SECTION I

GENERAL PHARMACOLOGY

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General considerations

Learning objectives

- Able to remember all the terms used in pharmacology
- To be aware of sources of drugs
- To enumerate various routes of administration of drugs and their advantages and disadvantages
- To describe the processes by which the drugs cross the biological membrane
- To know about pharmacokinetics
- To explain the absorption and bioavailability and factors influencing them
- To explain the enzyme induction and enzyme inhibition and their clinical significances
- To know about first pass metabolism, protein binding of drugs and their clinical significances
- To know about kinetics of elimination, elimination of drugs and their clinical significances
- To be aware of plasma half-life, therapeutic drug monitoring and their clinical significances
- To know about the steps involved in the development of new drug
- To explain how the drugs act and factors modify the effects of drugs
- To be aware of various adverse effects of drugs

Key terms

- ✓ Pharmacokinetic
- ✓ Pharmacodynamic
- ✓ Plasma half-life

CHAPTER 1 Introduction

It is better to know some terms commonly used in pharmacology before going to general pharmacology.

PHARMACOLOGY is derived from Greek word, ‘Pharmakon’=drug and ‘logos’=‘science’ or ‘study’. In short, Pharmacology means, ‘study of drugs’ (i.e., everything about the drugs).

The term DRUG is derived from French word ‘Drough’ means, ‘herb’. Since in the earlier days, most of the agents used in the treatment of diseases are derived from ‘herbs’.

Earlier the term Drug is defined as a chemical agent that is used to prevent, diagnose and cure or treat the diseases. But the oral contraceptive is used to prevent pregnancy, which is not a disease. It is physiological process and also general anaesthetic does not fit in the above definition. The general anaesthetic does not cure / prevent disease.

As per WHO, the definition of a drug is “any chemical agent used either to modify or explore pathological states or physiological system to the benefit of the recipients”.

PHARMACOKINETIC: (Fig.1) Kinetic means, movement. It deals with the study of the movement of drug in and out of the body. That is to study what happens to the drug from the entry till it comes out of the body.

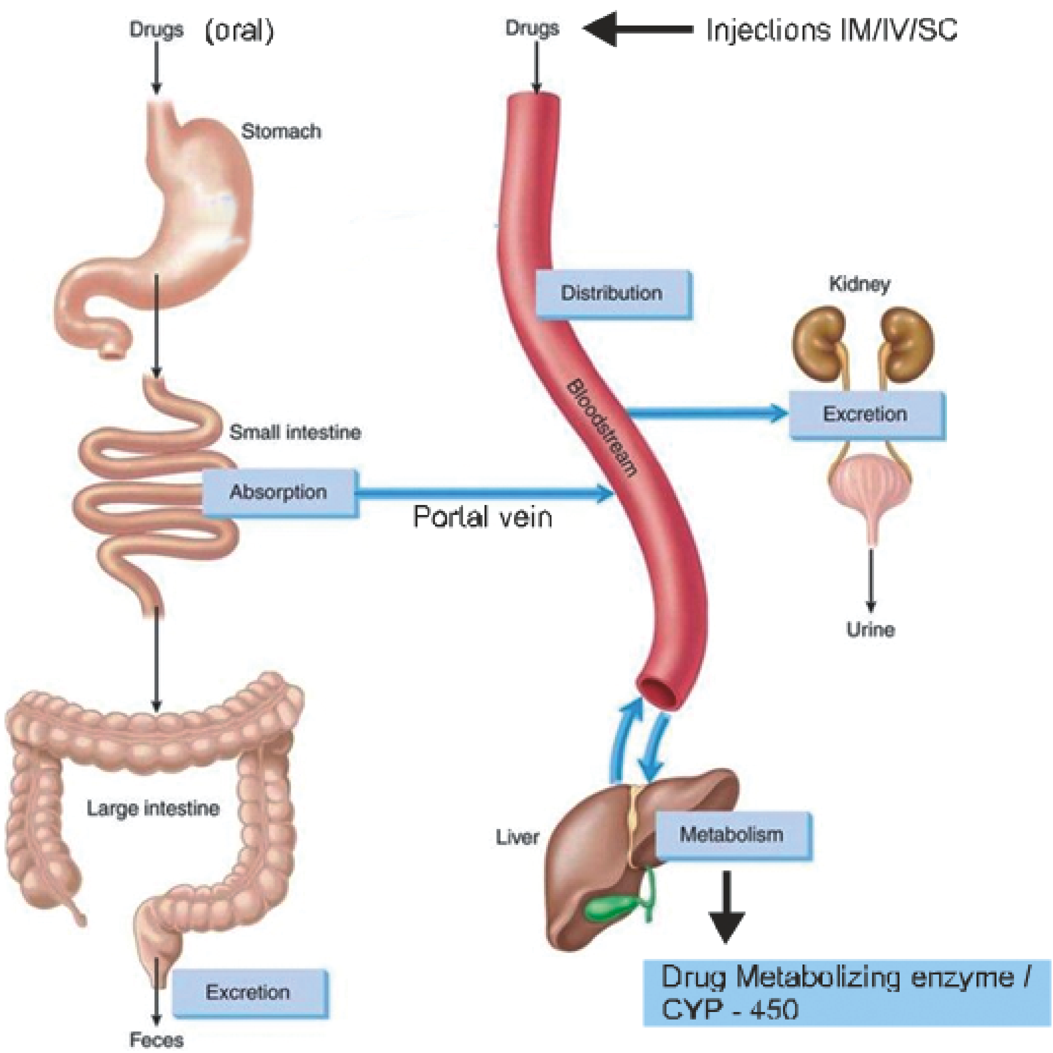


Fig. 01 : Pharmacokinetic

This includes absorption, metabolism, distribution and excretion of drugs and their CLINICAL SIGNIFICANCES. In short we can also refer this process as “what body does to the drug”.

PHARMACODYNAMIC: (Fig. 02) Dynamic means, power. It deals with the power of the drug i.e., to produce pharmacological actions and how it produces that actions? (Mechanism of action of drugs). In short it deals with the study of the pharmacological actions and mechanism of actions of drugs.

