treatment of Zollinger-Ellison syndrome.

Common adverse effects: muscular pain, headache, dizziness,

anti- androgenic effects at high doses such as impotence,gynecomastia,menstrual irregularities. Drug interactions may occur when it is co-adminstered with warfarin, theophylline, phenytoin, etc. and and the effects of the latter drugs is enhanced because of inhibition of the metabolism of them.

Proton pump inhibitors such as***, omeprazole***, ***lansoprazole, etc.*** inhibit H^+ -K^+-ATPase(proton pump) which is the common terminal step in aa the three secretagogues to release hydrogen ion into the gastric lumen.

Omeprazole dosage: - gastritis, gastroesophageal reflux disease, PO 20mg/day for 4-8 weeks; zollinger-Ellison syndrome, PO 60mg once daily initially -120mg/day.

Peptic ulcer disease, ***PO 10-60mg/day.*** Adverse effects include headache, diarrhea and nausea.

Anticholinergic agents such as pirenzepine, dicyclomine

Major clinical indication is prevention & treatment of peptic ulcer disease, Zollinger Ellison syndrome, reflux esophagitis.

Anticholinegic drugs are not used alone in the treatment of peptic ulcer. However, they are combined with ***H_2-antagonists to further decrease acid secretion***, with antacids to delay gastric empting and thereby prolong acid – neutralizing effects, or with any anti-ulcer drug for antispasmodic effect in abdominal pain.

C. Cytoprotective (mucosal protective) agents.

Locally active agents help to heal gastric and duodenal ulcers by forming a protective barrier between the ***ulcers*** and ***gastric acid, pepsin,*** and ***bile salts***.

- They do not alter the secretion of gastric acid. These drugs include ***sucralfate*** and ***colloid bismuth compounds***. (e.g. tripotassium, dicitratobismuthate)

- Colloidal bismuth compounds additionally exert bactericidal action against H.pylori

  Other drugs that can to eradicate H.pylori such as amoxicillin, metronidazole, clarithromycin and tetracycline are included in the anti-ulcer treatment regimens.

- Protaglandins have both antisecretory and mucosal protective effects.

  Example: **Misoprostol**- used for prevention of NSAID – induced ulcer.

II. Laxatives and cathartics (purgatives)

Laxatives and ***cathartics*** are drugs used orally to evacuate the bowels or to promote bowel elimination (defecation).

The term ***laxative*** implies ***mild effects***, and eliminative of soft formed stool. The term cathartic implies ***strong effects*** and ***elimination of liquid*** or ***semi liquid*** stool. Both terms are used interchangeably because it is the ***dose*** that determines the effects rather than a particular drug.

Example:- castor oil laxative effect= 4ml
Cathartic effect = 15-60ml

Laxative and cathartics are arbitrarily classified depending on mode of action as:

- Bulk forming laxatives: are substances that are largely unabsorbed from the intestine. They include hydrophilic colloids such as psyllium, bran, methylcellulose, etc. When water is added, the substances swell and become gel-like which increases the bulk of the fecal mass that stimulates peristalsis and defecation.

Osmotic laxatives such as magnesium sulfate, magnesium hydroxide, sodium phosphate, etc. also belong to bulk – forming laxatives.

These substances are not efficiently absorbed, thus creating a stronger than usual solution in the colon which causes water to be retained. The increase in pressure and volume causes stimulation of peristalsis.

- Stimulant (irritant) laxatives (cathartics): are substances that are themselves irritant or contain an irritant substance to produce purgation. Individual drugs are castor oil, bisacodyl, phenolphthalein, cascara sagrada, glycerine, etc.

They are the strongest and most abused laxative products that act by irritating the GI mucosa and pulling water into the bowel lumen. The feces is moved too rapidly and watery stool is eliminated as a result. Glycerine can be administered rectally as suppository only.

- Fecal softners – Decrease the surface tension of the fecal mass to allow water to penetrate into the stool. They have detergent – like property e.g. ***docusate***.
- They may also decrease water absorption through intestinal wall.
- Lubricant laxatives e.g. ***liquid paraffin*** (mineral oil). It lubricates the intestine and is thought to soften stool by retarding colonic *absorption of fecal water*.

- Used as retention enema.

Indications for use

Laxatives and cathartics are used:

1. To relieve constipation – bulk – forming
2. To prevent straining – stool softeners
3. To empty the bowel in preparation for bowel surgery or diagnostic procedures (saline or stimulant)
4. To accelerate elimination of potentially toxic substances from the GI tract (saline or stimulant)
5. To accelerate excretion of parasite after anthelmintic drugs (saline or stimulant) have been administered.

- Constipation is a common problem in older adults and laxatives are often used or overused. Non drug measures to prevent constipation (e.g. ***increasing intake of fluid*** and ***high –fiber foods, exercise***) are much ***preferred to laxatives***.

III. Antidiarrhoeals:

- Are used in the treatment of diarrhea, defined as the *frequent expulsion* of liquid or semi liquid stools → hinders absorption of fluids and electrolytes.
- In many instances, drug intervention is not required because is a protective mechanism used in an attempt by the body to flush out the offending pathogen or agent.

  Antidiarrheal drugs may be given to relive the symptom (non-specific therapy) or may be given to treat the underlying cause of the symptom (specific therapy).

- For symptomatic treatment of diarrhoea, opiates and opiate derivatives are the most effective. They decrease diarrhea by slowing propulsive movements in small and large intestine.

Morphine is effective but not used because of serious potential adverse effects, other synthetic drugs such as diphenoxylate and loperamide are commonly used

- Adsorbent – demulcent products such as kaolin – pectin preparation may be included in antidiarrheal preparations, unfortunately, they may adsornutrient and other drugs, including the antidiarrheal agents if given concurrently
- Anticholinergic agents e.g. atropine are occasionally used to decrease abdominal cramping and pain associated with diarrhea.
    - Specific therapy may include the use of antibacterial, which are recommended for use in carefully selected cases of bacterial enteritis.
    - Severe diarrhea by salmonella, shigella, campylobacter and clostridia. Species can be treated by antibiotics (ampicillin, chloramphinicol, colistin, co-trimoxazole etc.

Indications for use

1. severe or prolonged diarrhea (>2-3 days)
2. when specifice causes have been determined

Glucose – electrolyte solution should be given in severe cases for electrolyte and fluid replacement. It contains:

Glucose	20 gm
NaCl	3.5gm
$NaHCO_3$	2.5gm
KCl	1.5gm
Add water to	1000ml

IV. Antiemetics:

- Are drugs used to prevent or treat nausea and vomiting.

Nausea is an unpleasant sensation of abdominal discomfort accompanied by a desire to vomit.

Vomiting is the expulsion of stomach contents through the mouth Nausea may occur without vomiting and vomiting may occur without prior nausea, but the two symptoms most often occur together.

- Vomiting occurs when the vomiting center in the medulla oblongata is stimulated. Dopamine and acetylcholine play a major role in stimulating the vomiting center. To a certain extent, vomiting is a protective mechanism which can result from various noxious stimuli.

Drugs used in nausea and vomiting belong to several different therapeutic classifications.

- Most antiemetic agents relieve nausea and vomiting by acting on the vomiting center, CTZ, cerebral cortex, vestibular apparatus, or a combination of these.
- Antiemetic drugs are generally more effective in prophylaxis than treatment. Antiemetic drugs include:

Phenothiazines (neuroleptics) such as chlorpromazine

- Acts on CTZ and vomiting center
- Block dopamine receptors
- Are effective in prevention or treating nausea and vomiting induced by drugs, radiation therapy, surgery and most other stimuli
  (e.g. pregnancy).
- Are generally ineffective in motion sickness.

Antihistamines – such as promothazine, dimehydrinate etc.

- Are especially effective in prevention and treatment of motion sickness (but they may cause concurrent drowsiness, that may be troublesome for travellers)

Miscellaneous antiemetics

Metoclopramide has both central and peripheral antiemetic effects. Centrally, metoclopoamide antagonizes the action of dopamine.

Peripherally metoclopoamide stimulates the release of acetylcholine, which in turn, increases the rate of gastric emptying (used in esophapeal reflux)

Indication as chlorpromazine

- ***Scopolamine,*** an anticholinergic drug is very effective in reliving nausea & vomiting associated with motion sickness.
- Ondansetron- is serotonin antagonist (5-HT_3 receptors) found on the afferent fibers of the vagus nerve and in parts of the brain associated with CTZ.
- Controls chemical induced vomiting and nausea)

V. Drugs used to induce vomiting

In case of poisoning with noncorrosive agents, and assuming incomplete absorption of the poison has taken place, induction of vomiting can be carried out

The drug used for this purpose is emetine, the active ingredient of ipecacuanha (syrup of ipecac).

Emetine induces by direct irritation of the upper gut and on absorption, it also acts on CTZ.

VI. Drugs used in the treatment of haemorrhoids

Haemorrhoids are varicose veins of the anal canal which can be very distressing for the sufferer. There is no pharmacological cure for this disorder, which is often self-limiting, if not, may require surgical intervention.

The use of drugs may however, linder the sufferings:

- Stool softeners may alleviate constipation; lessen straining which can worsen the condition.
- Local anesthetics (e.g. lignocaine, benzocaine) relieve pain
- Corticosteroids (e.g. predniosolone) suppress inflammation, itching & swelling
- Vasoconstrictors (e.g. adrenaline, phenylephine) lessen venous swelling
- Astringent compounds (e.g. tannic acid) reduce swelling by precipitating cell surface proteins. Antihaemmorhoidal preparations contain one or more of these agents.

VII. Drugs used in inflammatory bowel disease (ulcerative colitis and crohn's disease)

- Ulcerative colitis is an inflammatory condition of the rectum and colon; crohni's disease can involve the whole intestine.
- Both diseases can lead to pain and ***abdominal discomfort***. Two groups of drugs used to treat both conditions are
    1. corticosteroids e.g. prednisolone
    2. drugs related to sulphonamides e.g. sulfasalazine.

CHAPTER SEVEN
DRUGS ACTING ON THE BLOOD
INFLAMMATION AND GOUT

Learning Objectives

After reading and studying this chapter the student should be able to

- Discuss the pharmacokinetics of iron, Vit B_{12} and folic acid.
- Explain the mechanisms of action of major anti anemic drugs
- Discuss the use of iron to treat iron deficiency anemia, the use of Vit B_{12} and folic acid to treat megaloblastic anemia.
- Describe how heparin and oral anticoagulants produce their effect.
- Discuss the indication of heparin and oral anticoagulants
- Identify major adverse reactions associated with heparin and oral anticoagulants

INTRODUCTION

Hematopoiesis, the production of circulating erythrocytes, platelets and leukocytes from undifferentiated stem cells, is a remarkable process that produces over 200 billion new cells per day in the normal person and even greater number of blood cells in people with conditions that causes loss or destruction of blood cells. The hemopoietic machinery resides primarily in the bone marrow in adults, and requires constant supply of three essential nutrients – iron, vitamin B12 and folic acid

ANEMIA – a deficiency in oxygen carrying erythrocytes and very common in developing countries

In this section anemia due to deficiency of iron, vit B_{12} or a folic acid will be dealt with.

AGENTS USED IN ANEMIAS

IRON

Iron forms the nucleus of the iron porphyrin heme ring, which together with globin chains forms hemoglobin that reversibly binds oxygen and provides the critical mechanism for oxygen

delivery from lungs to other tissues. In the absence of adequate iron, small erythrocytes with insufficient hemoglobin are formed resulting in microcytic hypochromic anemia.

Causes of Iron Deficiency Anemia

1. Nutritional deficiency

Low intake of iron containing foods, reduced absorption as a result of mucosal damage, co-administration of drugs that chelate iron e.g. antacids and after gastrectomy iron deficiency will take place.

2. Chronic blood loss

Chronic nose bleeding, Menorrhagia, Occult GI bleeding, Worm infestation and Ulers, e.g. PUD.

Pharmacokinetics of Iron

Daily requirement of Iron - Male 10mg
- Female 15 mg

Increases in growing children, pregnant and lactating women

Sources

- Dietary - mostly in the organic form from meat, cereals, etc.

Body composition of Iron

Total content of Iron in the body is about 4000mg in an adult male, of which about 2/3 – 2500 mg is present in circulating red blood cells see table.

Table: Iron distribution in normal adults

	Iron content (mg)	
	Men	**Women**
Hemoglobin	3050	1700
Myoglobin	430	30
Enzymes	10	8
Transport (transferin	8	6
Storage (ferritin and other form)	750	300
Total	4246	2314

N.B. The above estimations are based on the assumptions that:

The average male adult weighs 80 kg and has a mean Hb level of 16 g/dL and the female adult weighs 55 kg and has a mean Hb level of 14 g/dL.

Absorption

Iron is absorbed in duodenum and proximal jejunum. A normal individual with out iron deficiency absorbs 5-10 % of daily intakes.

Absorption is increased in states with increased requirements or deficiencies (low iron stores, pregnancy, menstruation, growing children, and blood loss) and/or dietary factors such as heme-iron (from meat, etc), HCl and vitamin C.

Absorption is decreased from non heme iron (Fe^{3+}), in the presence of phytates, antacids and other chelates, and following gastric resection.

Iron crosses the stinal mucosal cell by active transport; then according to mucosal iron store, it can either be available to transferrin to be transported to plasma or be stored in the mucosal cell as ferritin.

Storage: Iron is stored primarily as ferritin in intestinal mucosal cells and in macrophages in the liver, spleen and bone.

Elimination:

Very small amount are execrated in stool by exfoliation of intestinal mucosal cells and trace amounts are execrated in bile, urine and sweat with total daily excretion not more than 1mg/day.

TREATMENT OF IRON DEFICIENCY ANEMIA

The cause should always be identified and treated whenever possible. Treatment of iron deficiency anemia consists of administration of oral or parenteral iron preparation.

1. Oral Iron Therapy:

Only ferrous salts should be used because of most efficient absorption. Ferrous sulfate, ferrous gluconate, ferrous fumarate are the most commonly used oral iron preparations. About 25% of oral iron given as ferrous salt can be absorbed; therefore 200-400mg elemental irons should be given daily to correct iron deficiency most rapidly. Treatment should be continued for 3-6 months to replenish iron stores.

Side effects: Oral iron therapy can cause nausea, vomiting, epigastric discomfort, abdominal cramps, constipation and diarrhea.

2. Parenteral iron therapy:

Should be reserved for patient unable to tolerate or absorb oral iron. Patients with extensive chronic blood loss who can not be maintained with oral iron alone including patients with various post gastrectomy conditions, previous small bowel resection, inflammatory bowel disease involving proximal small bowel and malabsorption syndromes need parenteral iron therapy.

Drugs for parenteral administration include:

- Iron dextran
- Iron sorbitol

They may be given by deep IM or occasionally IV. Intravenous administration may result in very severe allergic reactions and thus should be avoided if possible.

Side effect: include local pain, tissue staining, headache, light headedness, fever, arthralgia, nausea, vomiting, urticaria, back pain, bronchospasm, and rarely anaphylaxis and death.

Acute iron Toxicity

Is exclusively seen in young children who ingest a number of iron tablets and rarely seen in adults as a result of suicide or repeated blood transfusions.

Signs and symptoms

Necrotizing gastroenteritis with vomiting, abdominal pain and bloody diarrhea, shock, metabolic acidosis, coma

Treatment

Whole bowel irrigation.

Deferoxamine- A potent iron chealating compound should be given systemically to bind iron and promote excretion through urine

VITAMIN B_{12}

Vitamin B_{12} is made up of a porphyrin-like ring with a central cobalt atom attached to a nucleotide. Daily vitamin B_{12} requirement is 2-5 mg. It is mainly obtained from animal products and serves as a co factor for essential biochemical reaction in humans. Ultimate source of vit B_{12} is from microbial synthesis.

Pharmacokinetics

Absorbed in distal ileum after combined with intrinsic factor secreted by stomach through a highly specific receptor mediated transport system once absorbed vit B_{12} is transported to various cells of the body bound to plasma glycoprotein, transcobalamin II. Excess vitamin B_{12} is transported to the liver for storage and excreted in the urine.

Physiologic function

- Acts as a coenzyme in the synthesis of DNA and is also essential for various metabolisms in the body.

Clinical uses

- Vit B_{12} is used to treat or prevent deficiency of vit B_{12}

Deficiency of Vit B_{12} results in:

- Megaloblastic anemia
- Neurological syndrome involving spinal cord and peripheral nerves

Causes:

The causes for Pernicious anemia are defective secretion of intrinsic factor necessary for absorption of vitB_{12}, partial or total gastrectomy, diseases that affect distal ileum, malabsoption syndrome e.g inflammatory bowel disease, small bowel resection etc.

Almost all cases of vit B_{12} deficiencies are caused by malabsorption

Treatment

Vit B_{12} therapeutic preparations are cyanocoblamin and hydroxycobalamin and For intrinsic factor deficiency the vitamin should be given parenterally and patients with pernicious anemia will need life-long therapy.

FOLIC ACID

Folic acids are required for essential biochemical reactions that provide precursors for the synthesis of amino acids, purines and DNA.Daily requirement is 50 -100μg. Folic acid deficiency is not uncommon.

Sources include yeast, liver, kidney and green vegetables.

Physiologic functions

It plays a role in the biosynthesis of purines and pyrimidines, i.e., DNA.

Folic acid → dehydrofolate→ tetrahdyroflate

↓ ↓

pyrmidens purine

↓ ↓

DNA

Phamacokinetics

Unaltered folic acid is readily and completely absorbed in the proximal jejunum. 5 -20 mg of folates are stored in the liver and other tissues. Body stores of folates are relatively low and daily requirement is high and hence folic acid deficiency and magaloblasitc anemia can develop within 1 -6 months after the in take of folic acid stops. Folates are excreted in the urine and stool.

Deficiency:

Common among elderly patients, poor patients, pregnant ladies. It results in megaloblasiic anemia. Congenital malformation in newborn like spina bifida are also consequences of folate deficiency during pregnancy.

Causes

Dietary deficiency, alcoholics with liver disease, hemolytic anemia, malabsorption syndrome, patients with cancer, leukemia, myeloprolferative disorders, chronic skin diseases, patients on renal dialysis and patients on drugs that impair absorption or metabolism e.g. phenrytoin, oral contraceptive, isoniazid, methotrexate etc.

Treatment

Folic acid 1mg orally per day.

N.B

- Folic acid supplementation to prevent folic acid deficiency should be considered in high-risk individuals including pregnant women, alcoholics and patients with hemolytic anemia, liver disease, certain skin disease, and patients on renal dialysis.

- The administration of folic acid in the setting of vitB_{12} deficiency will not prevent neurological manifestation even though it will largely correct the anemia caused by the vitamin B_{12} deficiency.

Drugs used in Disorder of coagulation

Introduction

Hemostasis is spontaneous arrest of bleeding from a damaged blood vessel. Steps: Vascular injury → vasospasm→ platelate adhesion→ platelate aggregation → coagulation cascades→ fibrin formation

Anticoagulants are the drugs which inhibit fibrin formation.

Classification

Based on mechanism of action

1. Fast and direct acting
   e.g: Heparin
2. Slow and indirect acting
   - Oral anticoagulants
     e.g Warfarin and Dicumarol

Heparin

It is a heterogeneous mixture of sulfated mucopolysaccharides

Mechanism of action

Heparin activates antithrobimin III (AT III) which inhibits clotting factor proteases and hence it inhibits the formation of fibrin clots, inhibits the conversion of fibrinogen to fibrin, and inactivates several of the factors necessary for the clotting of blood.

Clinical Uses

Prevention and treatment of venous thrombosis, atrial fibrillation with embolus formation, prevention of post operative thrombosis and embolism, in open heart surgery, in arterial embolus, treatment of coronary occlusion, acute myocardial infarction and peripheral arterial embolism

Administration:

Can be given IV or subcutaneous. Oral therapy is ineffective because it is inactivated by gastric acids and absorption is minimal because of large molecular size.Heparin must never be administered intramuscularly because of danger of hematoma formation at injection site.

Side effects:

Bleeding is the major side effect, allergy, alopecia, osteoporosis and thrombocytopenia

Contraindications

Contraindicated in patients who are hypersensitive to the drug, are actively bleeding or have hemophilia, thrombocytopenia, purpura, sever hypertension, intracranial hemorrhage, infective endocarditis, active tuberculosis, etc.

ORAL ANTICOAGULANTS

WARFARIN

This compound was originally employed as a rodent poison. It is the most widely used coumarin anticoagulant and may be considered to be the drug of choice as an oral anticoagulant.

Mechanism of action

- The anticoagulant prevents reductive metabolism of the inactive vitamin K epoxide back to its active form

Pharmacokinetics:

- It is administered orally as sodium salt and has 100% bioavailability.
- The drug has slow onset of action, and long half-life in plasma (36hr) because 99% of the drug is bound to albumin.

Clinical uses

Prevention and treatment of deep vein thrombosis, treatment of atrial fibrillation with thrombus formation, prevention and treatment of pulmonary embolus, as part of the treatment of coronary occlusion and prevention of thrombus formation after value replacement

Side effects

Birth defect in pregnancy, hemorrhagic disease of newborn, hemorrhagic infarcts and cutaneous necrosis

Contraindications – similar to heparin and the drug should never be administered during pregnancy.

Drug interactions

- The effect of warfarin will be increased when it is used with the following drugs.

Cimitidine, dsulfiram, metronidazole, phenylbutazone, ASA and cephalosporin (3rd generations)

- The effect of warfarin will be decreased when it is used with the following drugs.

Barbiturates, Cholestyramine, Rifampincin, Diuretics, vit K

THROMBOLYTIC AGENTS

Fibrinolytic agents rapidly lyse thrombi by catalyzing the formation of plasmin from plasminogen. All thrombolytic agents currently in use act directly or indirectly as plasminogen activators. The presently used plasminogen activators are:

a. Streptokinase- a protein synthesized by streptococci, combines with plasminogen to convert it to active plasmin.
b. Urokinase-human enzyme synthesized by the kidneys that directly converts plasminogne to active plasmin
c. Anistreptase (Acylated plasminongen -streptokinase activator)- bacterial streptokinase plus human plasminogen
d. Tissue plaminogen activator (tPA)-this activates preferentially plasminogen that is bound to fibrin.

Indications:

Multiple pulmonary emboli, central deep vein thrombosis and acute myocardial infarction.

Adverse Reactions:

Bleeding and allergic reactions are most common adverse effects thrombolytics.

Contra-indications:

Severe hypertension, recent cranial trauma and history of cerebrovascualr accident.

ANTIPLATELET DRUGS

Platelet function is regulated by three categories of substances

1. Agents outside the platelet that interact with platelet membrane receptors, e.g. catecholamines, prostacyclin
2. Agents generated within the platelets and interact with the membrane receptors, e.g. prostaglandin E_2 and serotonin

3. Agents generated within the platelet and act within the platelet, e.g. thromboxane A_2 and calcium ions

Antiplatelets act on any one of the above processes. They include aspirin, ticlopidine, dipyridamole.

ASPIRIN (ASA)

Thromoboxane A2 is an arachidonate product that causes platelet to change shape, to release their granules and to aggregate. Drugs that antagonize this pathway interfere with platelet aggregation and prolong bleeding time. Asprin at low dose is the prototype of this class of drugs. It inhibits the synthesis of thromboxane A2 by irreversible acetylation of the enzyme cyclo-oxygenase.

Therapeutic Uses:

Prophylaxis against myocardial infarction and prevention of stroke in patients at risk, e.g. those with transient ischemic attacks.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Aspirin

Aspirin and other nonsteroidal anti-inflammatory drugs are weak organic acids. They all inhibit prostaglandin biosynthesis. They decrease the production of free radicals and of superoxide and may interact with adenylyl cyclase to alter the cellular concentration of cAMP. Aspirin is the drug of choice for treating the majority of articular and musculoskeletal disorders. It is also the standard against which all anti-inflammatory agents are compared.

Pharmacokinetics: The salicylates are rapidly absorbed from the stomach and upper small intestine. The acid medium in the stomach keeps a large fraction of the salicylate in the nonionized form, promoting absorption. However, the drug may damage the mucosal barrier. Aspirin is absorbed as such and is rapidly hydrolyzed to acetic acid and salicylate by esterases in tissue and blood. Salicylate is bound to albumin. Ingested salicylate and that generated by the hydrolysis of aspirin may be excreted unchanged, but most is converted to water-soluble conjugates that are rapidly cleared by the kidney. Alkalinization of the urine increases the rate of excretion of free salicylate.

Pharmacodynamics

Mechanism of Action: Aspirin irreversibly blocks the enzyme cyclooxygenase; the drug decreases the formation of both the prostaglandins and thromboxane A_2 but not the leukotrienes.

Anti-inflammatory Effects: In addition to reducing the synthesis of eicosanoid mediators, aspirin also interferes with the chemical mediators of the kallikrein system. Thus, aspirin inhibits granulocyte adherence to damaged vasculature, stabilizes lysosomes, and inhibits the migration of polymorphonuclear leukocytes and macrophages into the site of inflammation.

Analgesic Effects: Aspirin is most effective in reducing pain of mild to moderate intensity. Muscular, vascular, and dental origin, postpartum states, arthritis, and bursitis are alleviated by aspirin. Aspirin acts peripherally through its effects on inflammation but probably also inhibits pain stimuli at a subcortical site.

Antipyretic Effects: Aspirin reduces elevated temperature. The fall in temperature is related to increased dissipation of heat caused by vasodilation of superficial blood vessels. The antipyresis may be accompanied by profuse sweating. Aspirin blocks the pyrogen-induced production of prostaglandins and the central nervous system response to interleukin-1.

Platelet Effects: Aspirin inhibits platelet aggregation by inhibition of thromboxane synthesis. Because its action is irreversible, aspirin inhibits platelet aggregation for up to 8 days (until new platelets are formed).

Clinical Uses

*Analgesic, antipyretics, and anti-inflammatory effects***:** Aspirin is one of the most frequently employed drugs for relieving mild to moderate pain of varied origin. Aspirin is not effective in the treatment of severe visceral pain (acute abdomen, renal colic, pericarditis, or myocardial infarction). It and other NSAIDs have been combined with opioid analgesics for treatment of cancer pain. Used in the treatment of rheumatoid arthritis, rheumatic fever, and other inflammatory joint conditions.

Inhibition of platelet aggregation: Aspirin has been shown to decrease the incidence of transient ischemic attacks and unstable angina in men. It reduces the incidence of thrombosis in coronary artery bypass grafts. It may also reduce the incidence of myocardial infarction.

Adverse Effects

Gastrointestinal Effects: the main adverse effect is gastric upset (intolerance). The gastritis that occurs with aspirin may be due to irritation of the gastric mucosa by the undissolved tablet, to absorption in the stomach of nonionized salicylate, or to inhibition of protective prostaglandins.

Central Nervous System Effects: With higher doses, patients may experience "salicylism" tinnitus, decreased hearing, and vertigo reversible by reducing the dosage. Still larger doses of salicylates cause hyperpnea through a direct effect on the medulla. At toxic levels, respiratory alkalosis may occur as a result of the increased ventilation. Later, acidosis supervenes from accumulation of salicylic acid derivatives and depression of the respiratory center.

Other Adverse Effects: Aspirin in a low daily dose usually increases serum uric acid levels, whereas doses exceeding 4 g daily decrease urate levels below 2.5 mg/dL. Salicylates may cause reversible decrease of glomerular filtration rate in patients with underlying renal disease. Asprin is contraindicated in children with viral upper respiratory tract infections, because it may precipitate Raye syndrome.

Newer Nonsteroidal Anti-Inflammatory Drugs

The newer NSAIDs inhibit of biosynthesis of prostaglandins. In addition they inhibit chemotaxis, down-regulate interleukin-1 production, and interfere with calcium-mediated intracellular events. These drugs are reversible inhibitors of cyclooxygenase.

Most of these drugs are well absorbed. Most of the NSAIDs are highly metabolized, some by phase I and phase II mechanisms and others by direct glucuronidation (phase II) alone. While renal excretion is the most important route, all undergo varying degrees of biliary excretion and reabsorption (enterohepatic circulation). All of the NSAIDs are highly protein-bound, usually to albumin.

Ibuprofen

Ibuprofen is extensively metabolized in the liver, and little is excreted unchanged. Gastrointestinal irritation and bleeding occur, though less frequently than with aspirin. In addition to the gastrointestinal symptoms, rash, pruritus, tinnitus, dizziness, headache, and fluid retention have been reported. Rare hematologic effects include agranulocytosis and aplastic anemia. Effects on the kidney include acute renal failure, interstitial nephritis, and nephrotic syndrome, occurring very rarely.

Diclofenac

Diclofenac is a potent cyclooxygenase inhibitor with antiinflammatory, analgesic, and antipyretic properties. The drug is rapidly absorbed following oral administration and has a half-life of 1-2 hours. It accumulates in the synovial fluid. The potency of diclofenac as a cyclooxygenase inhibitor is greater than that of naproxen. The drug is recommended for chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis and for the treatment of acute musculoskeletal pain. Adverse effects include gastrointestinal distress, occult gastrointestinal bleeding, and gastric ulceration.

Sulindac

Sulindac is a prodrug. Its active metabolite is, like diclofenac, an acetic acid derivative. The drug is effective only after it is converted by liver enzymes to a sulfide, which is excreted in bile and then reabsorbed from the intestine. The enterohepatic cycling prolongs the duration of action to 12-16 hours. The indications and adverse reactions are similar to those of other NSAIDs. Among the more severe reactions, Stevens-Johnson epidermal necrolysis syndrome, thrombocytopenia, agranulocytosis, and nephrotic syndrome have all been observed. Like diclofenac, sulindac may have some propensity to cause elevation of serum aminotransferase; it is also sometimes associated with cholestatic liver damage.

Mefenamic Acid

Mefenamic acid, another fenamate, possesses analgesic properties but is probably less effective than aspirin as an anti-inflammatory agent and is clearly more toxic.

Piroxicam

It is rapidly absorbed in the stomach and upper small intestine and reaches 80% of its peak plasma concentration in 1 hour. Gastrointestinal symptoms are encountered in 20% of patients. Other adverse reactions include dizziness, tinnitus, headache, and rash.

Nimesulide: It is a new NSAID and after oral administration it is rapidly and almost completely absorbed. Highly bound to plasma proteins. It is a weak inhibitor of prostaglandin synthesis.The advantage of nimesulide over other NSAIDs is that it causes minimal gastric irritation.

Rofecoxib: Rofecoxib is a highly selective and specific COX-2 inhibitor. It inhibits prostaglandin synthesis via inhibiting cyclooxygenase- 2. It is about 90% bound to plasma proteins. The main adverse effects are nausea, dyspepsia, epigastric discomfort, heart burn, diarrhea, fluid

retention etc. It is mainly useful in osteoarthritis, acute pain like dental pain & primary dysmenorrhoea.

NSAIDS FOR SPECIAL INDICATIONS

Indomethacin

Indomethacin is slightly more toxic but in certain circumstances more effective than aspirin. Indomethacin is well absorbed after oral administration and highly bound to plasma proteins. Metabolism occurs in the liver and unchanged drug and inactive metabolites are excreted in bile and urine.

Clinical Uses: treatment of patent ductus arteriosus, acute gouty arthritis and ankylosing spondylitis, pericarditis and pleurisy.

Adverse Effects: The gastrointestinal effects may include abdominal pain, diarrhea, gastrointestinal hemorrhage, and pancreatitis. CNS effects include be associated with dizziness, confusion, and depression. Serious hematologic reactions' including thrombocytopenia and aplastic anemia has been reported.

Acetaminophen

Acetaminophen is the active metabolite of phenacetin responsible for its analgesic effect. It is a weak prostaglandin inhibitor in peripheral tissues and possesses no significant anti-inflammatory effects.

Pharmacokinetics: Acetaminophen is administered orally. Absorption is related to the rate of gastric emptying. Acetaminophen is slightly bound to plasma proteins and is partially metabolized by hepatic microsomal enzymes.

Indications: It is an effective analgesic and antipyretic agent, but it lacks of anti-inflammatory properties. The drug is useful in mild to moderate pain such as headache, myalgia, and postpartum pain.

Adverse Effects: It is hepatotoxic (contraindicated in patients with known liver diseases), and also causes hemolytic anemia and methemoglobinemia

DRUGS USED IN GOUT

Gout is a familial metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of monosodium urate in joints and cartilage. Formation of uric acid calculi in the

kidneys may also occur. Gout is usually associated with high serum levels of uric acid, a poorly soluble substance that is the major end product of purine metabolism.

The treatment of gout is aimed at relieving the acute gouty attack and preventing recurrent gouty episodes and urate lithiasis. Urate crystals are initially phagocytosed by synoviocytes, which then release prostaglandins, lysosomal enzymes, and interleukin-1. Attracted by these chemotactic mediators, polymorphonuclear leukocytes migrate into the joint space and amplify the ongoing inflammatory process. In the later phases of the attack, increased numbers of mononuclear phagocytes (macrophages) appear, ingest the urate crystals, and release more inflammatory mediators.

Colchicine

Colchicine is absorbed readily after oral administration. Metabolites of the drug are excreted in the intestinal tract and urine.

Colchicine dramatically relieves the pain and inflammation of gouty arthritis without altering the metabolism or excretion of urates and without other analgesic effects. Colchicine produces its anti-inflammatory effects by inhibition of leukocyte migration and phagocytosis. It also inhibits the formation of leukotriene B_4.

Indications: Colchicine is used for alleviating the inflammation of acute gouty arthritis.

Adverse Effects: Colchicine often causes diarrhea and may occasionally cause nausea, vomiting, and abdominal pain. Colchicine may rarely cause hair loss and bone marrow depression as well as peripheral neuritis and myopathy. Acute intoxication after ingestion of large (nontherapeutic) doses of the alkaloid is characterized by burning throat pain, bloody diarrhea, shock, hematuria, and oliguria.

NSAIDS in Gout

Indomethacin and other NSAIDs inhibit urate crystal phagocytosis. Indomethacin may be used as initial treatment of gout or as an alternative drug when colchicine is unsuccessful or causes too much discomfort. Indomethacin is the agent most often used today to treat acute gout. All other NSAIDs except aspirin can be used to treat acute gouty episodes.

Uricosuric Agents

Probenecid and sulfinpyrazone are uricosuric drugs employed to decrease the body pool of urate in patients with tophaceous gout or in those with increasingly frequent gouty attacks. In a patient who excretes large amounts of uric acid, the uricosuric agents should be avoided so as

not to precipitate the formation of uric acid calculi. Uricosuric drugs are organic acids and act at the anionic transport sites of the renal tubule.

Pharmacokinetics: Probenecid is completely reabsorbed by the renal tubules and is metabolized very slowly. Sulfinpyrazone or its active hydroxylated derivative is rapidly excreted by the kidneys. Its effect after oral administration is almost that of probenecid.

Pharmacodynamics: Uric acid is freely filtered at the glomerulus. Like many other weak acids, it is also both reabsorbed and secreted in the middle segment of the proximal tubule. Uricosuric drugs probenecid, sulfinpyrazone, and large doses of aspirin affect these active transport sites so that net reabsorption of uric acid in the proximal tubule is decreased. Because aspirin in small doses causes net retention of uric acid by inhibiting the secretory transporter, it should not be used for analgesia in patients with gout.

Indications: Uricosuric therapy should be initiated if several acute attacks of gouty arthritis have occurred, when evidence of tophi appears, or when plasma levels of uric acid in patients with gout are so high that tissue damage is almost inevitable.

Adverse Effects: Both drugs cause gastrointestinal irritation, but sulfinpyrazone is more active in this regard. Probenecid is more likely to cause allergic dermatitis, but a rash may appear after the use of either compound. Nephrotic syndrome has resulted from the use of probenecid. Both sulfinpyrazone and probenecid may cause aplastic anemia.

Allopurinol

An alternative to increasing uric acid excretion in the treatment of gout is to reduce its synthesis by inhibiting xanthine oxidase with allopurinol.

Allopurinol is absorbed after oral administration. Like uric acid, allopurinol is itself metabolized by xanthine oxidase. The resulting compound, alloxanthine, retains the capacity to inhibit xanthine oxidase and has a long duration of action.

Pharmacodynamics: Dietary purines are not an important source of uric acid. The quantitatively important amounts of purine are formed from amino acids, formate, and carbon dioxide in the body. Those purine ribonucleotides not incorporated into nucleic acids and those derived from the degradation of nucleic acids are converted to xanthine or hypoxanthine and oxidized to uric acid. When this last step is inhibited by allopurinol, there is a fall in the plasma urate level and a decrease in the size of the urate pool with a concurrent rise in the more soluble xanthine and hypoxanthine.

Indications

- in chronic tophaceous gout
- for recurrent renal stones
- in patients with renal functional impairment;
- When serum urate levels are grossly elevated.

Adverse Effects: Gastrointestinal intolerance, including nausea, vomiting, and diarrhea, may occur. Peripheral neuritis and necrotizing vasculitis, depression of bone marrow elements may occur. Hepatic toxicity and interstitial nephritis have been reported.

Exercice

1. Discuss in detail the pharmacokinetics of iron?
2. Discuss various types of iron formulations with their side effects?
3. Explain the mechanism of action and effect of vit B_{12} and folic acid and the relation of the latter?
4. What are the effects and adverse reaction of heparin and oral anticoagulants?
5. What is the role of aspirin as an antiplatelet agent?

CHAPTER EIGHT

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

Learning Objectives

At the end this section the student will be able to:

1. Describe the major adverse effects of sedative hypnotic drugs.
2. Describe the drugs used in epilepsy.
3. Illustrate the approaches in the management of parkinsonism.
4. Explain the site of action, uses and adverse effects of antipsychotic drugs.
5. Describe the major adverse effects opioid analgesics.

INTRODUCTION

To facilitate the understanding of the pharmacological and unwanted effects of CNS drugs, the physiological functions of the main CNS neurotransmitters are discussed briefly.

Noradrenaline. Noradrenergic transmission is important in control of mood (functional deficiency resulting depression) controlling wakefulness, and alertness.

Dopamine. Dopamine is important in motor control (Parkinsonism is due to dopamine deficiency), has behavioural effects (excessive dopamine activity is implicated in schizophrenia), important in hormone release (prolactin, GH) and dopamine in chemoreceptor trigor zone causes nausea and vomiting.

5-HT. Physiological functions associated with 5-HT pathways include; feeding behaviour, behavioural response (hallucinatory behaviour), control of mood and emotion, control of body temperature and vomiting.

Acetylcholine(Ach). Ach has effects on arousal, on learning, and on short-term memory. Dementia and parkinsonism are associated with abnormalities in cholinergic pathways.

GABA. GABA is an inhibitory neurotransmitter in CNS.

Glycine. is an inhibitory neurotransmitter, acts on GABA like receptor in the spinal cord.

GENERAL ANESTHETICS

General anesthesia involves the physiological changes: Reversible loss of response to painful stimuli, loss of consciousness and loss of motor and autonomic reflexes. Loss of consciousness is associated with inhibition of the activity of reticular formation.

General anesthetics are administered by *inhalation* or by *intravenous* routes. They are classified into two on the basis of their route of administration as inhalation and intravenous anesthetics.

Inhalation anesthetics

The main agents are: Halothane, nitrous oxide, enflurane and ether.

1. Halothane: Is the most widely used agent, highly lipid soluble, potent. It causes arrhythmia, hangover and the risk of liver damage is high if used repeatedly.

2. Nitrous oxide: Oderless and colourless gas. It is rapid in action and also an effective analgesic agent. Its potency is low, hence must be combined with other agents. It is a relatively free of serious unwanted effects.

3. Enflurane: Halogenated ether (similar to halothane). Poorly metabolized in the liver, thus less toxic than halothane. It is faster in its action, less liable to accumulate in the body fat compared to halothane. It causes seizure during induction and following recovery from anaesthesia.

4. Ether: Has analgesic and muscle relaxant properties. It is highly explosive, causes respiratory tract irritation, postoperative nausea and vomiting. It is not widely used currently.

INTRAVENOUS ANESTHETICS

Intravenous anesthetics act much more rapidly, producing unconsciousness in about 20 seconds, as soon as the drug reaches the brain from the site of its injection. These agents used for induction of anaesthesia followed by inhalation agent. The main induction agent in current use is: thiopentone, etomidate, propofol, ketamine and short acting benzodiazepine (midazolam).

Thiopentone: Thiopentone is a barbiturate with very high lipid solubility. After intravenous administration the drug enters to tissues with a large blood flow (liver, kidneys, brain, etc) and more slowly to muscle. Uptake into body fat occurs slowly because of the low blood flow to this tissue, which may cause prolonged effect if given repeatedly. It causes cardiovascular depression.

Etomidate: It is more quickly metabolized and the risk of cardiovascular depression is less compared to thiopentone. Etomidate suppresses the adrenal cortex, which has been associated with an increase in mortality in severely ill patients.

Ketamine: acts more slowly than thiopentone and produces a different effect, known as dissociative anaesthesia in which there is a marked sensory loss and analgesia, as well as amnesia and paralysis of movement, without actual loss of consciousness. Ketamine causes dysphoria, hallucinations during recovery.

Benzodiazepines including diazepam, lorazepam, and midazolam are used in general anesthetic procedures. Compared with intravenous barbiturates, benzodiazepines produce a slower onset of central nervous system effects. Benzodiazepines prolong the postanesthetic recovery period but also cause a high incidence of amnesia for events occurring after the drug is administered.The benzodiazepines are useful in anesthesia as premedication and intraoperative sedation.

Opioid analgesic anesthesia: Opioid analgesics can be used for general anesthesia, in patients undergoing cardiac surgery and fentanyl and its derivates are commonly used for these purposes.

Preanesthetic medication: It is the use of drugs prior to the administration of anaesthetic agent with the important objective of making anaesthesia safer and more agreable to the patient. The drugs commonly used are, opioid analgesics, barbiturates, anticholinergics, anti emetics and glucocorticoids.

SEDATIVE AND HYPNOTIC DRUGS

Anxiolytic drugs are used to treat the symptoms of anxiety, where as **hypnotic drugs** used to treat insomnia. The same drugs are used for both purposes.

Classes of anxiolytic and hypnotic drugs: The main groups of the drugs are:

1. *Benzodiazepines.* Benzodiazepines are the most important group, used as sedative and hypnotic agents.
2. *5- HT_{1A} receptor agonist* (e.g. buspirone). It is recently introduced anxiolytic.
3. *Barbiturates* (phenobarbitone). They are nowadays less commonly used as sedative-hypnotics.
4. *β -adrenoceptor antagonists* (e.g. propranolol). They are used to treat some forms of anxiety, where physical symptoms (sweating, tremor, and tachycardia), are troublesome. They are not used as hypnotics.

5. *Miscellaneous drugs* (chloral hydrate, paraldehyde, and diphenhydramine). These drugs are not commonly recommended for axiety or insomia.

Benzodiazepines

Benzodiazepines are well absorbed when given orally. They bind strongly to plasma proteins, however, many of them accumulate gradually in the body fat (i.e. they are highly lipid soluble). Benzodiazepines are inactivated by the liver and excreted in the urine.

Based on their duration of action roughly divided into short acting (flurazepam, triazolam), medium acting (alprazepam, lorazepam) and long acting compounds (diazepam, chlordiazepoxide, clonazepam).

Pharmacodynamics

Act by binding to a specific regulatory site on the $GABA_A$ receptor, thus enhancing the inhibitory effects of GABA. Central nervous system effects of benzodiazepines include:

1. Reduction of anxiety and aggression.
2. Sedation and induction of sleep.
3. Reduction of muscle tone and coordination.
4. Anticonvulsant effects.

Clinical Uses

- Treatment insomnia
- Anxiety
- Preoperative mediations
- Acute alcohol withdrawal
- As anticonvulsants
- Chronic muscle spasm and spasticity

Unwanted effects

- Toxic effects due to acute overdosage causes prolonged sleep.
- Unwanted effects occurring during normal therapeutic use includes: drowsiness, confusion, amnesia, and impaired motor coordination.
- Tolerance and dependance: *Pharmacokinetic* and *tissue tolerance* and also cause physical dependance. i.e. stopping benzodiazepines treatment after weeks or months causes an increase in symptoms of anxiety.

5 - HT_{1A} receptor agonist

Buspirone is a potent agonist of. *5 - HT_{1A}* receptors. Anxiolytic effects take days to weeks to develop. Buspirone does not cause sedation, motor incoordiation and withdrawal effects. The main side effects are nausea, dizziness, headache, and restlessness.

Barbiturates

They are non-selective CNS depressants, which produce effects ranging from sedation and reduction of anxiety, to unconsciousness and death from respiratory and cardiovascular failure.

Barbiturates act by enhancing action of GABA, but less specific than benzodiazepines. They are potent inducers of hepatic drug metabolizing enzymes, hence likely to cause drug interaction. Tolerance and dependance occur, more than benzodiazepines.

ANTIEPILEPTIC DRUGS

Seizure is associated with the episodic high frequency discharge of impulses by a group of neurons in the brain.

Seizure may be partial or generalized depending on the location and the spread of the abnormal neuronal discharge. The attack mainly involves motor, sensory or behavioral phenomena.

Partial seizures are often associated with damage to the brain, whereas generalized seizure occurs without obvious cause. Two common forms of generalized seizures are grand mal and petit mal.

Mechanism of action

Anticonvulsant drugs act by two mechanisms: by reducing electrical excitability of cell membrane and by enhancing GABA mediated synaptic transmission.

The main drugs used in the treatment of epilepsy are **phenytoin, carbamazepine, valproate, ethosuximide and phenobarbitone.**

Phenytoin

It is commonly used antiepileptic drug. It is effective against different forms of partial and generalized seizures; however it is not effective in absence seizures.

Well absorbed when given orally. It is metabolised by the liver. It is liver enzyme inducer and therefore, increases the rate of metabolism of other drugs.

Main side effects are sedation, confusion, gum hyperplasia, skin rash, anaemia, nystagmus, and diplopia.

Carbamazepine

It is derived from tricyclic antidepressant. Its pharmacological action resembles those of phenytoin, however, it is chiefly effective in the treatment of partial seizure. It is also used in the treatment of trigeminal neuralgia and manic-depressive illness.

It is powerful inducer of liver microsomal enzymes, thus accelerates the metabolism of phenytoin, warfarin, oral contraceptives and corticosteroids.

Carbamazepine causes sedation, mental disturbances and water retention.

Valproate

Valproate is chemically unrelated to the other antiepileptic drugs. The mechanism of action is unknown. It is used in grand mal, partial, petit mal and myoclonic seizure.

Relatively has few side effects, however, it is potentially hepatotoxic. It is non sedating.

Ethosuximide

Has fewer side effects and used in the treatment of absence seizures.

Phenobarbitone

It is well absorbed after oral administration and widely distributed. Renal excretion is enhanced by acidification of the urine. Phenobarbitone is liver enzyme inducer and hence accelerates the metabolism of many drugs like oral contraceptives and warfarin.

The clinical use of phenobarbitone is nearly the same as that of phenytoin. The most important unwanted effect is sedation.

Benzodiazepines: Clonazepam and related compounds, clobazam are claimed to be relatively selective as antiepileptic drugs. Sedation is the main side effect of these compounds, and an added problem may be the withdrawal syndrome, which results in an exacerbation of seizures if the drug is stopped.

MANAGEMENT OF PARKINSONISM

Parkinsonism: Parkinsonism is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability. It is due to the imbalance between the cholinergic and dopaminergic influences on the basal ganglia. Thus, the aim of the treatment is either to increase

dopaminergic activity (by dopamine agonist) or to decrease cholinegic (antimuscarinic drugs) influence on the basal ganglia.

Levodopa

Levodopa, the immediate metabolic precursor of dopamine, does penetrate the blood brain barrier, where it is decarboxylated to dopamine. Levodopa is rapidly absorbed from the small intestine. Food will delay the appearance of levodopa in the plasma. It is extensively metabolized by peripheral dopa decarboxylase, hence given in combination with carbidopa, a peripheral dopa decarboxylase inhibitor.

When levodopa is given without carbidopa it causes vomiting (which is due to stimulation of emetic center to dopamine) and CVS disorder (tachycardia, ventricular extrasystoles, atrial fibrillation and due to increased catecholamine formation peripherally).

Dopamine agonists

The enzymes responsible for synthesizing dopamine are depleted in the brains of Parkinsonism patients, and drugs acting directly on dopamine receptors may therefore have a beneficial effect additional to that of levodopa. There are a number of dopamine agonists with antiparkinsonism activity.

e.g: Bromocryptine

Monoamine Oxidase Inhibitors: **Selegiline** (deprenyl), a selective inhibitor of monoamine oxidase B, hinders the breakdown of dopamine; as a result, it prolongs the antiparkinsonism effect of levodopa. Selegiline has only a minor therapeutic effect on parkinsonism when given alone. It may reduce disease progression.

Amantadine

Amantadine, an antiviral agent, was by chance found to have antiparkinsonism properties. Its mode of action in parkinsonism is unclear, but it may potentiate dopaminergic function by influencing the synthesis, release, or reuptake of dopamine.

Acetylcholine Blocking Drugs (*Benztropine, Trihexyphenidyl)*

A number of centrally acting antimuscarinic preparations are available that differ in their potency and in their efficacy in different patients. Treatment is started with a low dose of one of the drugs in this category, the level of medication gradually being increased until benefit occurs or adverse effects limit further increments. Antimuscarinic drugs may improve the tremor and rigidity of Parkinsonism but have little effect on bradykinesia.

Adverse Effects

Antimuscarinic drugs have a number of central nervous system effects, including drowsiness, mental slowness, inattention, restlessness, and confusion, agitation, delusions, hallucinations, and mood changes. Other common effects include dryness of the mouth, blurring of vision, mydriasis, urinary retention, nausea and vomiting, constipation, tachycardia, tachypnea, increased intraocular pressure, palpitations, and cardiac arrhythmias.

Contraindications*:* Acetylcholine-blocking drugs should be avoided in patients with prostatic hyperplasia, obstructive gastrointestinal disease, or angle-closure glaucoma.

ANTIPSYCHOTIC AGENTS

Psychotic illness is characterized by delusion, hallucinations, thought disorder, social withdrawal and flattering of emotional response. Antipsychotics are a group of drugs used mainly for treating schizophrenia.

Antipsychotic agents are classified into *typical neuroleptics* (chlorpromazine, thioridazine, haloperidol, flupenthixol) and *atypical neurolopitics* (clozapine, sulpiride).

Most antipsychotic drugs are readily but incompletely absorbed. Many of these drugs undergo significant first-pass metabolism. Very little of any of these drugs is excreted unchanged, as they are almost completely metabolized to more polar substances.

The phenothiazine antipsychotic drugs, with chlorpromazine as the prototype, have a wide variety of central nervous system, autonomic, and endocrine effects. It blocks receptors including; dopamine and alpha-adrenoceptor, muscarinic, H_1 histaminic, and serotonin (5-HT_2) receptors. Of these, the dopamine receptor effects quickly became the major focus of interest.

Clinical uses

- Schizophrenia
- Mania
- Vomiting

Adverse Reactions

- Extrapyramidal reactions
- Seizures
- Autonomic nervous system effects (antimuscarinic effects, orthostatic hypotension)
- Metabolic and Endocrine Effects (weight gain, hyperprolactinemia, infertility, loss of libido and impotence)

ANTIDEPRESSANT AGENTS:

Depression is one of the most common psychic disorders. Antidepressants are the drugs which are mainly used in the management of depression.

Types of antidepressant drugs

1. Tricyclic antidepressants (TCAs)
2. Monoamine oxidase inhibitors (MAOI)
3. 5-HT uptake inhibitors
4. Atypical antidepressants

Pharmacokinetics

Most tricyclics are incompletely absorbed and undergo significant first-pass metabolism. Highly protein bound and relatively high lipid solubility. Fluoxetine (Selective Serotonin Reuptake Inhibitors (SSRIs)) is well absorbed. The MAO inhibitors are readily absorbed from the gastrointestinal tract.

Mechanisms of action

Tricyclic antidepressanat (imipramine, amitriptyline) closely related in structure to phenothiazines are the most widely used antidepressants. TCAs block the uptake of amines (noradrenaline and 5-HT) by nerve terminals by competition for the carrier transport system. In addition, TCAs block α_1- adrenoceptors, muscarinic, histamine (H_1) and 5-HT receptors.

Monoamine oxidase inhibitors (MAOI): *Tranylcypromine* selectively inhibits MAO-A. MAO-A has a substrate preference for 5 –HT. MAOI causes a rapid and sustained increase in the 5-HT, noradrenaline and dopamine.

Selective 5-HT uptake inhibitors: *fluoxetine, fluvoxamine* lack antimuscarinic and cardiovascular effects.

Atypical antidepressant drugs have no common mechanisms of action, some are monoamine uptake blockers, but others act by unknown mechanisms.

Clinical Indications: The major indication of TCAs are endogenous depression, panic attacks, Phobic and obsessional states (clomipramine) and bed-wetting in children. MAOIs are used in severe depression refractory to other treatment and phobias.

Adverse Effects: Postural hypotension, dry mouth, blurred vision, constipation, urine retention, sedation, are the most important side effects of TCAs. MAOI cause postural hypotension, atropine-like effects, weight gain, and CNS stimulation causing restlessness, tremor, and insomnia.

TCA and MAO inhibitors cause atropine like effects and *postural hypotension.* MAOI cause *excessive central stimulation and weight gain.*

ANALGESICS

Opioid Analgesics

Opioid is any substance that can produce morphine like effects. Opium is an extract of the juice of the poppy *Papaver somniferum.* Opium contains many alkaloids related to morphine. The main group of drugs that are discussed in section are divided into two; morphine analogues and synthetic derivatives.

Morphine analogues. Compounds closely related in structure to morphine. They may be agonist (*codeine and heroin*), partial agonists (*nalorphine*) or antagonists (*naloxone*).

Synthetic derivatives. Pethidine, fentanyl, methadone, pentazocine are examples of synthetic derivatives.

Opioid receptors. Three receptors mediate the main pharmacological effects of opiates. mu receptors are responsible for the analgesic and major unwanted effects (respiratory depression, sedation and dependance). Delta for analgesia and peripheral effects of opiates and kappa contribute to analgesia at spinal level and dysphoria.

Agonists and antagonists of opioid receptors

Pure agonists. They all have high affinity to mu receptors and varying affinity to delta and kappa receptors (codeine, methadone, dextropropoxyphene).

Partial antagonists and mixed agonist-antagonists: Nalorphine, and pentazocine.

Pharmacokinetics: Most opioid analgesics are well absorbed from subcutaneous and intramuscular sites as well as from the mucosal surfaces of the nose or mouth. Although absorption from the gastrointestinal tract is rapid, some opioids given by this route are subject to first-pass metabolism by glucuronidation in the liver. All opioids bind to plasma proteins with varying degrees of affinity, the drugs rapidly leave the blood and localize in highest

concentrations in tissues that are highly perfused. The opioids are converted in large part to polar metabolites, which are then readily excreted by the kidneys.

Pharmacodynamics

A. Mechanism of Action: Opioid agonists produce analgesia by binding to specific receptors, located primarily in brain and spinal cord regions involved in the transmission and modulation of pain.

Effects of morphine and its synthetic derivatives

1. **Central nervous system effects-**The principal effects of the opioid analgesics with affinity for mu receptors are on the central nervous system; the more important ones include analgesia, euphoria, sedation, and respiratory depression. With repeated use, a high degree of tolerance occurs to all of these effects except respiratory depression. They also cause addiction and dependence.

    a. *Analgesia*-Pain consists of both sensory and affective (emotional) components. Opioids can change both aspects of the pain experience. In most cases, these drugs have a relatively greater effect on the affective component.

    b. *Euphoria***-**After a dose of morphine, a typical patient in pain experiences a pleasant floating sensation and freedom from anxiety and distress. Dysphoria is a state characterized by restlessness and a feeling of malaise.

    c. *Sedation***-**Drowsiness and clouding of mentation are frequent concomitants of opioid action.

    d. *Respiratory depression***-**All of the opioid analgesics can produce significant respiratory depression by inhibiting brain stem respiratory mechanisms.

    e. *Cough suppression***-**Suppression of the cough reflex is a well-recognized action of opioids. However, cough suppression by opioids may allow accumulation of secretions and thus lead to airway obstruction and atelectasis. e.g. codeine

    f. *Miosis***-**Constriction of the pupil is seen with virtually all opioid agonists.

    g. *Nausea and vomiting***-**The opioid analgesics can activate the brain stem chemoreceptor trigger zone to produce nausea and vomiting.

2. Peripheral effects

a. *Cardiovascular system:* Hypotension effects; has been attributed to a number of mechanisms including central depression of vasomotor-stabilizing mechanisms and release of histamine.

b. *Gastrointestinal tract:* Constipation. Opioid receptors exist in high density in the gastrointestinal tract, and the constipating effects of the opioids are mediated through an action on the local enteric nervous system as well as the central nervous system.

c. *Biliary tract:* The opioids constrict biliary smooth muscle, which may result in biliary colic. The sphincter of Oddi may constrict, resulting in reflux of biliary and pancreatic secretions and elevated plasma amylase and lipase levels.

d. *Genitourinary tract:* Renal function is depressed by opioids. It is believed that in humans this is chiefly due to decreased renal plasma flow.

e. *Uterus:* The opioid analgesics may prolong labor.

f. *Neuroendocrine:* Opioid analgesics stimulate the release of antidiuretic hormone, prolactin, and somatotropin but inhibit the release of luteinizing hormone.

B. Effects of mixed agonist-antagonists: Pentazocine and other opioids with agonist actions at some opioid receptors and antagonist actions at others usually produce sedation in addition to analgesia when given in therapeutic doses. At higher doses, sweating, dizziness, and nausea are common, but severe respiratory depression may be less common than with pure agonists.

Clinical use of opioid analgesics

Opioids are used in **s**evere, *constant* pain, acute pulmonary edema (pulmonary edema associated with left ventricular failure), cough suppression, diarrhea, and preanaesthetic medication.

CNS stimulants:

As compared to CNS depressants the stimulants of the centeral nervous system are therapeutically not so useful as they lack selectivity of action. Further, excessive stimulation of CNS is followed by its depression.

CNS stimulant can be classified into

1. *convulsants and respiratory stimulants* eg. Srychnine picrotoxin, nikethaimide
2. *psychomotor stimulants*

   Eg. Amphetamine, cocaine, caffeine
3. *psychotomimetic drug*

   Eg. Lysergic and diethylamide (LSD) psilocybin, phencyclidine.

Convlsants and respiratory stimulants: these are diverse group or drugs and have little clinical use. Certain short acting respiratory stimulants like doxapram, amiphenazole can be used in respiratory failure. Strychnine, picrotoxin and leptazole are used as chemical tools in experimental pharmacology in various animal models.

Psychomotor stimulants: Drugs like amphetamine cause increased motor activity, euphoria, excitement and anorexia due to release of noradrerline and dopamine.

Clinical uses: Amphaetamine is useful in the treatment of narcolepsy and attention deficit in children. Cocaine is occasionally used as a local aneasthetic, mainly in ophthalmology and minor nose and throat surgery.

Khat is another drug that belongs to this group and it is a major drug of abuse in Ethiopia. As drugs of abuse amphetamine khat and cocaine produce strong psychological dependence and carry a high risk of adverse reactions.

Psycho mimetic drugs: Drugs like LSD, phencyclidine and psilocybin cause sensory changes, hallucinations and delusions, resembling symptoms of acute schizophrenia. They are not used clinically but are important as drugs of abuse.

Drug dependence and drug abuse

There are many drugs that human beings consume because they choose to, and not because they are advised to by physicians. Society in general disapproves, because in most cases there is a social cost; for certain drugs, this is judged to out-weigh the individual benefit and their use is banned in many countries.

The main drugs of abuse are given the following table:

Type	example	dependence liability
Narcotic analgesics	Morphine	very strong
CNS depressants	Ethanol	strong
	Barbiturates	strong
Anxiolytic drugs	Benzodiazepines	moderate
Psychomotor stimulants	Amphetamine	strong
	Cocaine	very strong
	Nicotine	very strong
	Caffeine	weak
Psychomimetic drugs	LSD	weak or absent
	Mescaline	weak or absent
	Phencyclidine	moderate
	Cannabis	weak or absent

LOCAL ANESTHETICS

Local anesthetics are either esters (procaine, dibucaine, benzocaine, etc) or amides (lidocaine, prilocaine, bupivacaine, etc). The ester containing compounds are usually inactivated in the plasma and tissues by non-specific esterases. Local anesthetics block the initiation of action potentials by preventing the voltage-dependant increase in Na^+ conductance.

Local anesthetics are used in minor surgery, dentistry, abdominal surgery and painless childbirth. The unwanted effects are due the enterance of LA into systemic circulation and these are: CNS effects (agitation, confusion, respiratory depression, and convulsion), CVS effects (myocardial depression, hypotension) and occasional hypersensitivity reactions.

Table 1. Shows the methods of administration and clinical uses of local aesthetics.

Methods of administration	Uses	Drugs
Surface anaesthesia	Nose, mouth, urinary tract	Lidocaine
Infiltration anaesthesia	Direct injection into tissues to reach nerve braches and terminals. Minor surgery	Most
Regionanl anaesthesia	LA injected IV distal to a pressure cuff, limb surgery	Mainly lidocaine
Nerve block anaesthesia	LA injected close to nerve trunks. Dentistry	Most
Spinal anaesthesia	LA injected into subarachinoid space. Pelvis surgery	Mainly lidocaine
Epidural anaesthesia	LA injected into epidural space. Labour.	Mainly lidocaine

Exercice

1. What are intravenous anaesthetics? Write about their clinical uses.
2. Write about benzodiazepines and their therapeutic uses.
3. Write about mechanism of action and adverse effects of Phenytoin and carbamazepine.
4. Why levodopa is combined with carbidopa in the treatment of Parkinsonism?
5. Write about tricyclic antidepressants and their clinical indications.
6. List commonly abused drugs.

CHAPTER NINE

ENDOCRINE PHARMACOLOGY

Learning objective

At the end of this chapter the student is expected to learn the following:

- The effects of insulin on different organ/systems
- The types of insulin with their therapeutic uses and adverse reactions
- The mechanism of action, uses and side effects of oral hypoglycemic agents
- Drugs used as oxytocic agents
- Types of hormonal contraception with their uses and adverse effects including preparations
- Actions, therapeutic uses and adverse effects of glucocorticoids

I. ANTIDIABETIC DRUGS

INTRODUCTION

Diabetes Mellitus *is a* disease that occurs as a result of absolute or relative deficiency of insulin that results in metabolic and vascular abnormalities.

The ***etiologies*** include Obesity (because chronic calorie intake and prolonged stimulation of β cell causes a decrease in insulin receptor and also adipose tissue and muscle are less sensitive),hereditary,damage of pancreatic tissue, diabetogenic hormones(like growth hormone, thyroid, epinephrine), diabetogenic drugs like Thiazide diuretics, epinephrine, phenothiazines ,Other factors like Pregnancy.

The common *Signs and symptoms include* polydipsia, polyphagia, polyuria, dehydration due to glucosuria.

Diabetes has dangerous *complications: i*ncluding ketoacidosis (in types I), hyperglycemic osmolal non ketotic coma (in type II), cardiovascular (like atherosclerosis, myocardial infarction, peripheralarterialinsufficiency, Anemia, Hypertension,stroke), nephropathy, retinopathy, neuropathy.

It can *be* ***classified*** *as:* Type I: ***IDDM*** *(*or Juvenile type) occurs predominantly in children and young adults who have no insulin secretion and Type II: ***NIDDM*** (or maturity onset type) usually occur after the age of 40years.

Diabetic ketoacidosis (DKA) is serious complication of diabetes. It is severe metabolic disturbance due to insulin deficiency, which results in hyperglycemia, ketonimia and later acidosis. It is characterized by headache, nausea, vomiting, rapid pulse, dry skin, deep breathing, and change in mentation. Management includes Regular (soluble) insulin IV infusion, treatment of dehydration and precipitating factor.

Hypoglycemic Coma is more serious complication which usually occurs due to excess dose of insulin which produces severe lowering of blood glucose that may leads to coma.

The Sign /Symptom are mental confusion, in coordination, paresthesia, convulsion, coma and Signs of sympathetic over activity. *The aim of treatment* is to restore blood glucose to normal by giving glucose 50% 20 – 100 ml IV, or glucagon 1mg iv, im, sc

Antidiabetogenic drugs

I. INSULIN

Sources include pork or beef, combination of pork and beef and also human insulin (Recombinant DNA technique)

Actions:

- Insulin lower blood glucose level through increasing utilization of glucose by peripheral tissue and promoting synthesis and storage of glycogen
- The main actions of the hormone are exerted on metabolism of carbohydrate (CHO), fat and protein in liver, muscle & adipose tissue.

Effects of insulin

Carbohydrate metabolism

Liver: it increases glycogen synthesis from glucose and glucose utilization while decreases gluconeogenesis and glycogenolysis

Muscle: it increases glucose uptake, glucose utilization and glycogen synthesis.

Adipose tissue: it increases glucose uptake and glycerol synthesis (esterifies fatty acid)

Fat metabolism

Liver: it increases lipogenesis

Adipose tissue: it increases synthesis of triglycerides and synthesis of fatty acid

Protein metabolism

Liver: it increases protein catabolism

Muscle: it increases aminoacid uptake and protein synthesis

Other metabolic effect:

It increases uptake of K^+ and Ca^{++} into cells and synthesis of nucleic acids

There are some factors that increase insulin demand: like Infection, surgery, pregnancy and drugs (those that antagonize actions of insulin glucocorticoids, thyroid hormone, adrenaline)

Type of insulin preparation:

A. Short acting (rapid onset): Eg Regular Insuline
B. Intermediate acting Eg Lente insuline,NPH insuline
C. Long acting E.g Protamine Zn insuline

Types	Route	Onset (hrs)	Duration (hrs)
Regular insulin	IV, SC, IM	¼ - 1	5 – 7
Lente insulin	SC, IM	1 – 1½	18 – 24
Protamine Zn insulin	SC, IM	4 – 8	36

N.B. *It is only regular insulin that can be given by intravenous route.*

Therapeutic use -IDDM, NIDDM (not controlled by diet and oral hypoglycemic agents), diabetic ketoacidosis, Control of diabetes in pregnancy, during surgery and in infections.

They are also used in the treatment of hyper kalmia due to renal failure

Adverse Reaction*:* can be categorized as

Local: Atrophy or hypertrophy at site of injection, local hypersensitivity and secondary infections.

Systemic: Hypoglycemic coma and Immunologic reaction like hypersensitive and insulin resistance

II. ORAL HYPOGLYCEMICS

These are drugs administered orally to lower blood glucose level used in mild diabetes.

They are grouped as Sulphonylureas and Biguinides.

Sulphonyl ureas

These compounds are chemically related to sulphonamides.

First generation: Tolbutamide, Chlorpropamide

Second generation: Glibenclamide, Glipizide

Mechanism: hypoglycemic action is due to Stimulation of insulin release from β cell, Depression of glucagon secretion, Increase number of insulin receptor, Reduce insulin output from liver (Decrease hepatic gluconeogenesis and glycogenolysis)

Pharmacokinetics: They are rapidly absorbed from the gastrointestinal tract. They are also extensively plasma protein bound and are mainly metabolized in the liver.

Use: Mild diabetes mellitus in old patients (type II)

Adverse reaction*:* The toxicity of these compounds is remarkably low. The important toxic effects include: hypoglycemia, allergic skin rash and bone marrow depression, cholestatic jaundice (esp. chlorpropamide)

Side effects: Gastric irritation, prolonged hypoglycemia (esp. chlorpropamide), large doses confusion, vertigo, ataxia, leucopenia, aggranulocytosis, thrombocytopenia, and teratogenecity

***Drug interaction*:**

1. Hypoglycemia is enhanced by sulphonamides, phenylbutazone
2. Alcohol produces “Disulfirum” like action (flushing of the face, severe headache, vomiting etc.)
3. Sulphonyl ureas increase anticoagulant effect of oral anticoagulant
4. Thiazides oppose the action of sulphonylureas.

Biguinides

They potentiate the hypoglycemic action of insulin and sulphonyl ureas but they don’t produce clinical hypoglycemia in diabetics.

Biguanides include drugs like metformin and phenformin

Mechanism: They do not stimulate the release of insulin. They increase glucose uptake in skeletal muscle, and have effects on glucose absorption and hepatic glucose production. They also enhance anaerobic glycolysis.

Pharmacokinetics: Phenformin and metformin are rapidly absorbed from the gastrointestinal tract. Metformin is largely excreted unchanged in the urine and has a longer duration of action.

Side effects: Nausea, vomiting, anorexia, diarrhea, abdominal cramp, lactic acidosis (esp. phenformin)

Use: Obese diabetics (uncontrolled by diet alone), Supplement to sulphonyl urea

Contraindication: Diabetes with hepatic, renal insufficiency, In IDDM, NIDDM (with infection, fever, surgery) and during pregnancy

They have no value in diabetes complicated by acidosis or coma

II .OXYTOCICS

These are group of drugs that cause contraction of the uterus.

Oxytocin

Actions: 1. Oxytocin stimulates the uterus and cause physiologic type of contraction

2. It also causes ejection of milk through contraction of the myo-epithelial cells around the alveoli of the mammary gland.

Pharmacokinetics: It is inactivated orally and absorbed rapidly after intramuscular administration. It can also be absorbed from nasal and buccal membrane.

Use: Induction of labor in women with uterine inertia, Relief of breast engorgement during lactation (few minutes before breast feeding) as nasal spray, Postpartum hemorrhage.

Side effect: Oxytocin may cause over stimulation and leads to rupture of the uterus in the presence of cephalo-pelvic disproportion. Therefore it's contraindicated in woman with uterine scar. When given intravenously may cause water retention leading to water intoxication.

Prostaglandins

They induce labor at anytime during pregnancy but most effective at the third trimester. In female reproductive system prostaglandin E & F are found in ovaries, endometrium and menstrual fluid which is responsible for initiating and maintaining normal birth process. PGF, $PGF_{2\acute{\alpha},}$ PGE stimulate both the tone and amplitude of the uterine contraction.

Adverse reaction: nausa, vomiting, headache, diarrhea, fever, etc.

PGs should be used cautiously in the presence of hypertension, angina, and diabetes. They are contraindicated in the presence of cardiac, renal, pulmonary or hepatic disease

Ergometrine

It is one of the ergot alkaloids with the ability to cause contraction of the uterine smooth muscle.

It causes sustained uterine contraction. It is completely absorbed after subcutaneous and intravenous administration. It is metabolized in the liver and eliminated in the urine .Liver damage enhances the toxicity of ergot alkaloid.

Use: after delivery of placenta if bleeding is severe (Prevent postpartum bleeding)

Adverse effect: Nausa, vomiting but serious toxic effects are rare.

III. Female Sex Hormones and Hormonal Contraception

Oestrogens

These drugs can be classified into three groups.

1. Natural – estradiol, esterone, estriol
2. Semisynthetic – Ethnylestradiol
3. Synthetic: Diethylstibosterol

Natural

Estradiol: Estradiol is most potent, major secretory product of ovary.It is oxidized into esterone by liver; estrone is hydrated to estriol and synthesized by ovarian follicle, adrenal cortex, fetoplacental unit, and testis. Androgen and testestrone are precursor for estrogen. Certain tissue can make estrone from androgen.

Semisynthetic

Ethylestadiol: Highly potent, effective orally

*Absorption and Fate**:*** It is absorbed from GI and skin and rapidly metabolized in the liver

Physiologic actions:

Genital system

Ovary: estrogen affects the ovary through indirectly influencing the secretion of gonadotrophin

Uterus: it affects the 'proliferative phase' of the endometrium and also increases the growth and sensitivity of myometrium for oxytocin.

Cervix: it makes cervical mucus thin and alkaline

Vagina: Stratification, cornification and glycogen deposit is affected by estrogen.

Breast

Estrogen causes the growth of gland and duct system

Anterior pitutary

Estrogen inhibit release of gonadotrophins (FSH, LH)

Metabolic action:

a) Retention of salt and water
b) Plasma lipid level: it increases the level of high density lipoprotein and triglycerides while decreases the level of low density lipoprotein and cholesterol.
c) Increases Ca^{tt} bone deposition
d) It has a mild anabolic action

Blood coagulation

Enhance level of factor II, VII, IX, X so, increase the coagulability of blood and may predispose to thromboembolic condition

Therapeutic use: contraceptive in combination with progestogens, Functional uterine bleeding, Dysmenorrhea, Alleviation of menopausal disorder, Osteoporosis, Replacement therapy in ovarian failure, Prevents senile and atrophic vaginitis

Side effects: Thromboembolism, Sodium and water retention, Withdrawal bleeding, nausea, endometrial carcinoma

Contraindication: History of thromboembolism condition, Undiagnosed uterine bleeding, endometrial Carcinoma, liver disease

PROGESTOGENS

Progestrone is natural occuring progestational hormone.it is synthesized by corpus luteum, placenta, adrenal cortex, testis. It is less effective orally due to complete metabolism by liver so it's given through intramuscular route.

*Actions on g*enital organs:

Ovary - Inhibition of ovulation

Uterus - converts the endometrum for secretory phase and makes the myometrium less sensitive to oxytocin. It also causes relaxation of the uterus in late pregnancy.

Metabolic actions:

(a) Thermogenic action
(b) Competes with aldosterone at renal tubule so inhibits sodium reabsorption.

Synthetic /Senisynthetic progestogens:

Derivative of progestrone: Hydroxyprogesterone capriot/medroxyprogestrone

Derivative of testestrone: Dimethisterone

Nortestrone: Norethisterone

Therapeutic use: Hormonal contraception**,** functional uterine bleeding**,** dymennorrhea Ammenorrhea**,** Endometrial Carcinoma**,** Premenustral tension

ORAL CONTRACEPTIVEs

These are drugs taken orally to prevent conception. They are available in the following forms:

1. Combined regimen type
2. sequential regimen type
3. triphasic pill regimen

Combined regimen: involves the administration of pills containing combination of Estrogen and Progestogen. They are administered starting 5^{th} day of menustral cycle for 21 days.

They can also be classified as fixed dose combination (monophasic), biphasic and triphasic pills. Fixed dose combination: the commonest procedure is to administer one pill containing both an estrogen and progestin daily at bed time for 21 days. In biphasic and triphasic pills: these are combined oral contraceptive pills containing varying proportion of an estrogen and a progesterone designed to stimulate the normal pattern of menustral cycle.

Formulation:

a) low estrogen, low progesterone(0.03mg ethinylestradiol+0.15 mg norgestril
b) Low esterogen, high progestogen
   (0.03 mg ethinylestradiol + 1.5 mg norethindrone)

c) High estrogen, high progestrone
(0.05 mg ethinylestradiol + 0.5 mg norgestril)

Mechanism: includes inhibition of release of FSH and LH, increase viscosity of cervical mucus endometrial changes, interfere with contraction of cervix, uterus and fallopian tube

Single Entity preparation

A. Continuous progestrone

i) Oral progestrone

Norethindone (Norgestril)

ii) Depot

IM injection of long acting progestogen.

e.g. Medroxyprogestrone acetate (Depoprovera®)

iii) Subcutanous implant

L – norgestril (Norplant®)

Mechanism: It makes cervical mucus thick, though & hostile and also alter endometrial wall

B. Post coital "morning after" pill

Oestrogen like Diethyl stilbosterol used within 72 hrs

Combined oral contraceptive pills can also be used.

Side effects of oral contraceptive: Thromboembolic complication, Weight gain & fluid retention, Menstrual disorder, Breast tenderness & fullness, Skin changes, Nausea & vomiting, Depressed mood, Reduced lactation

Beneficial effects of estrogen /progesterone oral contraceptive

1) Reduced risk of endometrial Carcinoma, ovarian cyst
2) regular Menses, No excessive blood loss
3) Less premenustrual tension and dysmennorrhea
4) Relief of endometriosis

Contraindication: In patients withcardiovascular diseases (hypertension, coronary heart disease)

Thromboemolic disease, breast Cancer, diabetes mellitus, liver disease, women > 35 years (esp. smokers and hypertensives)

Drug interaction:

1. Effect reduced when taken with enzyme inducers like Rifampicin, Phenytoin, Phenobarbitone etc. It may result in unexpected pregnancy and spotting.
2. Oral contraceptive antagonize the effect of Coumarin anticoagulant and some antihypertensives

Ovulation inducing drug

These are drugs used in the treatment of infertility due to ovulatory failure.

Clomiphen

It is antiestrogenic drug. It interferes with estrogen feedback inhibition at hypothalamus and anterior pitutary so enhance secretion of FSH, LH causing ovarian stimulation which finally leads to ovulation.

ADRENCORTCCAL HORMONES

Adenocortical hormones control the metabolism of carbohydrate (CHO), protein, fat and water /electrolytes

Adencortical hormones are classified into:

a) Glucocorticoid - Cortisone
   - Hydrocortisone (Cortisol)
b) Mineralocorticoid - Aldosterone
   - Desoxycorticosterone
c) Sex Hormone - Estrogen
   - Androgen

Glucocorticoids

The important glucorticoid secreted in man is *hydrocortisone.* It posseses some mineralocorticoid activity as well. Cortisone is less potent and is converted to hydrocortisone by liver.

They are classified as

1. Short acting e.g cortisone, hydrocortisone
2. Intermediate acting e.g predinsolone, triamcinolone
3. Long acting e.g dexamethasone, betamethasone)

Dexamethasone and betamethasone have got a high glucorticoid activity while cortisone and hydrocortisone have high mineralocorticoid action. Therapeutic activity in inflammatory disorder is proportional to the glucocorticoid activity.

Actions on CHO metabolism:

- antinsulinic effect
- decreases Peripheral utilization of glucose,
- increases gluconeogenesis
- promote glycogen storage

Protein metabolism:

- Inhibit protein synthesis,
- Increases catabolism

Fat metabolism:

- Interferes with fat storage causing deposits with characteristic distribution (neck, supraclavicular area, and face

Electrolyte and H_2O metabolism

- Sodium and water retention
- Hypokalmia

Suppression of pitutary adenocortical system

CNS: Euphoria and stimulation

CVS: Restore vascular reactivity

GIT: Increase gastric acid secretion

Blood: Increase number of RBC, Hypercoagulability

Uric acid: Increased excretion

Calcium metabolism: increased Ca^{++}excretion, interfere with Ca^{++} absorption

Antinflammatory: Inhibit exudation, capillary dilatation, migration of phagocyte, fibroblast, inhibit fibrous tissue formation

Antiallergic: through inhibition of antibody production suppress tissue inflammatory response.

Absorption and fate: It has fair absorption, bound to α -globuin (transcortin).And in the liver, cortisone is converted into hydrocortisone.

Therapeutic use

1) Replacement therapy: In Addisons disease and Addisonian crisis
2) Antinflammatory: in conditions like Collagen disease (rheumatoid carditis, arthritis),
3) Hypersensitivity reactions: (Bronchial Asthma, status asthmatic), Blood disease due to circulating antibodies (autoimmune disease), Skin disease (eczema), Eye disease (allergic inflammation of the eye), Nephrotic syndrome, Acute gout.
4) Immunosuppression: In tissue / organ transplantation.

Precautions

- Check weight for fluid retention
- Test urine for sugar
- Follow blood pressure through measurement and check bones by X-ray for osteoporosis
- Doses should be tapered slowly (Don't stop abruptly)
- Increase dose in surgery, infection
- Encourage diet rich in K^+, protein and adequate calcium, low Nacl
- Rule- out infection before initiation of treatment

Side effects:

- Due to prolonged use: Weight gain and edema hypokalmia, hyperglycemia, osteoporosis, psychiatric disturbance, susceptibility to infection (like TB), peptic ulceration, cushing syndrome, retarded growth
- Complication with rapid withdrawal results in adrenacortical insufficiency due to depression of adrenocortical activity

Contraindication:

They are contraindicated in patients with peptic ulcer disease, acute infection like active tuberculosis, diabetes mellitus, psychosis, pregnancy

Mineralocorticoid

Aldosterone

It is the main mineralocorticoid of adrenal cortex. It increases absorption of Na at distal tubule and increases K^+ excretion. They are not widely used in therapeutics rather its antagonists are of value in cases of edema.

Thyroid and Antithyroid Drugs

They inhibit the function of the thyroid gland and used in hyperthyroidism.

Antithyroid drugs include:

1. Thiourea compounds, e.g. , propylthiouracil, methimazole, carbimazole
2. Ionic inhibitors, e.g. , potassium percholate, potassium thiocyanate
3. Iodide, e.g. , Lugol's iodine, potassium iodide
4. Radioactive iodine (^{131}I)

Thiourea Compounds

Inhibit the formation of throid hormone through inhibiting the oxidation of iodide to iodine by peroxidase enzyme and blocking the coupling of iodothryosines to form iodothyronines.

They are contraindicated in pregnant and lactating women.

Toxicities include drug fever, skin rashes, increased size and vascularity of the thyroid gland, and agranulocytosis.

Ionic Inhibitors

Potassium percholate prevents the synthesis of thyroid hormones through inhibition of uptake and concentration of iodide by the gland. It has the risk of aplastic anemia, therefore no longer used in the treatment of hyperthyroidism.

Iodides:

Improve manifestations of hyperthyroidism by decreasing the size and vascularity of the gland so they are required for preoperative preparation of the patient for partial thyroidectomy.

Iodides act through inhibition of the "protease" enzyme which releases T_3 and T_4 from thyroglobulin, and organification.

Radioactive Iodine:

It is used in hyperthyroidism as sodium ^{131}I orally. It is trapped and concentrated as ordinary iodine, which emits beta rays that act on parenchymal cells of the gland.

It is contraindicated in pregnancy and lactation as it affects thyroid gland in the fetus and the infant. Its important toxicity is hypothyroidism.

Propranolol

This is an important drug which controls the peripheral manifestations of hyperthyroidism (tachycardia, tremor). In addition, it decreases the peripheral conversion of T_4 to T_3.

Thryoid Storm (Crisis)

This is a sudden acute exacerbation of all the symptoms of thyrotoxic which rarely occur after thyroidectomy. Manifestations include hyperpyrexia, gastrointestinal symptoms, dehydration, tachycardia, arrhythmia, restlessness, etc. which may progress to shock and death.

Management: It consists of infusion of intravenous fluids, supportive management, and also administration of propylthiouracil, sodium iodide, hydrocortisone, and propranolol.

Exercise

1. List the important organ/system effects of insulin.
2. Write about the clinical aspects of oral antidiabetic drugs.
3. Discuss the mechanism and beneficial effects of combined oral contraceptive pills.
4. Discuss the pharmacological action and adverse effects of glucorticoids.
5. Write about anti thyroid drugs.

CHAPTER TEN

CHEMOTHERAPEUTIC DRUGS

Learning Objectives

At the end this section the student will able to:

1. Describe the general mechanisms of action of antimirobial drugs.
2. Illustrate the mechanims of antimicrobial drug resistance.
3. Explain the indications, and adverse effects of frequently used antibiotics.
4. Describe the major adverse effects and clinical uses of aminoglycosides.
5. Describe the mechanims of action and the adverse effects of antituberculois drugs.
6. Classify antifungal drugs.
7. Classify antiretroviral drugs.
8. Explain the common adverse effects of anti cancer drugs.
9. Describe the clinical uses, and the major adverse effects of antimalarial drugs.
10. Discuss drugs used in the treatment of different forms of amoebiasis.
11. Describe drugs used for gardiasis and trichomonisis.
12. Discuss drugs used in the treatment of toxoplasmosis, and pneumocystiois.
13. Explain drugs used in the treatment of leshmaniasis and trypanosomiasis.
14. Discuss the use, mechanism of action and problems associated with anthelminthic drugs.

INTODUCTION

Chemotherapy: is the use of chemical agents (either synthetic or natural) to destroy infective agents (microorganisms' i.e bacteria, fungus and viruses, protozoa, and helminthes) and to inhibit the growth of malignant or cancerous cells.

Chemotherapeutic agents: are chemical which are intended to be toxic for parasitic cell but non toxic to the host, such selective toxicity depends on the existence of exploitable biochemical difference between the parasite and the host cell.

Antimicrrobials: are chemical agents (synthetic/natural) used to treat bacterial, fungal and viral infections. *Antibiotics:* are substances produced by various species of microorganisms (bacteria, fungi, actinomycetes) that suppress the growth of other microorganisms. Antimicrobial drug exhibits *selective toxicity*. I.e. the drug is harmful to the parasite without being harmful to the host.

Bactericidal versus bacteriostatic action: When antimicrobial agents lead to the death of the susceptible microbe (e.g. bacteria) it is said have bactericidal action but when it merely inhibits the growth and therefore spread of the microbial population it is said to have bacteriostatic action.

Anticancer agents: Drugs or chemicals used to manage neoplastic diseases.

Antiprotozoals: are drugs used to treat malaria, amoebiasis, gardiasis, trichomoniasis, toxoplasmosis, pneumocystis carinii pneumonia, trypanosomiasis and leshmaniasis.

Anthelminthics: are drugs used in the treatment of intestinal and tissue worms.

The classificastion, pharmacokinetics, pharmacodynamics, clinical uses, adverse effects of commonly used antimicrobias, antiprotozoals, antihelimenthics are disscused. Brief introduction is given regading the treatment of cancer.

ANTIMICROBIAL DRUGS

Mechanisms of antimicrobial drug action:

1. Inhibition of cell wall synthesis
2. Cell membrane function inhibitors
3. Inhibition of protein synthesis
4. Inhibition of nucleic acid synthesis
5. Antimetabolites

Mechanisms of resistance to antibiotics

1. Production of enzymes that inactivate the drug (eg. β -lactamase, which inactivates beta lactam antibiotics; acetyl transferases, which inactivate chloramphenicol; kinases and other enzymes, which inactivate aminoglycosides.

2. Alteration of the drug-binding site: this occurs with penicillins, aminoglycosides and erythromycin.
3. Reduction of drug uptake by the bacterium: eg. Tetracyclines
4. Alteration of enzymes: eg. Dihydrofolate reductase becomes insensitive to trimethoprim.

Anibacterial agents

Cell wall synthesis inhibitors

Members the group: Beta-lactam antibiotics, vancomycin, bacitracine, and cycloserine

Beta-lactam antibiotics: Penicillins, cephalosporins, carbapenems, and monobactams are members of the family. All members of the family have a beta-lactam ring and a carboxyl group resulting in similarities in the pharmacokinetics and mechanism of action of the group members. They are water-soluble, elimination is primary renal and organic anion transport system is used.

Penicillins

Penicillins have similar structure, pharmacological and toxicological properties. The prototype of penicillins is penicillin G and is naturally derived from a genus of moulds called penicillium.

Classification: Penicillins can be classified into three groups: *Natural Penicillins, Antistaphylococcal penicillins,* and *Extended-spectrum penicillins.*

Mechanism of Action: Penicillins inhibit bacterial growth by interfering with a specific step in bacterial cell wall synthesis (block the transpeptidation reaction). Sensitive pencillins are inactivatived by betalactamase enzymes.

Pharmacokinetics: Penicillin G is unstable in acid media, hence destroyed by gastric juice. Ampicillin, amoxicillin, and dicloxacillin are acid-stable and relatively well absorbed after oral adminstraion. Oral penicillins should be given 1-2 hours before or after meals to minimize binding to food proteins and acid inactivation (except ampicilin). The absorption of most penicillin is complete and rapid after IM administration. The kidneys rapidly excrete penicillin. Renal excretion is by glomerular filtration (10%) and by tubular secretion (90%). Blood levels of all penicillins can be raised by simultaneous administration of probenecid orally, which impairs tubular secretion of weak acids.

Clinical Uses

Natural Penicillins: Penicillin G and penicillin V are natural penicillins. Penicillin G is the drug of choice for infections caused by streptococci, meningococci, enterococci, penicillin-susceptible pneumococci, non-beta-lactamase-producing staphylococci, Treponema pallidum and many other spirochetes, Bacillus anthracis, Clostridium species, Actinomyces, and other gram-positive rods and non-beta-lactamase-producing gram-negative anaerobic organisms. Penicillin V is acid stable but it is less potent than penicillin G.

Antistaphylococcal Penicillins: [Methicillin, Nafcillin, isoxazolyl penicillins (Oxacillin, cloxacillin, and dicloxacillin)]. The only indication is infections caused by beta-lactamase-producing staphylococci. Oral isoxazolyl penicillin is suitable for treatment of mild localized staphylococcal infections, for serious systemic staphylococcal infections, oxacillin or nafcillin, is given by intermittent intravenous infusion.

Extended Spectrum Penicillins: Aminopenicillins (ampicillin, amoxicillin), Carboxypenicillins (Carbenicillin, ticarcillin, effective at lower doses), and Ureidopenicillins (piperacillin, mezlocillin, and azlocillin): Spectrum of activity similar to penicillin G, though having greater activity against gram-negative bacteria due to their enhanced ability to penetrate the gram-negative outer membrane. The aminopenicillins have the same spectrum and activity, but amoxicillin is better absorbed from the gut. These drugs are given orally to treat urinary tract infections, sinusitis, otitis, and lower respiratory tract infections. Ampicillin IV is useful for treating serious infections caused by penicillin-susceptible organisms, including anaerobes, enterococci, Listeria monocytogenes, and susceptible strains of gram-negative cocci and bacilli such as E coli, H influenzae, and Salmonella species. Carboxypenicillins extend the ampicillin spectrum of activity to include Pseudomonas aeruginosa and Enterobacter species. The ureidopenicillins resemble ticarcillin except that they are also active against selected gram-negative bacilli, such as Klebsiella pneumoniae. Because of the tendency of P aeruginosa to develop resistance during monotherapy, antipseudomonal penicillins generally is used in combination with an aminoglycoside for pseudomonal infections.

Adverse Reactions: Grouped into three: *Allergy*: Cross sensitivity and cross reactivity among beta-lactams is common. Reactions include: Skin rashes, fever, bronchospasm, Oral lesions, interstitial nephritis (autoimmune reaction to penicillin-protein complex), eosinophilia, hemolytic anemia, vasculitis and anaphylactic shock. *Biological:* antibiotic assoicated enterocolitis (ampicillin), and *Toxic:* diarrhea (ampicillin), nephritis, especially methicillin, and platelet dysfunction (antipseudomonal penicillins).

Cephalosporins

Cephalosporins can be classified into four generations depending mainly on the spectrum of antimicrobial activity. First-generation compounds have better activity against gram-positive organisms and the later compounds exhibit improved activity against gram-negative aerobic organisms.

First-generation cephalosporins

Members: Cefadroxil, cefazolin, cephalexin, and cephalothin. These drugs are very active against gram-positive cocci (pneumococci, streptococci, and staphylococci). Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis are often sensitive, but activity against Pseudomonas aeruginosa, indole-positive Proteus, Enterobacter, Serratia marcescens, Citrobacter, and Acinetobacter is poor. Anaerobic cocci (eg, Peptococcus, Peptostreptococcus) are usually sensitive, but B fragilis is not.

Cephalexin, and cefadroxil are absorbed from the gut to a variable extent. Urine concentration is usually very high, but in most tissues levels are and generally lower than in serum. Cefazolin is given IM/IV (the only first generation administered parentrally). Excretion is via the kidney and probenecid may increase serum levels substantially.

Clinical Uses: Oral drugs may be used for the treatment of urinary tract infections, for minor staphylococcal lesions, or for minor polymicrobial infections such as cellulitis or soft tissue abscess.

Second-generation cephalosporins

Members: Cefaclor, cefamandole, and cefuroxime. The group is heterogeneous, with marked individual differences in activity, pharmacokinetics, and toxicity. All second-generation cephalosporins are less active against gram-positive bacteria than the first-generation drugs; however, they have an extended gram-negative coverage. Klebsiella and H influenzae are usually sensitive. Can be given orally or parentrally

Clinical Uses: Sinusitis, otitis, or lower respiratory tract infections, mixed anaerobic infections, and community-acquired pneumonia.

Third-generation cephalosporins

Members: cefotaxime, ceftazidime, ceftriaxone, and proxetil.

Antimicrobial activity: The major features of these drugs are the ability of some to cross the blood-brain barrier and their expanded gram-negative coverage (active against Citrobacter, Serratia marcescens, Providencia, and beta-lactamase-producing strains of Haemophilus and Neisseria). Ceftazidime is effective in pseudomonas infections.

They can be given orally or IM or IV. They penetrate body fluids and tissues well. Cefotaxime, ceftazidim, and ceftriaxone crosses blood brain barrier, hence inhibit most pathogens, including gram-negative rods.

Clinical uses: Gonorrhea (ceftriaxone and cefixime), meningitis (pneumococci, meningococci, H influenzae, and susceptible enteric gram-negative rods), penicillin-resistant strains of pneumococci (ceftriaxone, cefotaxime), and sepsis

Fourth-generation cephalosporins (e.g.cefepime)

It is similar to third-generation agents; however, it is more resistant to hydrolysis by beta-lactamases. It has good activity against P aeruginosa.

Adverse Effects: Cephalosporins are sensitizing and may elicit a variety of hypersensitivity reactions that are identical to those of penicillins. Overgrowth of resistant organisms and fungi may induce superinfection.

Monobactams contain a monocyclic beta-lactam ring(e.g. aztreonam). They are relatively resistant to beta-lactamases and active against gram-negative rods. It resembles aminoglycosides in its spectrum of activity.

Carbapenems include imipenem and meropenem and have a broad spectrum of activity (against most Gram-positive and negative bacteria). Imipenem is inactivated by a renal proteolytic enzyme and must therefore be combined with cilastatin which inhibits the enzyme.

*Beta-lactamase inhibitors: (*clavulanic acid, sulbactam, and tazobactam)**.**

They have no antimicrobial activity, and usually combined with beta lactamase labile antibiotics, irreversibly inhibit beta-lactamases. Examples: Ticarcillin and clavulanate [Timentin], Ampicillin and sulbactam [Unasyn], Amoxicillin and clavulanate [Augmentin]

Vancomycin

Vancomycin is active only against gram-positive bacteria, particularly staphylococci. It inhibits cell wall synthesis.

Vancomycin is poorly absorbed from the intestinal tract and is administered orally only for the treatment of antibiotic-associated enterocolitis caused by Clostridium difficile. Parenteral doses must be administered intravenously. The drug is widely distributed in the body. Ninety percent of the drug is excreted by glomerular filtration.

Clinical Uses: Parenteral vancomycin is indicated for sepsis or endocarditis caused by methicillin-resistant staphylococci. It irritates the tissues surrounding the injection site and is known to cause a red man or red neck syndrome.

Bacitracin

Bacitracin is active against gram-positive microorganisms. It inhibits cell wall formation. It is markedly nephrotoxic if administered systemically, thus limited to topical use. Bacitracin is poorly absorbed.

Cycloserine

Cycloserine inhibits many gram-positive and gram-negative organisms, but it is used almost exclusively to treat tuberculosis caused by strains of M tuberculosis resistant to first-line agents. It is widely distributed in tissues. Most of the drug is excreted in active form into the urine. Cycloserine causes serious dose-related central nervous system toxicity with headaches, tremors, acute psychosis, and convulsions.

Cell Membrane Function Inhibitors

Antimirobials such as polymyxins acting on gram negative bacteria and affects the functional integrity of the cytoplasmic membrane, macromolecules and ions escape from the cell and cell damage and death occurs. The two most well known agents are poymyxin B and colistin. Polymyxins are effective against Gram-negative bacteria, particularly pseudomonas species. The major adverse effects are nephrotoxicity dizziness, alterd sensation and neuromuscular paralysis.

Protien Synthesis Inhibitors

Bacteria have two ribosomal subunits; 30S and 50S. The 30S subunit binds mRNA in initiation and holds growing peptide chain. The 50S subunit accepts / translocates charged tRNAs. Protien synthesis inhibitors are divided into two groups: bacteriostatic and bactericidal. Chloramphenicol, macrolides, clindamycin (Lincosamides), and tetracyclines are bacteriostatic whereas aminoglycosides are bactericidal**.**

Mechanisms of action:

Chloramphenicol blocks proper binding of 50S site which, stops protein synthesis. It does inhibit mitochondrial ribosomal protein synthesis because these ribosomes are 70S, the same as those in bacteria. It does not bind to the 80S mammalian ribosomes. This may be responsible for the dose related anemia caused by chloramphenicol.

Macrolides, clindamycin, prevent transfer of the growing polypeptide chain within the 50S site so a new charged tRNA cannot bind to the ribosome so, stops protein synthesis.

Tetracyclines bind to 30S ribosomal subunit at a site that blocks binding of charged tRNA to the 50S site of the ribosome. Tetracyclines can inhibit mammalian protein synthesis, but because they are "pumped" out of most mammalian cells do not usually reach concentrations needed to significantly reduce mammalian protein synthesis.

Aminoglycosides: Protein synthesis is inhibited by aminoglycosides in at least three ways: (1) They interfere with the "initiation complex" of peptide formation; (2) they induce misreading of mRNA, which causes incorporation of incorrect amino acids into the peptide, resulting in a non-functional or toxic protein; and (3) they cause a breakup of polysomes into nonfunctional monosomes. These activities occur more or less simultaneously, and the overall effect is irreversible and lethal for the cell.

Chloramphenicol

Chloramphenicol is a bacteriostatic broad-spectrum antibiotic that is active against both aerobic and anaerobic gram-positive and gram-negative organisms. It is active also against rickettsiae*. Haemophilus influenzae, N. meningitidis,* and some strains of *Bacteroides* are highly susceptible, and for them chloramphenicol may be bactericidal. Clinically significant resistance emerges and may be due to production of chloramphenicol acetyltransferase, an enzyme that inactivates the drug.

Pharmacokinetics: Following oral administration, chloramphenicol is rapidly and completely absorbed. It is widely distributed to virtually all tissues and body fluids. The drug penetrates cell membranes readily. Excretion of active chloramphenicol and of inactive degradation products occurs by way of the urine. A small amount of active drug is excreted into bile or feces. Newborns less than a week old and premature infants clear chloramphenicol inadequately.

Clinical Uses: Because of potential toxicity, bacterial resistance, and the availability of other effective drugs, chloramphenicol may be considered mainly for treatment of serious rickettsial infections, bacterial meningitis caused by a markedly penicillin-resistant strain of pneumococcus or meningococcus, and thyphoid fever.

Adverse Reactions

Gastrointestinal disturbances: Adults occasionally develop nausea, vomiting, and diarrhea. Oral or vaginal candidiasis may occur as a result of alteration of normal microbial flora.

Bone marrow disturbances: Chloramphenicol commonly causes a dose-related reversible suppression of red cell production at dosages exceeding 50 mg/kg/d after 1-2 weeks. Aplastic anemia is a rare consequence of chloramphenicol administration by any route. It is an idiosyncratic reaction unrelated to dose, though it occurs more frequently with prolonged use. It tends to be irreversible and can be fatal.

Toxicity for newborn infants: Newborn infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol. Consequently, when infants are given dosages above 50 mg/kg/d, the drug may accumulate, resulting in the gray baby syndrome, with vomiting, flaccidity, hypothermia, gray color, shock, and collapse.

Interaction with other drugs: Chloramphenicol inhibits hepatic microsomal enzymes that metabolize several drugs. Like other bacteriostatic inhibitors of microbial protein synthesis, chloramphenicol can antagonize bactericidal drugs such as penicillins or aminoglycosides.

Tetracyclines

The tetracyclines are a large group of drugs with a common basic structure and activity. Tetracyclines are classified as short acting (chlortetracycline, tetracycline, oxytetracycline), intermediate acting (demeclocycline and methacycline), or long-acting (doxycycline and minocycline) based on serum half-lives.

Antimicrobial activity: Tetracyclines are broad-spectrum antibiotics. They are active against for many gram-positive and gram-negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasmas, and are active against some protozoa. The main mechanisms of resistance to tetracycline is decreased intracellular accumulation due to either impaired influx or increased efflux by an active transport protein pump.

Pharmacokinetics: Tetracyclines mainly differ in their absorption after oral administration and their elimination. Doxycycline better absorbed after oral administration than tetracycline. A portion of an orally administered dose of tetracycline remains in the gut lumen, modifies intestinal flora, and is excreted in the feces. Absorption occurs mainly in the upper small intestine and is impaired by food (except doxycycline and minocycline); by divalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}) or Al^{3+}; by dairy products and antacids, which contain multivalent cations; and by alkaline pH. They are distributed widely to tissues and body fluids except for cerebrospinal fluid. Minocycline reaches very high concentrations in tears and saliva, which makes it useful for eradication of the meningococcal carrier state. Tetracyclines cross the placenta to reach the fetus and are also excreted in milk. Doxycycline, in contrast to other tetracyclines, is eliminated by nonrenal mechanisms.

Clinical uses: A tetracycline is the drug of choice in infections with Mycoplasma pneumoniae, chlamydiae, rickettsiae, and some spirochetes. They are used in combination regimens to treat gastric and duodenal ulcer disease caused by Helicobacter pylori. They may be employed in various gram-positive and gram-negative bacterial infections, including Vibrio infections. A tetracycline in combination with an aminoglycoside is indicated for plague, tularemia, and brucellosis. Tetracyclines are sometimes employed in the treatment of E. histolytica or P. falciparum.

Adverse reactions

Gastrointestinal adverse effects: Nausea, vomiting, and diarrhea are the most common and these effects are attributable to direct local irritation of the intestinal tract. Tetracyclines suppress susceptible coliform organisms and causes overgrowth of Pseudomonas, Proteus, staphylococci, resistant coliforms, clostridia, and Candida. This can result in intestinal functional disturbances, anal pruritus, vaginal or oral candidiasis, or enterocolitis (associated with *Clostridium difficile*) with shock and death. Pseudomembranous enterocolitis should be treated with metronidazole.

Bony structures and teeth: Tetracyclines are readily bound to calcium deposited in newly formed bone or teeth in young children. It causes discoloration, and enamel dysplasia; they can also be deposited in bone, where it may cause deformity or growth inhibition. If the drug is given to children under 8 years of age for long periods, similar changes can result.

They are hepato and nephrotoxic drug, the also induce sensitivity to sunlight (demeclocycine) and vestibular reactions (doxycycline, and minocycline).

Macrolides: include erythromycin, clarithromycin and azithromycin.

Erythromycin

Erythromycin is poorly soluble in water but dissolves readily in organic solvents. They Erythromycins are usually dispensed as various esters and salts.

Antimicrobial Activity: Erythromycin is effective against gram-positive organisms, especially pneumococci, streptococci, staphylococci, and corynebacteria. Mycoplasma, Legionella, Chlamydia trachomatis, Helicobacter, Listeria, Mycobacterium kansasii, and Mycobacterium scrofulaceum are also susceptible. Gram-negative organisms such as Neisseria species, Bordetella pertussis, Treponema pallidum, and Campylobacter species are susceptible.

Pharmacokinetics: Erythromycin base is destroyed by stomach acid and must be administered with enteric coating. Food interferes with absorption. Stearates and esters are fairly acid-resistant and somewhat better absorbed. Large amounts of an administered dose are excreted in the bile and lost in feces. Absorbed drug is distributed widely except to the brain and cerebrospinal fluid.

Clinical Uses: Erythromycin is the drug of choice in corynebacterial infections (diphtheria, corynebacterial sepsis, erythrasma); in respiratory, neonatal, ocular, or genital chlamydial infections; and in treatment of community-acquired pneumonia because its spectrum of activity includes the pneumococcus, Mycoplasma, and Legionella. Erythromycin is also useful as a penicillin substitute in penicillin-allergic individuals with infections caused by staphylococci, streptococci, or pneumococci.

Adverse Reactions

Gastrointestinal Effects: Anorexia, nausea, vomiting, and diarrhea.

Liver Toxicity: Erythromycins, particularly the estolate, can produce acute cholestatic hepatitis (reversibile).

Drug Interactions: Erythromycin metabolites inhibit cytochrome P450 enzymes; hence increase the serum concentrations of theophylline, oral anticoagulants, and terfenadine. It increases serum concentrations of oral digoxin by increasing its bioavailability.

Clarithromycin

Clarithromycin is derived from erythromycin. It is better absorbed compared with erythromycin. Clarithromycin and erythromycin are virtually identical with respect to antibacterial activity except that clarithromycin has high activity against H. influenzae, *M. leprae* and *T. gondii.* Clarithromycin penetrates most tissues, with concentrations equal to or exceeding serum concentrations. It is metabolized in the liver. A portion of active drug and major metabolite is eliminated in the urine. It has drug interactions similar to those described for erythromycin. The advantages of clarithromycin compared with erythromycin are lower frequency of gastrointestinal intolerance and less frequent dosing.

Azithromycin

The spectrum of activity and clinical uses of azithromycin is identical to those of clarithromycin.It is rapidly absorbed and well tolerated orally. Azithromycin does not inactivate cytochrome P450 enzymes like erythromycin.

Clindamycin

Clindamycin is active against streptococci, staphylococci, bacteroides species and other anaerobes, both grampositive and gram-negative. It resembles erythromycin in activity and mechanisms of resistance. Clindamycin is well absorbed orally and about 90% protein-bound. Excretion is mainly via the liver, bile, and urine. It penetrates well into most tissues.

Clinical uses: Clindamycin is used for the treatment of severe anaerobic infection caused by Bacteroides. It is used for prophylaxis of endocarditis in patients with valvular heart disease who are undergoing certain dental procedures. Clindamycin plus primaquine is an effective for moderate to moderately severe Pneumocystis carinii pneumonia. It is also used in combination with pyrimethamine for AIDS-related toxoplasmosis of the brain.

Adverse effects: Diarrheas, nausea, and skin rashes, impaired liver functions are common. Severe diarrhea and enterocolitis is caused by toxigenic C difficile (infrequently part of the normal fecal flora but is selected out during administration of oral antibiotics).

Aminoglycosides:

Members: Streptomycin, neomycin, kanamycin, amikacin, gentamicin, netilmicin.

Pharmacokinetics: Aminoglycosides are absorbed very poorly from the intact gastrointestinal tract. After intramuscular injection, aminoglycosides are well absorbed. They are highly polar compounds that do not enter cells readily. The kidney clears aminoglycosides, and excretion is directly proportionate to creatinine clearance.

Adverse effects: Aminoglycosides damage the VIII nerve and the kidneys. Ototoxicity can manifest itself either as auditory damage, resulting in tinnitus and high-frequency hearing loss initially; or as vestibular damage, evident by vertigo, ataxia, and loss of balance. Nephrotoxicity results in rising serum creatinine levels or reduced creatinine clearance. Neomycin, kanamycin, and amikacin are the most ototoxic agents. Streptomycin and gentamicin are the most vestibulotoxic.

Streptomycin

Streptomycin is mainly used as a first-line agent for treatment of tuberculosis.

Adverse Reactions: Disturbance of vestibular function (vertigo, loss of balance) is common. The frequency and severity of this disturbance are proportionate to the age of the patient, the blood levels of the drug, and the duration of administration. Vestibular dysfunction may follow a few weeks of unusually high blood levels or months of relatively low blood levels. Vestibular toxicity tends to be irreversible. Streptomycin given during pregnancy can cause deafness in the newborn.

Gentamicin

Gentamicin inhibits many strains of staphylococci and coliforms and other gram-negative bacteria. It is a synergistic companion with beta-lactam antibiotics, against *Pseudomonas, Proteus, Enterobacter, Klebsiella, Serratia, Stenotrophomonas,* and other gram-negative rods that may be resistant to multiple other antibiotics.

Gentamicin is also used concurrently with penicillin G for bactericidal activity in endocarditis due to viridans streptococci. Creams, ointments, or solutions gentamicin sulfate are for the treatment of infected burns, wounds, or skin lesions.

Amikacin

Amikacin is a semisynthetic derivative of kanamycin; it is less toxic than the parent molecule. It is resistant to many enzymes that inactivate gentamicin and tobramycin, and it therefore can be employed against some microorganisms resistant to the latter drugs. Strains of multidrug-resistant Mycobacterium tuberculosis, including streptomycin-resistant strains, are usually susceptible to amikacin.

Kanamycin, Neomycin, Paromomycin

These drugs are closely related is also a member of this group. All have similar properties. Neomycin and kanamycin are too toxic for parenteral use and are now limited to topical and oral use. Neomycin is given orally in preparation for elective bowel surgery. In hepatic coma, the coliform flora can be suppressed for prolonged periods by giving 1 g every 6-8 hours together with reduced protein intake, thus reducing ammonia intoxication. Paromomycin has been effective in intestinal amebiasis.

Spectinomycin

Spectinomycin is an aminocyclitol antibiotic that is structurally related to aminoglycosides. Spectinomycin is used almost solely as an alternative treatment for gonorrhea in patients who are allergic to penicillin or whose gonococci are resistant to other drugs. It is rapidly absorbed after intramuscular injection. A single dose of 2 g (40 mg/kg) is given. There is pain at the injection site and occasionally fever and nausea.

Nucleic Acid Synthesis Inhibitors

Nalidixic acid

Nalidixic acid is the first antibacterial quinolone. It is not fluorinated and is excreted too rapidly to have systemic antibacterial effects. They inhibit normal transcription and replication of bacterial DNA. Because of their relatively weak antibacterial activity, these agents were useful only for the treatment of urinary tract infections and shigellosis.

Fluoroquinolones

Quinolones are synthetic fluorinated analogs of nalidixic acid, that nucleic acid synthesis. Ofloxacin and ciprofloxacin inhibit gram-negative cocci and bacilli, including *Enterobacteriaceae, Pseudomonas, Neisseria, Haemophilus, and Campylobacter.* Many staphylococci also are sensitive these drugs. Intracellular pathogens such as *Legionella, Chlamydia, M tuberculosis and M avium complex,* are inhibited by fluoroquinolones.

Pharmacokinetics: After oral administration, the fluoroquinolones are well absorbed and distributed widely in body fluids and tissues. Oral absorption is impaired by divalent cations, including those in antacids. The fluoroquinolones are excreted mainly by tubular secretion and by glomerular filtration. All fluoroquinolones accumulate in renal failure.

Clinical Uses: Fluoroquinolones are effective in urinary tract infections even when caused by multidrug-resistant bacteria, eg, Pseudomonas. Norfloxacin 400 mg, ciprofloxacin 500 mg, and ofloxacin 400 mg given orally twice daily and all are effective. These agents are also effective for bacterial diarrhea caused by Shigella, Salmonella, toxigenic E coli, or Campylobacter. Fluoroquinolones (except norfloxacin, which does not achieve adequate systemic concentrations) have been employed in infections of soft tissues, bones, and joints and in intra-abdominal and respiratory tract infections, including those caused by multidrug-resistant organisms such as Pseudomonas and Enterobacter. Ciprofloxacin and ofloxacin are effective for gonococcal infection, including disseminated disease, and ofloxacin is effective for chlamydial urethritis or cervicitis.

Adverse Effects: The most common effects are nausea, vomiting, and diarrhea. Concomitant administration of theophylline and quinolones can lead to elevated levels of theophylline with the risk of toxic effects, especially seizures. Fluoroquinolones may damage growing cartilage and cause an arthropathy. Thus, they are not routinely recommended for use in patients under 18 years of age. Since fluoroquinolones are excreted in breast milk, they are contraindicated for nursing mothers.

Rifampin

Rifampin binds strongly to the bacterial DNA-dependent RNA polymerase and thereby inhibits RNA synthesis. It is well absorbed after oral administration and excreted mainly through the liver into bile. Rifampin is distributed widely in body fluids and tissues. It is relatively highly protein-bound, and so adequate cerebrospinal fluid concentrations are achieved only in the presence of meningeal inflammation. Rifampin is used in the treatment of mycobacterial infections.

Rifampin causes a harmless orange color to urine, sweat, and tears. Occasional adverse effects include rashes, thrombocytopenia, nephritis, cholestatic jaundice and occasionally hepatitis. Rifampin induces microsomal enzymes (cytochrome P450), which increases the elimination of anticoagulants, anticonvulsants, and contraceptives. Administration of rifampin with ketoconazole, or chloramphenicol results in significantly lower serum levels of these drugs.

Antimetabolites

Sulfonamides

Sulfonamides can be divided into three major groups: (1) oral, absorbable; (2) oral, nonabsorbable; and (3) topical. The oral, absorbable sulfonamides can be classified as short-, medium-, or long acting on the basis of their half-lives.

Mechanisms of action: Microorganisms require extracellular para-aminobenzoic acid (PABA) to form dihydrofolic acid, an essential step in the production of purines and the synthesis of nucleic acids. Sulfonamides are structural analogs of PABA that competitively inhibit dihydropteroate synthase. They inhibit growth by reversibly blocking folic acid synthesis.

Sulfonamides inhibit both gram-positive and gram-negative bacteria, *Nocardia, Chlamydia trachomatis,* and some protozoa. Some enteric bacteria, such *as E coli, Klebsiella, Salmonella, Shigella, and Enterobacter*, are inhibited.

Pharmacokinetics: They are absorbed from the stomach and small intestine and distributed widely to tissues and body fluids, placenta, and fetus. Absorbed sulfonamides become bound to serum proteins to an extent varying from 20% to over 90%. A portion of absorbed drug is acetylated or glucuronidated in the liver. Sulfonamides and inactivated metabolites are then excreted into the urine, mainly by glomerular filtration.

Clinical Uses

Oral Absorbable Agents: Sulfisoxazole and sulfamethoxazole are short- to medium-acting agents that are used to treat urinary tract infections, respiratory tract infections, sinusitis, bronchitis, pneumonia, otitis media, and dysentery. Sulfadiazine in combination with pyrimethamine is first-line therapy for treatment of acute toxoplasmosis. Sulfadoxine, long-acting sulfonamide, in combination with pyrimethamine used as a second-line agent in treatment for malaria.

Oral Nonabsorbable Agents: Sulfasalazine is widely used in ulcerative colitis, enteritis, and other inflammatory bowel disease. Sulfasalazine is split by intestinal microflora to yield sulfapyridine and 5-aminosalicylate. Salicylate released in the colon in high concentration is responsible for an antiinflammatory effect. Comparably high concentrations of salicylate cannot be achieved in the colon by oral intake of ordinary formulations of salicylates because of severe gastrointestinal toxicity.

Topical Agents: Sodium sulfacetamide ophthalmic solution or ointment is effective treatment for bacterial conjunctivitis and as adjunctive therapy for trachoma. Silver sulfadiazine is a much less toxic topical sulfonamide and is preferred to mafenide for prevention of infection of burn wounds.

Adverse Reactions: The most common adverse effects are fever, skin rashes, exfoliative dermatitis, photosensitivity, urticaria, nausea, vomiting, and diarrhea. Stevens-Johnson syndrome, crystalluria, hematuria, hemolytic or aplastic anemia, granulocytopenia, and thrombocytopenia occur less frequently. Sulfonamides taken near the end of pregnancy increase the risk of kernicterus in newborns.

Trimethoprim

Trimethoprim inhibits bacterial dihydrofolic acid reductase. Dihydrofolic acid reductases convert dihydrofolic acid to tetrahydrofolic acid, a stage leading to the synthesis of purines and ultimately to DNA.

Trimethoprim is usually given orally. It is absorbed well from the gut and distributed widely in body fluids and tissues, including cerebrospinal fluid. Trimethoprim concentrates in prostatic fluid and in vaginal fluid, which are more acid than plasma. Therefore, it has more antibacterial activity in prostatic and vaginal fluids than many other antimicrobial drugs.

Trimethoprim can be given alone in acute urinary tract infections, because most community-acquired organisms tend to be susceptible to the high concentrations.

Trimethoprim produces the predictable adverse effects of an antifolate drug, especially megaloblastic anemia, leukopenia, and granulocytopenia. This can be prevented by the simultaneous administration of folinic acid, 6-8 mg/d.

Trimethoprim-Sulfamethoxazole(Cotrimoxazole)

The half-life of trimethoprim and sulfamethoxazole is similar. Trimethoprim, given together with sulfamethoxazole, produces sequential blocking in this metabolic sequence, resulting in marked enhancement of the activity of both drugs. The combination often is bactericidal, compared to the bacteriostatic activity of a sulfonamide alone.

Clinical uses: Trimethoprim-sulfamethoxazole is effective treatment for Pneumocystis carinii pneumonia, shigellosis, systemic Salmonella infections, urinary tract infections, and prostatitis. It is active against many respiratory tract pathogens; P*neumococcus, Haemophilus species, Moraxella catarrhalis, and Klebsiella pneumoniae.*

ANTIMYCOBACTERIAL DRUGS

Mycobacterial infections are the most difficult of all bacterial infections to cure. Mycobacteria are slowly growing organisms (can also be dormant) and thus completely resistant to many drugs, or killed only very slowly by the few drugs that are active. The lipid-rich mycobacterial cell wall is impermeable to many agents. A substantial proportion of mycobacterial organisms are intracellular, residing within macrophages, and inaccessible to drugs that penetrate poorly. Finally, mycobacteria are notorious for their ability to develop resistance to any single drug. Combinations of drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy. The response of mycobacterial infections to chemotherapy is slow, and treatment must be administered for months to years depending on which drugs are used. Antimycobacterial drugs can be devided into three groups: drugs used in the treatmen of tuberculosis, drugs used in the treatment of atypical mycobacterial infection, and drugs used in the treatment of leprosy.

Drugs Used In Tuberculosis

First-Line Antimycobacterial Drugs

Members: Isoniazid (INH), rifampin, pyrazinamide, ethambutol, and streptomycin are the five first-line agents for treatment of tuberculosis. INH and rifampin are the two most active drugs.

Isoniazid (INH)

INH is the most active drug for the treatment of tuberculosis caused by susceptible strains. It is structurally similar to pyridoxine. It is bactericidal for actively growing tubercle bacilli. INH is able to penetrate into phagocytic cells and thus is active against both extracellular and intracellular organisms.

INH inhibits synthesis of mycolic acids, which are essential components of mycobacterial cell walls.

INH is readily absorbed from the gastrointestinal tract, and it diffuses readily into all body fluids and tissues. Metabolism of INH, especially acetylation by liver N-acetyltransferase, is genetically determined. INH metabolites and a small amount of unchanged drug are excreted mainly in the urine. The dose need be adjusted in severe hepatic insufficiency.

Clinical Uses: Used in the treatment and prevention of tuberculosis.

Adverse Reactions: The incidence and severity of untoward reactions to INH are related to dosage and duration of administration. INH-induced hepatitis is the most frequent major toxic effect and the risk of hepatitis greater in old age, alcoholics and possibly during pregnancy and the post-partum period.

Peripheral neuropathy is more likely to occur in slow acetylators and patients with predisposing conditions such as malnutrition, alcoholism, diabetes, AIDS, and uremia. Neuropathy is due to a relative pyridoxine deficiency. INH promotes excretion of pyridoxine, and this toxicity is readily reversed or can be prevented by administration of pyridoxine. *CNS system toxicity,* which is less common, includes memory loss, psychosis, and seizures, and may also respond to pyridoxine.

Rifampin

Rifampin is administered together with INH, ethambutol, or another antituberculous drug in order to prevent emergence of drug resistant mycobacteria. Rifampin is an alternative to INH for prophylaxis in patients who are unable to take INH or who have had close contact with a case of active tuberculosis caused by an INH-resistant, rifampin-susceptible strain.

Ethambutol

Ethambutol inhibits synthesis of mycobacterial cell wall. Ethambutol is well absorbed from the gut. It accumulates in renal failure. Ethambutol crosses the blood-brain barrier only if the meninges are inflamed.

Ethambutol hydrochloride given as a single daily dose in combination with INH or rifampin for the treatment of tuberculosis. The higher dose is recommended for treatment of tuberculous meningitis.

The most common serious adverse event is retrobulbar neuritis causing loss of visual acuity and red-green color blindness is a dose-related side effect. Ethambutol is relatively contraindicated in children too young to permit assessment of visual acuity and red-green color discrimination.

Pyrazinamide

Pyrazinamide (PZA) is a relative of nicotinamide, stable, slightly soluble in water. Drug is taken up by macrophages and kills bacilli residing within this acidic environment. PZA is well absorbed from the gastrointestinal tract and widely distributed in body tissues, including inflamed meninges. Tubercle bacilli develop resistance to pyrazinamide fairly readily. Major

adverse effects of pyrazinamide include hepatotoxicity, nausea, vomiting, drug fever, and hyperuricemia. Hyperuricemia may provoke acute gouty arthritis.

Streptomycin

Most tubercle bacilli are inhibited by streptomycin. Streptomycin penetrates into cells poorly, and thus it is active mainly against extracellular tubercle bacilli. Streptomycin crosses the blood-brain barrier and achieves therapeutic concentrations with inflamed meninges. It is employed principally in individuals with severe, possibly life-threatening forms of tuberculosis (meningitis and disseminated disease), and in treatment of infections resistant to other drugs.

Combination Chemotherapy of Tuberculosis

The duration of therapy for a patient with tuberculosis depends upon the severity of the disease, the organ affected and the combination of agents. There are two phases in the treatment of tuberculosis; the intensive phase, which lasts 8 weeks, makes the patients noninfectious. The continuation phase, which lasts 6 months or more and at least two drugs should be taken. Four types of drug regimen are currently employed in Ethiopia; Directly Observed Treatment Short Course (DOTS), Re- treatment Regimen, and Short course Chemotherapy and long course chemotherapy (LCC)

Drug Regimens and Treatment Categories

1. Directly Observed Treatment Short Course (DOTS)

Used in new Pulmonary TB smear positive patients; new Pulmonary TB smear negative and Extrapulmonary TB patients who are seriously ill; TB in children < 6 years. It consists of 8 weeks of treatment with Streptomycin, Rifampicin, Isoniazid and Pyrazinamide during the intensive phase followed by 6 monthes of Ethambutol and Isoniazid or 4 months of rifampin and isoniazid (RH). (2S (RHZ)/6(EH). Children <6 years receive 4 monthes of Rifampicin and INH (RH) in the continuation phase. Drugs have to be collected daily during the intensive phase of DOTS and taken under direct observation by the health worker. During the continuation phase drugs have to be collected every month and self-administered by the patient.

2. Re- treatment Regimen

Used for patients previously treated for more than one month with short course chemotherapy (SCC) and Long course chemotherapy (LCC) and are still smear positive. These patients are: - Relapses; Treatment failures; Returns after default who are pulmonary tuberculosis positive. It consists of 2 months of treatment using Streptomycin, INH, Ethambutol, Rifampicin and

Pyrazinamide then 1month of INH, Ethambutol, Rifampicin and Pyrazinamide in the intensive phase, Followed by 5 months of ethambutol, Rifampicin and INH. [2SE (RH) Z/1E (RH) Z/$5E_3$ $(RH)_3$]. (Streptomycin should not be included in the retreatment regimen for pregnant women). The drugs should be taken under direct observation of the health worker throughout the duration of Retreatment including the continuation phase.

3. Short course Chemotherapy

Is recommended for new patients with smear negative pulmonary TB, new patients with extra pulmonary tuberculosis and TB in children of 6 years and older. It consists of 8 weeks of treatment with Rifampicin, Isoniazid and Pyrazinamide during the intensive phase followed by 6 months of Ethambutol and Isoniazid. [2(RHZ)/6(EH)].

4. Long course chemotherapy (LCC)

Is to be prescribed in all cases of TB in regions/Zones where the DOTS program is not yet started. 2 months of Streptomycin, Ethambutol and INH in the intensive phase followed by 10 months of Ethambutol and INH.

Second-line antitubercular drugs include ethionamide, para-aminosalicylic acid, capreomycin, cycloserine, amikacin, ciprofloxacin, etc. These agents are considered during failure of clinical response to first-line drugs under supervision of their adverse effects.

Drugs Active against Atypical Mycobacteria

Disease caused by "atypical" mycobacteria is often less severe than tuberculosis and not communicable from person to person. M avium complex is an important and common cause of disseminated disease in late stages of AIDS.

Azithromycin or clarithromycin, plus ethambutol are effective and well-tolerated regimen for treatment of disseminated disease. Some authorities recommend use of a third agent, ciprofloxacin or rifabutin. Rifabutin in a single daily dose of 300 mg has been shown to reduce the incidence of M avium complex bacteremia in AIDS. Clarithromycin also effectively prevents MAC bacteremia in AIDS patients.

Drugs used in Leprosy

Leprosy is caused by mycobacterium leprae. I t can be treated dapsone, rifampin, clofazimine, ethionamide, etc.

Because of increasing reports of dapsone resistance, treatment of leprosy with combinations of the drugs is recommended.

Dapsone

Dapsone (diaminodiphenylsulfone) is the most widely used drugs in the treatment of leprosy and it inhibits folate synthesis. Resistance can emerge in large populations of M leprae. Therefore, the combination of dapsone, rifampin, and clofazimine is recommended for initial therapy. Sulfones are well absorbed from the gut and widely distributed throughout body fluids and tissues. Excretion into urine is variable, and most excreted drug is acetylated.

Dapsone is usually well tolerated. Gastrointestinal intolerance, fever, pruritus, and rashes occur. Erythema nodosum often develops during dapsone therapy in lepromatous leprosy. Erythema nodosum leprosum may be suppressed by corticosteroids. Hemolysis and methemoglobinemia can occur.

Rifampin

This drug is effective in lepromatous leprosy. Because of the probable risk of emergence of rifampin-resistant M leprae, the drug is given in combination with dapsone or another antileprosy drug.

Clofazimine

The absorption of clofazimine from the gut is variable, and a major portion of the drug is excreted in feces. Clofazimine is stored widely in reticuloendothelial tissues and skin. Clofazimine is given for sulfone-resistant leprosy or when patients are intolerant to sulfone. A common dosage is 100 mg/d orally. The most prominent untoward effect is skin discoloration ranging from red-brown to nearly black.

ANTIFUNGAL AGENTS

Fungal infections have increased in incidence and severity in recent years, due to increased in the use of broad-spectrum antimicrobials and the HIV epidemic. The antifungal drugs fall into two groups: antifungal antibiotics and synthetic antifungals.

Antifungal antibiotics

Amphotericin B

Amphotericin B is poorly absorbed from the gastrointestinal tract. Oral amphotericin B is thus effective only on fungi within the lumen of the tract. The drug is widely distributed in tissues, but only 2-3% of the blood level is reached in CSF, thus occasionally necessitating intrathecal therapy for certain types of fungal meningitis.

Mechanism of Action: Amphotericin B binds to ergosterol (a cell membrane sterol) and alters the permeability of the cell by forming amphotericin B-associated pores in the cell membrane. The pore allows the leakage of intracellular ions and macromolecules, eventually leading to cell death.

Adverse Effects: The toxicity of amphotericin B which may occur immediately or delayed include fever, chills, muscle spasms, vomiting, headache, hypotension (related to infusion), renal damage associated with decreased renal perfusion (a reversible) and renal tubular injury (irreversible). Anaphylaxis, liver damage, anemia occurs infrequently.

Antifungal Activity: Amphotericin B is a broad-spectrum antifungal agent. It has activity against yeasts including; Candida albicans and Cryptococcus neoformans; molds, Aspergillus fumigatus.

Clinical Use: Amphotericin B remains the drug of choice for nearly all life-threatening mycotic infections. Used as the initial induction regimen for serious fungal infections (immunosuppressed patients, severe fungal pneumonia, and cryptococcal meningitis with altered mental status).

Nystatin

Nystatin has similar structure with amphotericin B and has the same pore-forming mechanism of action. It is too toxic for systemic use and is only used topically. It is not absorbed from skin, mucous membranes, or the gastrointestinal tract. Nystatin is active against most Candida species and is most commonly used for suppression of local candidal infections. Nystatin is used in the treatment of oropharyngeal thrush, vaginal candidiasis, and intertriginous candidal infections.

Griseofulvin

Griseofulvin is a fungistatic and used is in the treatment of dermatophytosis. Absorption is improved when it is given with fatty foods. Griseofulvin is deposited in newly forming skin where it binds to keratin, protecting the skin from new infection. It must be administered for 2-6 weeks for skin and hair infections to allow the replacement of infected keratin by the resistant structures. Nail infections may require therapy for months to allow regrowth of the new protected nail and is often followed by relapse. Adverse effects include an allergic syndrome much like serum sickness, hepatitis, and drug interactions with warfarin and phenobarbital. Griseofulvin has been largely replaced by newer antifungal medications such as itraconazole and terbinafine.

Synthetic Antifungal Agents

Flucytosine

Flucytosine is related to fluorouracil (5-FU). Its spectrum of action is much narrower than that of amphotericin B. It is well absorbed orally. It is poorly protein-bound and penetrates well into all body fluid compartments including the CSF. It is eliminated by glomerular filtration. Toxicity is more likely to occur in AIDS patients and in the presence of renal insufficiency.

Flucytosine is converted intracellularly first to 5-FU and then to 5-fluorodeoxyuridine monophosphate (F-dUMP) and fluorouridine triphosphate (FUTP), which inhibit DNA and RNA synthesis, respectively.

Clinical Use: Active against Cryptococcus neoformans, some Candida species, and the dematiaceous molds that cause chromoblastomycosis. Clinical use at present is confined to combination therapy, either with amphotericin B for cryptococcal meningitis or with itraconazole for chromoblastomycosis.

Adverse Effects: The adverse effects of flucytosine result from metabolism (intestinal flora) to the toxic antineoplastic compound flucytosine. Bone marrow toxicity with anemia, leukopenia, and thrombocytopenia are the most common adverse effects, with derangement of liver enzymes occurring less frequently.

Azoles

Azoles are synthetic compounds that can be classified as *imidazoles* and *triazoles.* The imidazoles consist of *ketoconazole, miconazole, and clotrimazole*. The triazoles include *itraconazole and fluconazole*.

The antifungal activity of azole drugs results from the reduction of ergosterol synthesis by inhibition of fungal cytochrome P450 enzymes. The specificity of azole drugs results from their greater affinity for fungal than for human cytochrome P450 enzymes. Imidazoles exhibit a lesser degree of specificity than the triazoles, accounting for their higher incidence of drug interactions and side effects.

Azoles are active against many Candida species, Cryptococcus neoformans, the endemic mycoses (blastomycosis, coccidioidomycosis), the dermatophytes, and, Aspergillus infections (itraconazole). Adverse Effects: The azoles are relatively nontoxic. The most common adverse reaction is minor gastrointestinal upset. Most azoles cause abnormalities in liver enzymes and, very rarely, clinical hepatitis.

Imidazoles

Ketoconazole

Ketoconazole is less selective for fungal P450 than are the fluconazole and itraconazole (inhibit mammalian cytochrome P450 enzymes).

Clinical use: it has limited use because of the drug interactions, endocrine side effects, and of its narrow therapeutic range. Oral formulation that is best absorbed at a low gastric pH. Ketoconazole is used in treatment of mucocutaneous candidiasis and nonmeningeal coccidioidomycosis. It is also used in the treatment of seborrheic dermatitis and pityriasis versicolor (Topical/ shampoo).

Adverse effects: First, ketoconazole inhibition of human cytochrome P450 enzymes interferes with biosynthesis of adrenal and gonadal steroid hormones, producing significant endocrine effects such as gynecomastia, infertility, and menstrual irregularities. Second, the interaction with P450 enzymes can alter the metabolism of other drugs, leading to enhance toxicity of those agents (eg. increased levels and enhanced arrhythmogenic effects of the nonsedating antihistamines, and terfenadine).

Clotrimazole and miconazole

Clotrimazole and miconazole are available over-the-counter and are often used for vulvovaginal candidiasis. Oral clotrimazole troches are available for treatment of oral thrush and are a pleasant-tasting alternative to nystatin. In cream form, both agents are useful for dermatophytic infections, including tinea corporis, tinea pedis, and tinea cruris. Absorption is negligible, and adverse effects are rare.

Triazoles

Itraconazole

Itraconazole is available in an oral formulation and its absorption is increased by food and by low gastric pH. Undergoes extensive hepatic metabolism. Itraconazole is the azole of choice in the treatment of dermatophytoses and onychomycosis and is the only agent with significant activity against Aspergillus species.

Fluconazole

Fluconazole has good cerebrospinal fluid penetration. Can be given by the intravenous or the oral route. Fluconazole has the least effect on hepatic microsomal enzymes. Thus, has a wide

therapeutic window. Fluconazole is the azole of choice in the treatment and secondary prophylaxis of cryptococcal meningitis. It is also effective for mucocutaneous candidiasis.

ANTIVIRAL AGENTS

Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cell. Viral replication consists of several steps: (1) adsorption to and penetration into susceptible host cells; (2) uncoating of viral nucleic acid; (3) synthesis of early, regulatory proteins, eg, nucleic acid polymerases; (4) synthesis of RNA/ DNA; (5) synthesis of late, structural proteins; (6) assembly (maturation) of viral particles; and (7) release from the cell.

Antiviral agents can potentially target any of these steps. Most of the antiviral agents currently available act on synthesis of purines and pyrimidines (step 4); reverse transcriptase inhibitors block transcription of the HIV RNA genome into DNA, thereby preventing synthesis of viral mRNA and protein. The protease inhibitors act on synthesis of late proteins and packaging (steps 5 and 6). In this section drugs used in the treatment of herps, human immunodeficiency virus and other antiviral agents will be discussed.

Antiherpes Agents

Acyclovir

Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms: competitive inhibition of the viral DNA polymerase and by binding to the DNA template as an irreversible complex..

Acyclovir is available in oral, intravenous, and topical formulations. Acyclovir diffuses into most tissues and body fluids to produce concentrations that are 50-100% of those in serum. Cerebrospinal fluid concentrations are 50% of serum values.

Clinical Uses: Oral acyclovir is effective for treatment of primary infection and recurrences of genital and labial herpes. Intravenous acyclovir is the treatment of choice for herpes simplex encephalitis, neonatal HSV infection and for severe primary, recurrent HSV genital and labial infections and for those who cannot ingest oral pills

Adverse Reactions: Acyclovir is generally well tolerated. Nausea, diarrhea, and headache have occasionally been reported. IV infusion may be associated with renal insufficiency or neurologic toxicity.

Ganciclovir

The activated compound competitively inhibits viral DNA polymerase, causing an unstable complex, but does not result in chain termination. Ganciclovir has activity against CMV, HSV, VZV, and EBV; its activity against CMV is up to 100 times greater than that of acyclovir.

Clinical Uses: Intravenous ganciclovir is indicated for the treatment of CMV retinitis in patients with AIDS. The drug also reduces the incidence of symptomatic CMV disease if administered before organ transplantation. Administration of intravenous ganciclovir to treat CMV pneumonitis in immunocompromised patients is often beneficial, particularly in combination with intravenous cytomegalovirus immunoglobulin. Intravenous ganciclovir has also been used to treat CMV colitis and esophagitis.

Adverse Reactions: The most common side effect of treatment with ganciclovir is myelosuppression, particularly neutropenia. Myelosuppression may be additive in patients receiving both ganciclovir and zidovudine. Central nervous system toxicity (changes in mental status, seizures) has been rarely reported.

Foscarnet

Foscarnet is an inorganic pyrophosphate compound that inhibits viral DNA polymerase, RNA polymerase, or HIV reverse transcriptase directly. It has in vitro activity against HSV, VZV, CMV, EBV, HHV-6, HBV, and HIV.

The drug is available in an intravenous formulation only. Cerebrospinal fluid concentrations are approximately two-thirds of steady state serum concentrations. Clearance of foscarnet is primarily by the kidney. The initial elimination half-life is 4-8 hours, followed by a prolonged terminal elimination half-life of 3-4 days in patients with normal renal function.

Clinical Uses: Foscarnet is used for patients with CMV retinitis and acyclovir-resistant HSV infection Foscarnet has also been used to treat CMV colitis and esophagitis and acyclovir-resistant VZV infection.

Adverse Reactions: The potential adverse effects include renal insufficiency, hypocalcemia or hypercalcemia, and hypo- or hyperphosphatemia. Genital ulcerations associated with foscarnet therapy may be due to high levels of ionized drug in the urine. Central nervous system toxicities include hallucinations, and seizures.

Idoxuridine

Idoxuridine (IDU, IUDR) is a substituted pyrimidine analog that was the first antiviral agent to be approved. It is used topically in the treatment of herpes keratitis (0.1% solution), but because of its lack of selectivity it is too toxic for systemic administration.

Vidarabine

Vidarabine as a 3% ointment is effective treatment for acute keratoconjunctivitis, superficial keratitis, and recurrent epithelial keratitis due to HSV. Intravenous vidarabine (10-15 mg/kg daily) is effective for treatment of HSV encephalitis, neonatal herpes, and VZV infection in immunocompromised patients. The drug is eliminated primarily by renal mechanisms as the hypoxanthine metabolite. Potential toxicities include gastrointestinal intolerance, neurologic manifestations (confusion, myoclonus, seizures), and myelosuppression.

Antiretroviral Agents

Antiretroviral drugs are synthetic agents that have antiviral activity against HIV and are used in the management of HIV infection. There are four different classes of antiretroviral agents commercially available currently: Nucleoside reverse transcriptase inhibitors (NRTI), Protease inhibitors, Nonnucleoside reverse transcriptase inhibitors (NNRTI), and Fusion inhibitors.

Reverse transcriptase inhibitors

Zidovudine

Zidovudine (AZT) is a deoxythymidine analog that requires anabolic phosphorylation for activation to the 5'-triphosphate form. After entering the cell by passive diffusion, zidovudine is phosphorylated via three cellular kinases; the triphosphate is a competitive inhibitor of deoxythymidine triphosphate for the reverse transcriptase. Additionally, it acts as a chain terminator in the synthesis of proviral DNA. Zidovudine has in vitro activity against HIV-1, HIV-2, and the human T cell lymphotropic viruses.

Resistance: Zidovudine resistance is due to mutations in the reverse transcriptase gene and is more frequent in persons with advanced HIV infection. Withdrawal of zidovudine exposure may permit the reversion of HIV-1 isolates to the susceptible (wild-type) phenotype.

Pharmacokinetics: Zidovudine is available in intravenous and oral formulations. It is well absorbed from the gut and distributed to most body tissues and fluids, including the cerebrospinal fluid, where drug levels are approximately 60% of those in serum. Substantial

first-pass metabolism to an inactive glucuronidated metabolite results in a systemic bioavailability of approximately 65%.

Clinical Uses: Zidovudine inhibits replication of HIV-1 in infected individuals and has been shown to decrease the rate of clinical disease progression and prolong survival. Zidovudine has efficacy in the treatment of HIV-associated encephalopathy and thrombocytopenia, and in the prevention of vertical (mother to newborn) transmission of HIV. Clinical efficacy is limited by the relatively rapid development of resistance, particularly when used as monotherapy.

Adverse Reactions: The most common adverse effect is myelosuppression gastrointestinal intolerance, headaches, and insomnia may occur but tend to resolve if ingestion is continued. Less frequent unwanted effects include thrombocytopenia, acute cholestatic hepatitis, and myopathy.

Didanosine

Didanosine (ddI) is a synthetic analog of deoxyadenosine. It is metabolized intracellularly by a series of cellular enzymes; its active moiety, 2,3-dideoxyadenosine-5-triphosphate, inhibits viral replication by competitive inhibition of HIV reverse transcriptase and by chain termination.

Pharmacokinetics: Absorption is decreased by food. Cerebrospinal fluid concentrations of the drug are approximately 20% of serum concentrations. The elimination half-life is 0.6-1.5 hours, but the intracellular half-life of the activated compound is approximately 12 hours. The drug is eliminated by glomerular filtration and tubular secretion.

Clinical Uses: Didanosine is effective in slowing clinical progression of disease in HIV-infected individuals when administered as monotherapy or in combination with zidovudine. The dosage should be reduced for low body weight.

Adverse Reactions: The major clinical toxicity associated with didanosine therapy is dose-dependent pancreatitis. Other reported adverse effects have included peripheral neuropathy, diarrhea, hepatotoxicity, hematocytopenias, and central nervous system toxicity (headache, irritability). A rise in uric acid during therapy with didanosine may precipitate attacks of gout in susceptible individuals.

Lamivudine

Lamivudine (3TC) is a nucleoside analog with in vitro activity against HIV-1, including zidovudine resistant strains, and HBV. Lamivudine inhibits the reverse transcriptase of HIV-1 and is synergistic with zidovudine against HIV-1. As with zidovudine, lamivudine requires

intracellular triphosphorylation for activation. Lamivudine, administered in combination with zidovudine or another nucleoside analog to retard the emergence of resistance, is indicated for treatment of advanced HIV disease. Potential side effects are headache, insomnia, fatigue, and gastrointestinal discomfort, though these are typically mild.

Zalcitabine

Zalcitabine (ddC) is a pyrimidine nucleoside that inhibits the replication of HIV-1. Like zidovudine, intracellular activation by triphosphorylation is catalyzed by cellular enzymes; competitive inhibition of the reverse transcriptase and chain termination result. The drug is effective as treatment for patients with HIV infection. It is available in oral formulation only and is typically prescribed in combination with zidovudine. Zalcitabine therapy is associated with a dose-dependent peripheral neuropathy that appears to occur more frequently in patients with low serum cobalamin levels and in those with a history of excessive ethanol consumption. Other reported toxicities include pancreatitis, esophageal ulceration and stomatitis, and arthralgias. Coadministration of drugs that cause either peripheral neuropathy or pancreatitis may increase the frequency of these adverse effects.

Stavudine

Stavudine (d4T) is a thymidine analog that requires intracellular triphosphorylation for activation, acting as a competitive inhibitor of HIV-1 reverse transcriptase and as a chain terminator. The major dose-limiting toxicity is peripheral sensory neuropathy. Less common adverse effects include pancreatitis, arthralgias, and elevation in serum transaminases.

Protease Inhibitors

Indinavir

Indinavir is a specific inhibitor of the HIV-1 protease, an enzyme essential for the production of mature, infectious virions. It is currently used for the treatment of individuals with HIV-1 infection and is recommended for use in combination with a reverse transcriptase inhibitor to delay emergence of resistance. The drug must be consumed on an empty stomach for maximal absorption. Oral bioavailability is excellent.

Resistance: Resistance to indinavir is mediated by the expression of multiple and variable protease amino acid substitutions. At least two-thirds of indinavir-resistant strains are cross-resistant to saquinavir and ritonavir; however, saquinavir-resistant isolates tend to retain susceptibility to indinavir.

Adverse Effects: The most common adverse effects reported thus far are indirect hyperbilirubinemia and nephrolithiasis. Thrombocytopenia, nausea, diarrhea, and irritability have also been reported in some patients. Indinavir and ritonavir are inhibitors of as well as substrates for cytochrome P450 CPY3A4. Serum levels of indinavir will increase in the presence of antifungal azoles (themselves CYP3A4 inhibitors) and decrease in the presence of rifabutin and rifampin (CYP3A4 inducers). Increased levels of rifabutin (also a CYP3A4 substrate) that result from use of indinavir require a reduction in the rifabutin dosage by 50%. Increased levels of antihistamines, cisapride, and benzodiazepines may also occur with potential toxicity from these drugs. More precise delineation of drug interactions is underway.

Ritonavir

Ritonavir is an inhibitor of HIV-1 protease with a high bioavailability (60-80%). The most common adverse effects of ritonavir are gastrointestinal disturbances, circumoral paresthesia, elevated hepatic aminotransferase levels, altered taste, and hypertriglyceridemia. Caution is advised when administering the drug to persons with impaired hepatic function. This drug should be refrigerated for storage. HIV-1 isolates resistant to ritonavir are cross-resistant to indinavir.

Saquinavir

Saquinavir is a synthetic peptide-like substrate analog that inhibits the activity of HIV-1 protease and prevents the cleavage of viral polyproteins. The in vitro activity of saquinavir against HIV-1 is additive to or synergistic with that of reverse transcriptase inhibitors. As with other agents of this class, it is likely that combination therapy with nucleoside agents will be optimal clinically. To date there is little evidence of cross-resistance between saquinavir and other protease inhibitor compounds or between saquinavir and nucleoside analogs.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)

Nonnucleoside reverse transcriptase inhibitors are a group of structurally diverse antiretroviral agents that have a similar mechanism of action. Nonnucleoside reverse transcriptase inhibitors interfere with the function of reverse transcriptase by binding directly to the enzyme in a noncompetitive fashion. The NNRTIs do not depend on intracellular conversion to an active metabolite.There are 2 nonnucleoside reverse transcriptase inhibitors commercially available

Delavirdine (DLV)

Delavirdine a synthetic antiretroviral agent, is a nonnucleoside reverse transcriptase inhibitor.Delavirdine differs structurally from nevirapine, a dipyridodiazepinone derivative nonnucleoside reverse transcriptase inhibitor. The drug inhibits replication of HIV-1 by interfering with viral RNA- and DNA-directed polymerase activities of reverse transcriptase. The mechanism of action of DLV derivatives appears to be similar to that of other nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine, loviride, efavirenz). All nonnucleoside reverse transcriptase inhibitors appear to bind to a common region of reverse transcriptase and exhibit similar kinetic characteristics in their mode of retroviral inhibition.

Spectrum: Delavirdine is a highly specific antiretroviral agent with a very limited spectrum of activity. The drug has in vitro virustatic activity against HIV-1, but is inactive against HIV-2.

Resistance: Strains of HIV-1 with reduced susceptibility to delavirdine (i.e., 10- to 100-fold decrease in susceptibility from baseline) have been produced in vitro by serial passage of the retrovirus in the presence of increasing concentrations of the drug. The mechanism of resistance or reduced susceptibility to delavirdine has not been fully determined, but mutation of HIV reverse transcriptase appears to be involved.

Clinical Uses: Oral delavirdine is used in combination with other antiretroviral agents for the management of human immunodeficiency virus type 1 (HIV-1) infection in adults.

Adverse reactions: Rash is the major toxicity associated with delavirdine therapy. Severe or life-threatening rash (e.g., erythema multiforme, Stevens-Johnson syndrome) have been reported rarely and resolved after the drug was discontinued. Rash usually is evident within 1-3 weeks (median: 11 days) following initiation of delavirdine therapy and typically is diffuse, maculopapular, erythematous, and often pruritic; rash occurs mainly on the upper body and proximal arms with decreasing intensity of the lesions on the neck and face and progressively less on the rest of the trunk and limbs.

Nevirapine

Nevirapine is a nonnucleoside reverse transcriptase inhibitor. The drug inhibits replication of human immunodeficiency virus type 1 (HIV-1) by interfering with viral RNA- and DNA-directed polymerase activities of reverse transcriptase. Nevirapine binds directly to HIV-1 reverse transcriptase and exerts a virustatic effect by acting as a specific, noncompetitive HIV-1 reverse transcriptase inhibitor. Nevirapine is a highly specific antiretroviral agent with a very limited spectrum of activity.

Pharmacokinetics: Nevirapine is administered orally. The drug may be taken without regard to meals. Systemic availability of nevirapine is not affected by concomitant administration with a substantial meal, an antacid, or with didanosine formulated with an alkaline buffering agent. Because nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidneys, the drug should be used with caution in patients with renal or hepatic dysfunction. The manufacturer states that data currently are insufficient to recommend a nevirapine dosage for patients who have hepatic dysfunction or renal insufficiency or are undergoing hemodialysis.

Oral nevirapine is labeled for use in combination with dideoxynucleoside reverse transcriptase inhibitors for the treatment of HIV-1 infections in adults.

Resistance: Strains of HIV-1 with reduced susceptibility to nevirapine have been produced in vitro. Strains of HIV-1 resistant to nevirapine may be cross-resistant to some other nonnucleoside reverse transcriptase inhibitors.

Adverse effects: The drug appears to be well tolerated when administered in combination with zidovudine (with or without didanosine). The major toxicity associated with nevirapine to date is rash, including severe or life-threatening rash. Manifestations of severe rash or rash associated with constitutional symptoms.

Fusion Inhibitors

Enfuvirtide (T-20): Enfuvirtide is the first approved agent in fusion inhibitors. Can be prescribed in combination with other anteretroviral agents, for experienced HIV patients whose viral load remains detectable despite ongoing therapy. HIV-1 isolates resistant to NRTIs, NNRTIs ans PIs were susepteble to enfuvirtide. Enfuvirtide has a robust safety profile.

Other Antiviral Agents

Amantadine, Rimantadine

Amantadine/ rimantadine inhibit uncoating of the viral RNA of influenza A within infected host cells, thus preventing its replication. Both agents are effective in the prevention of influenza a virus infection in high-risk individuals. Additionally, both drugs can be used in the treatment of influenza A, effectively reducing the duration of symptoms when administered within 48 hours after their onset. The most common side effects are gastrointestinal intolerance and central nervous system effects (eg, nervousness, difficulty in concentrating, lightheadedness).

Antineoplastic agents

Cancer refers to a malignant neoplasm or new growth. Cancer cells manifest uncontrolled *proliferation, loss of function due to loss of capacity to differentiate, invasiveness, and the ability to metastasize.*

Cancer arises as a result of genetic changes in the cell, the main genetic changes being; *inactivation of tumor suppressor genes and activation of oncogenes*.

There are three approaches for the management of cancer:

1. Radiotherapy
2. Surgery
3. Chemotherapy

Most anticancer drugs are antiproliferative, and hence affect rapidly growing dividing normal cells. Anticancer drugs are broadly classified into two: *cytotoxic* drugs and *hormones.*

Cytotoxic drugs are further classified into:

- *Alkylating agents and related compounds* (e.g. cyclophosphamide, lomustine, thiotepa, cisplatin): These groups of drugs act by forming covalent bonds with DNA and thus impending DNA replication.
- *Antimetabolites* (e.g. methotrexate, fluorouracil, mercaptopurine): These drugs blocks or destabilize pathways in DNA synthesis.
- *Cytotoxic antibiotics (e.g.* Doxorubucin, bleomycin, dactinomycin): These drugs inhibit DNA or RNA synthesis or cause fragmentation to DNA chains or interfere with RNA polymerase and thus inhibit transcription.
- *Plant derivatives (e.g.* vincristine): Inhibits mitosis

Hormones and their antagonists are used in hormone sensitive tumors (eg. glucocorticoids for lymphomas, oestrogens for prostatic cancer, tamoxifen for breast tumors).

General toxic effects of anticancer drugs:

- Bone marrow toxicity.
- Impaired wound healing.
- Sterility.
- Loss of hair.
- Damage to gastrointestinal epithelium.

TREATMENT OF PROTOZOAL INFECTIONS

1. Treatment of Malaria

Four species of Plasmodium are responsible for human malaria: P. vivax, P. malariae, P. ovale, and P. falciparum. Although all may cause severe illness, P falciparum causes most of the serious complications and deaths. The effectiveness of antimalarial agents varies between parasite species and between stages in their life cycles.

1.1. Parasite Life Cycle

The mosquito becomes infected by taking human blood that contains parasites in the sexual form. The sporozoites that develop in the mosquito are then inoculated into humans at its next feeding. In the exoerythrocytic stage, the sporozoites multiply in the liver to form tissue schizonts. Then, parasites escape from the liver into the bloodstream as merozoites. The merozoites invade red blood cells, multiply in them to form blood schizonts, and finally rupture the cells, releasing a new crop of merozoites. This cycle may be repeated many times. The gametocytes (the sexual stage) form and are released into the circulation, where they may be taken in by another mosquito. P falciparum and P malariae have only one cycle of liver cell invasion and multiplication, and liver infection ceases spontaneously in less than 4 weeks. Then, multiplication is confined to the red blood cells. So, treatment that eliminates these species from the red blood cells four or more weeks after inoculation of the sporozoites will cure these infections. In P vivax and P ovale infections, sporozoites also induce in hepatic cells the dormant stage (the hypnozoite) that causes subsequent recurrences (relapses) of the infection. Therefore, treatment that eradicates parasites from both the red cells and the liver is required to cure these infections.

1.2. Drug Classification

The antimalarial drugs are classified by their selective actions on the parasite's life cycle.

1) Tissue schizonticides: drugs that eliminate tissue schizonts or hypnozoites in the liver (eg, primaquine).
2) Blood schizonticides: drugs that act on blood schizonts (eg, chloroquine, amodiaquine, proguanil, pyrimethamine, mefloquine, quinine) .
3) Gametocides are drugs that prevent infection in mosquitoes by destroying gametocytes in the blood (eg, primaquine for P falciparum and chloroquine for P vivax, P malariae, and P ovale.).

4) Sporonticidal agents are drugs that render gametocytes noninfective in the mosquito (eg, pyrimethamine, proguanil).

None of these drugs prevent infection except for pyrimethamine and proguanil which prevent maturation of P falciparum hepatic schizonts. Blood schizonticides do destroy circulating plasmodia. Primaquine destroys the persisting liver hypnozoites of P vivax and P ovale.

1.3. Individual antimalarial drugs

1.3.1. Chloroquine

Pharmacokinetics: Chloroquine is a synthetic 4-aminoquinoline. It is rapidly and almost completely absorbed from the gastrointestinal tract, and is rapidly distributed to the tissues. From these sites it is slowly released and metabolized. The drug readily crosses the placenta. Renal excretion is increased by acidification of the urine.

Antimalarial Action: Chloroquine is a highly effective blood schizonticide and is most widely used in chemoprophylaxis and in treatment of attacks of vivax, ovale, malariae, or sensitive falciparum malaria. It is moderately effective against gametocytes of P. vivax, P. ovale, and P. malariae, but not against those of P falciparum. Chloroquine is not active against the preerythrocytic plasmodium and does not effect radical cure.

The exact mechanism of action has not been known. Selective toxicity for malarial parasites depends on a chloroquine-concentrating mechanism in parasitized cells. Chloroquine's concentration in normal erythrocytes is 10-20 times that in plasma; in parasitized erythrocytes, its concentration is about 25 times that in normal erythrocytes.

Clinical uses: Acute Malaria Attacks (it clears the parasitemia of acute attacks of P vivax, P ovale, and P malariae and of malaria due to nonresistant strains of P falciparum), and chemoprophylaxis (It is the preferred drug for prophylaxis against all forms of malaria except in regions where P falciparum is resistant to 4-aminoquinolines).

Adverse Effects: Gastrointestinal symptoms, mild headache, pruritus, anorexia, malaise, blurring of vision, and urticaria are uncommon. A total cumulative dose of 100 g (base) may, contribute to the development of irreversible retinopathy, ototoxicity, and myopathy.

Contraindications: It is contraindicated in patients with a history of liver damage, alcoholism, or neurologic or hematologic disorders, psoriasis or porphyria, in whom it may precipitate acute attacks of these diseases.

1.3.2. Primaquine

Primaquine phosphate is a synthetic 8-aminoquinoline derivative. After oral administration, the drug is usually well absorbed, completely metabolized, and excreted in the urine.

Primaquine is active against the late hepatic stages (hypnozoites and schizonts) of P vivax and P ovale and thus effects radical cure of these infections. Primaquine is also highly active against the primary exoerythrocytic stages of P falciparum. When used in prophylaxis with chloroquine, it protects against P vivax and P ovale. Primaquine is highly gametocidal against the four malaria species.

Clinical Uses

1. Terminal prophylaxis of vivax and ovale malaria.
2. Radical cure of acute vivax and ovale malaria.
3. Gametocidal action.
4. Pneumocystis carinii pneumonia

Adverse Effects: Primaquine is generally well tolerated. It infrequently causes nausea, epigastric pain, abdominal cramps, and headache. Serious adverse effects like leukopenia and agranulocytosis are rare.

1.3.3. Quinine

Quinine is rapidly absorbed, reaches peak plasma levels in 1-3 hours, and is widely distributed in body tissues. The elimination half-life of quinine is 7-12 hours in normal persons but 8-21 hours in malaria-infected persons in proportion to the severity of the disease. Bulk of the drug is metabolized in the liver and excreted for the most part in the urine. Excretion is accelerated in acid urine.

Quinine is a rapidly acting, highly effective blood schizonticide against the four malaria parasites. The drug is gametocidal for P vivax and P ovale but not very effective against P falciparum gametocytes. The drug's molecular mechanism is unclear.

Clinical Uses

1. Parenteral Treatment of Severe Falciparum Malaria
2. Oral Treatment of Falciparum Malaria Resistant to Chloroquine
3. Prophylaxis

4. Other Uses: Quinine sulfate sometimes relieves night time leg cramps.

Adverse Effects: Quinine often causes nausea, vomiting, hypoglycemia. Cinchonism; a less common effect and manifested by headache, nausea, slight visual disturbances, dizziness, and mild tinnitus and may subside as treatment continues. Severe toxicity like fever, skin eruptions, gastrointestinal symptoms, deafness, visual abnormalities, central nervous system effects (syncope, confusion), and quinidine-like effects occurs rarely.

1.3.4. Proguanil and Pyrimethamine

Pyrimethamine and proguanil are dihydrofolate reductase inhibitors. They are slowly but adequately absorbed from the gastrointestinal tract.

Pyrimethamine and proguanil are slow acting blood schizonticides against susceptible strains of all four malarial species. Proguanil (but not pyrimethamine) has a marked effect on the primary tissue stages of susceptible P falciparum and therefore may have causal prophylactic action.

Resistance to pyrimethamine and proguanil is found worldwide for P falciparum and somewhat less ubiquitously for P vivax.

Clinical uses

1. Chemoprophylaxis
2. Treatment of Chloroquine-Resistant Falciparum Malaria
3. Toxoplasmosis treatment

Adverse Effects: In malaria treatment, pyrimethamine and proguanil are well tolerated. In the high doses pyrimethamine causes megaloblastic anemia, agranulocytosis and thrombocytopenia (leucovorin calcium is given concurrently).

1.3.5. Sulfones and Sulfonamides

Sulfonamides and sulfones have blood schizonticidal action against P falciparum by inhibition of dihydrofolic acid synthesis. But, the drugs have weak effects against the blood schizonts of P vivax, and they are not active against the gametocytes or liver stages of P falciparum or P vivax. When a sulfonamide or sulfone is combined with an antifol, synergistic blockade of folic acid synthesis occurs in susceptible plasmodia. Sulfadoxine with pyrimethamine (Fansidar) and dapsone with pyrimethamine (Maloprim) are the most used combination.

1.3.6. Pyrimethamine-Sulfadoxine (Fansidar)

Pyrimethamine-Sulfadoxine (Fansidar) is well absorbed. Its components display peak plasma levels within 2-8 hours and are excreted mainly by the kidneys. Average half-lives are about 170 hours for sulfadoxine and 80-110 hours for pyrimethamine.

Pyrimethamine-Sulfadoxine is effective against certain strains of falciparum malaria. But, quinine must be given concurrently in treatment of seriously ill patients, because fansidar is only slowly active. It is not effective in the treatment of vivax malaria.

Clinical uses

1. Treatment of Chloroquine-Resistant Falciparum
2. Presumptive Treatment of Chloroquine-Resistant Falciparum Malaria

Adverse Effects: Rare adverse effects to single-dose Fansidar are those associated with sulfonamide allergy, including the hematologic, gastrointestinal, central nervous system, dermatologic, and renal systems. Fansidar is no longer used in prophylaxis because of severe reactions. However, in our situation, it used for prevention of malaria in pregnant women after the first trimester.

Contraindications: Fansidar is contraindicated in patients who have had adverse reactions to sulfonamides, in pregnancy at term, in nursing women, or in children less than 2 months of age. Fansidar should be used with caution in those with severe allergic disorders, and bronchial asthma.

1.3.7. Mefloquine

Mefloquine is used in prophylaxis and treatment of chloroquine-resistant and multidrug-resistant falciparum malaria. It is also effective in prophylaxis against P. vivax, P. ovale, P. malariae, and P. falciparum.

Mefloquine hydrochloride is chemically related to quinine. It can only be given orally because intense local irritation occurs with parenteral use. It is well absorbed. The drug is highly bound to plasma proteins, concentrated in red blood cells, and extensively distributed to the tissues, including the central nervous system. Mefloquine is cleared in the liver. Its acid metabolites are slowly excreted, mainly in the feces. Its elimination half-life, which varies from 13 days to 33 days, tends to be shortened in patients with acute malaria.

Mefloquine has blood schizonticidal activity against P falciparum and P vivax. Sporadic and low levels of resistance to mefloquine have been reported from Southeast Asia and Africa. Resistance to the drug can emerge rapidly, and resistant strains have been found in areas where the drug has never been used.

Clinical uses: Prophylaxis of Chloroquine-Resistant Strains of P falciparum and Treatment of Chloroquine-Resistant P falciparum Infection

Adverse Reactions: The frequency and intensity of reactions are dose-related. In rophylactic doses it causes; gastrointestinal disturbances, headache, dizziness, syncope, and extra systoles and transient neuropsychiatric events (convulsions, depression, and psychoses). In treatment doses; the incidence of neuropsychiatric symptoms (dizziness, headache, visual disturbances, tinnitus, insomnia, restlessness, anxiety, depression, confusion, acute psychosis, or seizures) may increase.

Contraindications: A history of epilepsy, psychiatric disorders, arrhythmia, sensitivity to quinine and the first trimester of pregnancy.

1.3.8. Doxycycline

Doxycycline is generally effective against multidrug-resistant P falciparum. The drug is also active against the blood stages of the other Plasmodium species but not against the liver stages. In the treatment of acute malaria, it is used in conjunction with quinine.

1.3.9. Halofantrine

Halofantrine hydrochloride is an oral schizonticide for all four malarial species. A fatty food increases absorption up to six fold. Thus, the drug should not be given from 1 hour before to 3 hours after a meal. Excretion is mainly in the feces.

1.3.10. Qinghaosu (Artemisinin)

These drugs are especially useful in treatment of cerebral falciparum malaria. The drugs produce abdominal pain, diarrhea.

2. Drugs used in amebiasis

Amebiasis is infection by the protozoan parasite Entamoeba histolytica. E histolytica infection may present as a severe intestinal infection (dysentery), a mild to moderate symptomatic intestinal infection, an asymptomatic intestinal infection, ameboma, liver abscess, or other type

of extraintestinal infection. The choice of drug depends on the clinical presentation and on the desired site of drug action, ie, in the intestinal lumen or in the tissues.

All of the antiamebic drugs act against Entamoeba histolytica trophozoites, but most are not effective against the cyst stage. Antiamebic drugs are classified as tissue amebicides and luminal amebicides.

2.1. Tissue amebicides eliminate organisms primarily in the bowel wall, liver, and other extraintestinal tissues and are not effective against organisms in the bowel lumen.

2.1.1. Metronidazole, and tinidazole are highly effective against amebas in the bowel wall and other tissues.

2.1.2. Emetine and dehydroemetine act on organisms in the bowel wall and other tissues but not on amebas in the bowel lumen.

2.1.3. Chloroquine -Active principally against amebas in the liver.

2.2. Luminal Amebicides act primarily in the bowel lumen.

2.2.1. Diloxanide furoate

2.2.2. Iodo-quinol

2.2.3. Tetracyclines, paromomycin and erythromycin

2.3. Treatment of Amebiasis

2.3.1. Asymptomatic Intestinal Infection: The drugs of choice, diloxanide furoate and iodoquinol. Alternatives are metronidazole plus iodoquinol or diloxanide.

2.3.2. Intestinal Infection: The drugs of choice, metronidazole and a luminal amebicide.

2.3.3. Hepatic Abscess: The treatment of choice is metronidazole. Diloxanide furoate or iodoquinol should also be given to eradicate intestinal infection whether or not organisms are found in the stools. An advantage of metronidazole is its effectiveness against anaerobic bacteria, which are a major cause of bacterial liver abscess. Dehydroemetine and emetine are potentially toxic alternative drugs.

2.3.4. Ameboma or Extraintestinal Forms of Amebiasis: Metronidazole is the drug of choice. Dehydroemetine is an alternative drug; chloroquine cannot be used because it does not reach high enough tissue concentrations to be effective (except in the liver). A simultaneous course of a luminal amebicide should also be given.

2.4. Antiamoebic drugs

2.4.1. Metronidazole

Pharmacokinetics : Oral metronidazole is readily absorbed and permeates all tissues including cerebrospinal fluid, breast milk, alveolar bone, liver abscesses, vaginal secretions, and seminal fluid. Intracellular concentrations rapidly approach extracellular levels whether administered orally or intravenously. Protein binding is low. The drug and its metabolites are excreted mainly in the urine.

Mechanism of Action: The nitro group of metronidazole is chemically reduced by ferredoxin within sensitive organisms. The reduction products appear to be responsible for killing the organisms by reacting with various intracellular macromolecules.

Clinical Uses: Metronidazole is active against amebiasis, urogenital trichomoniasis, giardiasis, anaerobic infections, acute ulcerative gingivitis, cancrum Oris, decubitus ulcers, and bacterial vaginitis and Helicobacter pylori infection.

Adverse effects: Nausea, headache, dry mouth, or metallic tastes occur commonly. Rare adverse effects include vomiting, diarrhea, insomnia, weakness, dizziness, stomatitis, rash, urethral burning, vertigo, and paresthesias. It has a disulfiram-like effect.

2.4.2. Other Nitroimidazoles

Other nitroimidazole derivatives include tinidazole, and ornidazole. They have similar adverse effects Because of its short half-life, metronidazole must be administered every 8 hours; the other drugs can be administered at longer intervals. However, with the exception of tinidazole, the other nitroimidazoles have produced poorer results than metronidazole in the treatment of amebiasis.

2.4.3. Chloroquine

Chloroquine reaches high liver concentrations and is highly effective when given with emetine in the treatment and prevention of amebic liver abscess. Chloroquine is not active against luminal organisms.

2.4.4. Dehydroemetine Emetine

Emetine and dehydroemetine are administered parenterally. They are stored primarily in the liver, lungs, spleen, and kidneys. They are eliminated slowly via the kidneys.These drugs act only against trophozoites, which they directly eliminate.

Clinical Uses: Severe Intestinal Disease (Amebic Dysentery): Parenterally administered emetine and dehydroemetine rapidly alleviate severe intestinal symptoms but are rarely curative even if a full course is given.

Adverse Effects: Sterile abscesses, pain, tenderness, and muscle weakness in the area of the injection are frequent. Emetine and dehydroemetine should not be used in patients with cardiac or renal disease, in patients with a history of polyneuritis, or in young children or liver abscess. They should not be used during pregnancy.

2.4.5. Diloxanide Furoate

Diloxanide furoate is directly amebicidal, but its mechanism of action is not known. In the 2gut, diloxanide furoate is split into diloxanide and furoic acid; about 90% of the diloxanide is rapidly absorbed and then conjugated to form the glucuronide, which is rapidly excreted in the urine. The unabsorbed diloxanide is the active antiamebic substance. Diloxanide furoate is the drug of choice for asymptomatic infections. For mild intestinal disease, and other forms of amebiasis it is used with another drug.

2.4.6. Iodoquinol

Iodoquinol is effective against organisms in the bowel lumen but not against trophozoites in the intestinal wall or extraintestinal tissues. The mechanism of action of iodoquinol against trophozoites is unknown. Iodoquinol is an alternative drug for the treatment of asymptomatic or mild to moderate intestinal amebiasis.

Adverse Effects: Reversible severe neurotoxicity (optic atrophy, visual loss, and peripheral neuropathy). Mild and infrequent adverse effects that can occur at the standard dosage include diarrhea, which usually stops after several days, anorexia, nausea and vomiting, gastritis, abdominal discomfort, slight enlargement of the thyroid gland, headache, skin rashes, and perianal itching.

2.4.7. Paromomycin Sulfate

Paromomycin is an alternative drug for the treatment of asymptomatic amebiasis. In mild to moderate intestinal disease, it is an alternative luminal drug used concurrently with metronidazole. Paromomycin is both directly and indirectly amebicidal; the indirect effect is caused by its inhibition of bowel bacteria. It can be used only as a luminal amebicide and has no effect in extraintestinal amebic infections.

2.4.8. Other Antibiotics

The tetracyclines (oxytetracycline) have very weak direct amebicidal action, and useful with a luminal amebicide in the eradication of mild to severe intestinal disease. Erythromycin although less effective can be used in the treatment of luminal amebiasis.

3. Drugs used in Giardiasis and Trichomoniasis

Metronidazole is a drug of choice for gardiasis and trichomoniasis, and the alternate drug is tinidazole.

4. Treatment of Leishmaniasis

Kala-azar, cutaneous, and mucocutaneous leishmaniasis are caused by the genus Leishmania. Treatment of leishmaniasis is difficult because of drug toxicity, the long courses of treatment, treatment failures, and the frequent need for hospitalization. The drug of choice is sodium antimony gluconate (sodium stibogluconate). Alternative drugs are amphotericin B and pentamidine.

4.1. Amphotericin B

Amphotericin B is injected slowly intravenously. Patients must be closely monitored in hospital, because adverse effects may be severe.

5. Treatment of Pneumocystis Carinii Pneumonia, Trypanosomiasis

5.1. Pentamidine

Pentamidine is administered parenterally because it is not well absorbed from the gastrointestinal tract. The drug leaves the circulation rapidly and is bound avidly by the tissues, especially the liver, spleen, and kidneys. The drug is excreted slowly and unchanged in the urine. Pentamidine does not cross the blood-brain barrier.

Antiparasitic Action: The mechanisms of pentamidine's antiparasitic action are not well known. The drug may interfere with the synthesis of DNA, RNA, phospholipids, and proteins.

Clinical Uses

1. Leishmaniasis
2. Trypanosomiasis: In African trypanosomiasis, pentamidine is an alternative in the hemolymphatic stage of the disease to (1) suramin in Trypanosoma brucei gambiense and T b rhodesiense infections or to (2) eflornithine in T b gambiense infection.
3. Pneumocystosis

Adverse Effects: Pain at the injection site is common; infrequently, a sterile abscess develops and ulcerates. Occasional reactions include rash, gastrointestinal symptoms, neutropenia, abnormal liver function tests, serum folate depression, hyperkalemia, and hypocalcemia. Severe hypotension, hypoglycemia, hyperglycemia, hyponatremia, and delayed nephrotoxicity.

TREATMENT OF HELMINTHIC INFECTIONS

Anthelmintic drugs are used to eradicate or reduce the numbers of helminthic parasites in the intestinal tract or tissues of the body. Most anthelmintics are active against specific parasites; thus, parasites must be identified before treatment is started.

Individual Drugs

Albendazole

Albendazole, a broad-spectrum oral anthelmintic, is used for pinworm infection, ascariasis, trichuriasis, strongyloidiasis, and infections with both hookworm species. Albendazole is also the drug of choice in hydatid disease and cysticercosis.

Anthelmintic Actions: Albendazole blocks glucose uptake by larval and adult stages of susceptible parasites, depleting their glycogen stores and decreasing formation of ATP. As a result the parasite is immobilized and dies. The drug has larvicidal effects in necatoriasis and ovicidal effects in ascariasis, ancylostomiasis, and trichuriasis. The drug is teratogenic and embryotoxic in some animal species and contraindicated in the first trimester.

Clinical Uses

1. Ascariasis, Trichuriasis, and Hookworm and Pinworm Infections: For pinworm infections, ancylostomiasis, and light ascariasis, necatoriasis, or trichuriasis, a single dose of 400 mg is given orally for adults and in children over two years of age. In pinworm infection, the dose should be repeated in 2 weeks.
2. Strongyloidiasis: 400 mg twice daily for three days (with meals).
3. Hydatid Disease: 800 mg/kg/d in divided doses for three months
4. Neurocysticercosis: 15 mg/kg /d for 8 days
5. Other Infections: At a dosage of 200-400 mg twice daily, albendazole is the drug of choice in treatment of cutaneous larval migrans (give daily for 3-5 days) and in intestinal capillariasis (10-day course).

Adverse Reactions: Mild and transient epigastric distress, diarrhea, headache, nausea, dizziness. In 3-month treatment courses causes jaundice, nausea, vomiting, abdominal pain, alopecia, rash or pruritus occurs.

Diethylcarbamazine Citrate

Diethylcarbamazine is a drug of choice in the treatment of filariasis, loiasis, and tropical eosinophilia.

Anthelmintic Actions: Diethycarbamazine immobilizes microfilariae and alters their surface structure, making them more susceptible to destruction by host defense mechanisms. The mode of action of diethylcarbamazine against adult worms is unknown.

Clinical Uses:

1. Wuchereria bancrofti, Loa loa: Diethycarbamazine is the drug of choice for treatment of infections with these parasites, given its high order of therapeutic efficacy and lack of serious toxicity. Microfilariae of all species are rapidly killed; adult parasites are killed more slowly, often requiring several courses of treatment.
2. Onchocerca volvulus: Diethylcarbamazine temporarily kills microfilariae but are poorly effective against adult worms. If diethylcarbamazine is used in onchocerciasis treatment, suramin (a toxic drug) must be added to the regimen to kill the adult worms.

Adverse Reactions

Reactions to the drug itself are mild and transient includes: headache, malaise, anorexia, and weakness are frequent. Reactions Induced by dying Parasites: As a result of the release of foreign proteins from dying microfilariae or adult worms in sensitized patients. Reactions in onchocerciasis affect the skin and eyes in most patients. The reactions may be severe, if infection is heavy. Vision can be permanently damaged as a result of dying microfilariae in the optic disks and retina. Reactions in W bancrofti, and L loa infections are usually mild in W bancrofti, and occasionally severe in L loa infections. Reactions include fever, malaise, papular rash, headache, gastrointestinal symptoms, cough, chest pains, and muscle or joint pains.

Ivermectin

Ivermectin is the drug of choice in individual and mass treatment of onchocerciasis and for strongyloidiasis. The drug is rapidly absorbed. The drug has a wide tissue distribution. It apparently enters the eye slowly and to a limited extent. Excretion of the drug and its metabolites is almost exclusively in the feces.

Anthelmintic Actions: Ivermectin paralyze nematodes and arthropods by intensifying GABA-mediated transmission of signals in peripheral nerves. In onchocerciasis, ivermectin is microfilaricidal and affects embryogenesis. The mode of action of ivermectin on microfilariae is uncertain.

Clinical Uses: Onchocerciasis, Bancroftian Filariasis, Strongyloidiasis, scabies and cutaneous larva migrans

Adverse Reactions: The adverse effects of ivermectin are the Mazotti reaction, which starts on the first day after a single oral dose and peaks on the second day. The reaction is due to killing of microfilariae and its intensity correlates with skin microfilaria loads. The Mazotti reaction includes fever, headache, dizziness, somnolence, weakness, rash, increased pruritus, diarrhea, joint and muscle pains, hypotension, tachycardia, lymphadenitis, lymphangitis, and peripheral edema. The Mazotti reaction diminishes with repeated dosing. Steroids may be necessary for several days.

Levamisole

Levamisole hydrochloride is highly effective in eradicating Ascaris and moderately effective against both species of hookworm.

Mebendazole

Mebendazole has a broad spectrum of anthelmintic activity and a low incidence of adverse effects. Poorly absorbed after oral adminstration. It rapidly metabolized and excreted mostly in the urine, either unchanged or as decarboxylated derivatives.

Mebendazole inhibits microtubule synthesis in nematodes, thus irreversibly impairing glucose uptake. As a result, intestinal parasites are immobilized or die slowly.

Clinical Uses: The drug can be taken before or after meals; the tablets should be chewed before swallowing.

1. Pinworm Infection: Give 100 mg once and repeat the dose at 2 and 4 weeks
2. Ascaris lumbricoides, Trichuris trichiura, and Hookworm
3. Hydatid Disease: Mebendazole is the alternative.
4. Taeniasis: In Taenia solium infection, mebendazole has a theoretic advantage over niclosamide in that proglottids are expelled intact.
5. Strongyloidiasis.

Adverse Reactions: Mild nausea, vomiting, diarrhea, and abdominal pain have been reported infrequently, more often in children heavily parasitized by Ascaris.

Metrifonate

Metrifonate is a safe, alternative drug for the treatment of Schistosoma haematobium infections. Metrifonate, an organophosphate compound, is rapidly absorbed after oral administration. Clearance appears to be through nonenzymatic transformation to its active metabolite (dichlorvos). Metrifonate and the active metabolite are well distributed to the tissues and are completely eliminated in 24-48 hours.

Adverse Reactions: mild and transient cholinergic symptoms, including nausea and vomiting, diarrhea, abdominal pain, bronchospasm, headache, sweating, fatigue, weakness, dizziness, and vertigo.

Niclosamide

Niclosamide is a drug of choice for the treatment of most tapeworm infections. It appears to be minimally absorbed from the gastrointestinal tract: neither the drug nor its metabolites have been recovered from the blood or urine.

Clinical Uses: Niclosamide should be given in the morning on an empty stomach. The tablets must be chewed thoroughly and are then swallowed with water.

1. T saginata, T solium, and Diphyllobothrium latum: A single 2 g dose of niclosamide results in cure rates of over 85% for D latum and about 95% for T saginata.
2. Hymenolepis nana and H: Niclosamide is effective against the adult parasites in the lumen of the intestine. The minimum course of treatment must be 7 days
3. Intestinal Fluke Infections: Niclosamide can be used as an alternative drug for the treatment of intestinal flukes.

Adverse Reactions: Adverse effects, mild, and transitory. It causes nausea, vomiting, diarrhea, and abdominal discomfort.

Oxamniquine

Oxamniquine is used for the treatment of S mansoni infections. It is active against both mature and immature stages of S mansoni. It has also been used extensively for mass treatment. Oxamniquine is readily absorbed orally.

Clinical Uses: Oxamniquine is safe and effective in all stages of S mansoni disease, including advanced hepatosplenomegaly. It is better tolerated if given with food, although food delays absorption. In mixed infections with S mansoni and S haematobium, oxamniquine has been successfully used in combination with metrifonate.

Adverse Reactions: Central nervous system symptoms are most common; nausea and vomiting, diarrhea, colic, pruritus, and urticaria also occur.

Piperazine

The piperazine salts are alternative drugs in the treatment of ascariasis. Piperazine is readily absorbed from the gastrointestinal tract, and maximum plasma levels are reached in 2-4 hours. Most of the drug is excreted unchanged in the urine in 2-6 hours.

Anthelmintic Actions: Piperazine causes paralysis of Ascaris by blocking acetylcholine at the myoneural junction. The paralyzed roundworms are unable to maintain their position in the host and are expelled live by normal peristalsis.

Clinical Uses: Ascariasis

Adverse Reactions: Piperazine cause nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache.

Praziquantel

Praziquantel is effective in the treatment of schistosome infections of all species and most other trematode and cestode infections, including cysticercosis. The drug's safety and effectiveness as a single oral dose have also made it useful in mass treatment of several of the infections. It is rapidly absorbed after oral administration. Most of the drug is rapidly metabolized to inactive products after a first pass in the liver. Excretion is mainly via the kidneys and bile.

Anthelmintic Actions: Praziquantel drug increases cell membrane permeability to calcium, resulting in marked contraction, followed by paralysis of worm musculature. Vacuolization and disintegration of the tegumen occur, and parasite death follows.

Clinical Uses:

1. Schistosomiasis: Praziquantel is the drug of choice for all forms of schistosomiasis.
2. Taeniasis and Diphyllobothriasis: A single dose of praziquantel, 10 mg/kg.
3. Neurocysticercosis: The praziquantel dosage is 50 mg/kg/d in three divided doses for 14 days.

4. H nana: Praziquantel is the drug of choice for H nana infections and the first drug to be highly effective. A single dose of 25 mg/kg is used.

Adverse Reactions: Most frequent are headache, dizziness, drowsiness, and lassitude; others include nausea, vomiting, abdominal pain, loose stools, pruritus, urticaria, arthralgia, myalgia, and low-grade fever. Praziquantel appears to be better tolerated in children than in adults. Adverse effects may be more frequent in heavily infected patients, especially in S mansoni infections.

Pyrantel Pamoate

Pyrantel pamoate is a broad-spectrum anthelmintic highly effective for the treatment of pinworm and Ascaris. Pyrantel pamoate because it is poorly absorbed from the gastrointestinal tract, it is active mainly against luminal organisms.

Anthelmintic Actions: Pyrantel is effective against mature and immature forms of susceptible helminths within the intestinal tract but not against migratory stages in the tissues or against ova. The drug is a depolarizing neuromuscular blocking agent that causes release of acetylcholine and inhibition of cholinesterase; this results in stimulation of ganglionic receptors and worm paralysis, which is followed by expulsion from the host's intestinal tract.

Clinical Uses: The standard dose is 11 mg (base)/kg (maximum, 1 g), given with or without food. Pyrantel is given as a single dose and repeated in 2 and 4 weeks is effective in Enterobius vermicularis, A lumbricoides, and hookworm infections.

Suramin

Suramin is an alternative drug for the eradication of adult parasites of Onchocerca volvulus and a drug of choice in the treatment of the hemolymphatic stage of African trypanosomiasis due to Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense. Suramin is a nonspecific inhibitor of many enzymes. Toxic reactions are frequent and sometimes severe, including nausea, vomiting, urticaria, fever, nephrotoxicity, peripheral neuritis, anemia, jaundice, and exfoliative dermatitis. The drug should be given only under expert guidance.

Thiabendazole

Thiabendazole is the drug of choice for the treatment of strongyloidiasis and an alternative drug for cutaneous larva migrans. It may also be tried in trichinosis and visceral larva migrans, given in the absence of other effective drugs. It is no longer recommended for the treatment of pinworm, ascarid, trichurid, or hookworm infection unless the safer drugs of choice are not

available. Thiabendazole is rapidly absorbed after ingestion. The drug is almost completely metabolized in the liver. Ninety percent of the drug is excreted in the urine.

Anthelmintic Actions: Thiabendazole has anti-inflammatory properties, which may be an important factor in its ability to relieve symptoms in some parasitic diseases. It also has immunomodulating effects on T cell function appears to be an immunorestorative agent. Thiabendazole also has antipyretic and mild antifungal and scabicidal actions. Thiabendazole's vermicidal action may be a result of interference with microtubule aggregation acting through inhibition of the enzyme fumarate reductase. The drug has ovicidal effects for some parasites.

Clinical Uses: The standard dose is 25 mg/kg (maximum, 1.5 g). The drug should be given after meals. Effective in Strongyloides stercoralis (The standard dose is given twice daily for 2 days). In patients with hyperinfection syndrome, the standard dose is continued twice daily for 5-7 days. Thiabendazole is highly effective in the treatment of cutaneous larva migrans. Cutaneous Larva Migrans (Creeping Eruption) The standard dose is given twice daily for 2 days.

Adverse Reactions: Adverse effects are generally mild and transient but can be severe; the most common are dizziness, anorexia, nausea, and vomiting.

Exercise

1. Describe the mechanisms of action of antimicrobials
2. What is the difference between bacteriostatic and bactericidal drug action?
3. What are the potential adverse effects of aminoglycosides?
4. How can chloroquine - resistant Falciparum malaria be treated?
5. Discuss the antiretroviral drugs with regard to their efficacy and safety.

CHAPTER ELEVEN

TOXICOLOGY

Learning objectives:

After completing this chapter the student will be able to:

1. describe commonly encountered poisons
2. understand the measures employed for the management of poisoning

INTRODUCTION

Toxicology is concerned with the deleterious effects of chemical and physical agents on all living systems. The terms poison, toxic substance and toxicant are synonymous. The most important axiom of toxicology is that “the dose makes the poison”, indicating that any chemical or drug can be toxic if the dose or exposure becomes high enough. Poisoning occurs by non-therapeutic substances such as household and environmental agens, and due to over-dosage of therapeutic substances. Poison may be ingested accidentally or deliberately. A difficult challenge to the health care provider is the identification of the toxicant and limited availability of antidotes. Thus, the health care provider in most cases, may be limited with symptomatic therapy.

“Treat the patient, not the poison” remains the most basic and important principle of clinical toxicology.

A toxic response can occur with in minutes or after a delay of hours, days, months or years. Acute toxicities are of particular interest for practicing health care provider.

General measures in poisoning

The treatment of a poisoned patient requires a rapid and genuine approach.

There are three principles underlying the management of poisoning:

- Life support
- Drug identification
- Drug detoxification

Drug overdose or poisoning by other chemicals can often manifest itself as an acute clinical emergency. The kinds of life-threatening emergencies include seizures, cardiac arrhythmias, circulatory shock and coma. Massive damage to liver, lungs or kidneys can also lead to death with in a relatively short period of time. Immediate supportive measures may take precedence over identification and detoxification of the offending agent. Therefore, maintenance of vital functions such as respiration, circulation, suppression of seizures, etc. is given priority.

Drug identification and the amount taken may have to be deduced frrm a combination of client history, clinical manifestations and laboratory findings.

The first action for drug detoxification is to cease the administration of the offending agent until the crisis is under control. The effectiveness of the approaches employed for detoxification may depend on the route of administration of the poison.

The general approaches employed to reduce systemic absorption of an ingested poison where the client still has an intact gag reflex is to administer an emetic (eg. Syrup of epecac), a cathartic (eg. Magnesium sulphate), an adsorbent (eg. Activated charcoal) or a combination of these. Emesis is contraindicated after ingestion of corrosive chemicals.

Within clinical environment, more invasive procedures such as gastric lavage and haemodialysis can be performed.

Specific antidotes can also be used as detoxifying agents. Antidotes are available against poisoning with the following substances and are able to reverse the toxic manifestations (see table 11.1).

Table 11.1 : Specific antidotes for poisoning with substances.

Substance	**Specific antidote**
Paracetamol	Acetylcysteine, methionine
Anticholinesterases	Atropine, pralidoxime
Antimuscarinics	Physostigmine
Iron	Desferrioxamine
Opioid drugs	Naloxone, naltrexone
Benzodiazepines	Flumazenil
Heparin	Protamine sulfate
Warfarin	Vitamin K_1
Digoxin	Digoxin-specific antibodies
Methoanol	Ethanol
CO	O_2
Lead	Calicum disodium edetate
Arsenic, gold, mercury, bismuth, antimony	Dimercaprol
Copper, Zinc, gold	D-penicillamine

Exercises

1. Describe poisoning management measures that hinder the absorption of the poison from the gut.
2. List down heavy metal chelators

CHAPTER TWELVE

PRESCRIPTION WRITING AND RATIONAL USE OF DRUGS

Learning objectives:

At the end of this chapter the student will be able to understand:

1. Construction of prescription
2. Prescription incompatibility
3. Patients compliance
4. Objectives and criteria for rational prescription
5. Prevention of irrational prescription.

1. **What is a prescription?** A prescription is a written order by a registered physician, dentist or veterinarian to prepare and/or dispense pharmacological agents for patient.It is a legal document for both the prescriber and the pharmacist. A number of drugs thart can be purchased without a prescription are termed as *over the counter* (OTC) drugs.These drugs are safer and can be self medicated. It includes antacids, antidiarrheals, antipyretics and antiseptics. A drug that requires a prescription from a licenced prescriber to be dispended by a pharmacist is termed *legend drug*.

2. **Types of prescription:** Prescriptions are of two types. Precompounding and extemporaneous. In precompounded prescription, drugs prescribed are supplied by the pharmaceutical companies in ready prepared form by its nonproprietary or trade name.

   e.g: Cap Rifampicin 150 mg (nonproprietary name)

   or

   Cap Firifam 150 mg (a trade name)

In extemporaneous prescription, the pharmacist prepares the medication according to the drugs, doses and dosage form designed by the physician. Now a days we are not using this method.

3. **Constructin of a prescription:** A ideal prescription should contain a) the name, qualification, registration number, full address, telephone number and working hours of the physician; b) the full name, sex, age and address of the patient; c) the diagnosis, the drug preparation, total amount, frequency of administration advises and signature of the prescriber.

The name of the drug preparation begins with the symbol Rx means *take thou* derived from a Roman symbol for Jupiter.

4. **Prescription incompatibility:** In competency or careless of the prescriber results incompatable prescription.It may lead to failure of desired therapeutic goal, may prove harmful or even death to the patient. Incompatibility may be pharmaceutical, chemical or therapeutic.

5. **Patient's compliance:** A matter of concern for prescriber with regard to prescription is patient's noncompliance i.e patient's failure to take medication as intended by their physicians. Noncompliance includes taking of inadequate doses, improper timing, preterm discontinuation of drug.

6. **Rational use of drugs:** According WHO rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own requirements for an adequate period of time, and lowest cost to them and their community.

Criteria for rational prescribing: Rationa prescribing should meet the certain criteria such as appropriate diagnosis, indication, drug, patient, dosage, duration, route of administration, information and monitoring.

7. **Irrational prescription**: Over use of antibiotics, indiscriminate use of injections, excessive use of drugs, use of anabolic steroids for growth and use of tonics and multivitamins for malnutrition are some of irrational practices.

Prevention of irrational prescribing: To prevent irrational prescription the following measures should be taken-a) making correct diagnosis b) limiting the number of the drugs c) encouraging the availability of essential drugs d)providing adequate training,drug information and standard treatment guidelines(STG) to the prescribers incorporating the concept of essential drugs e) teaching of rational prescribing into the curricula of medicine,pharmacy,dentistry and nursing and f) finally providind effective public education to the consumers.

Exercise

1. What is meant by compliance?

2. What do you understand by irrational prescribing, dispensing and use of drugs?

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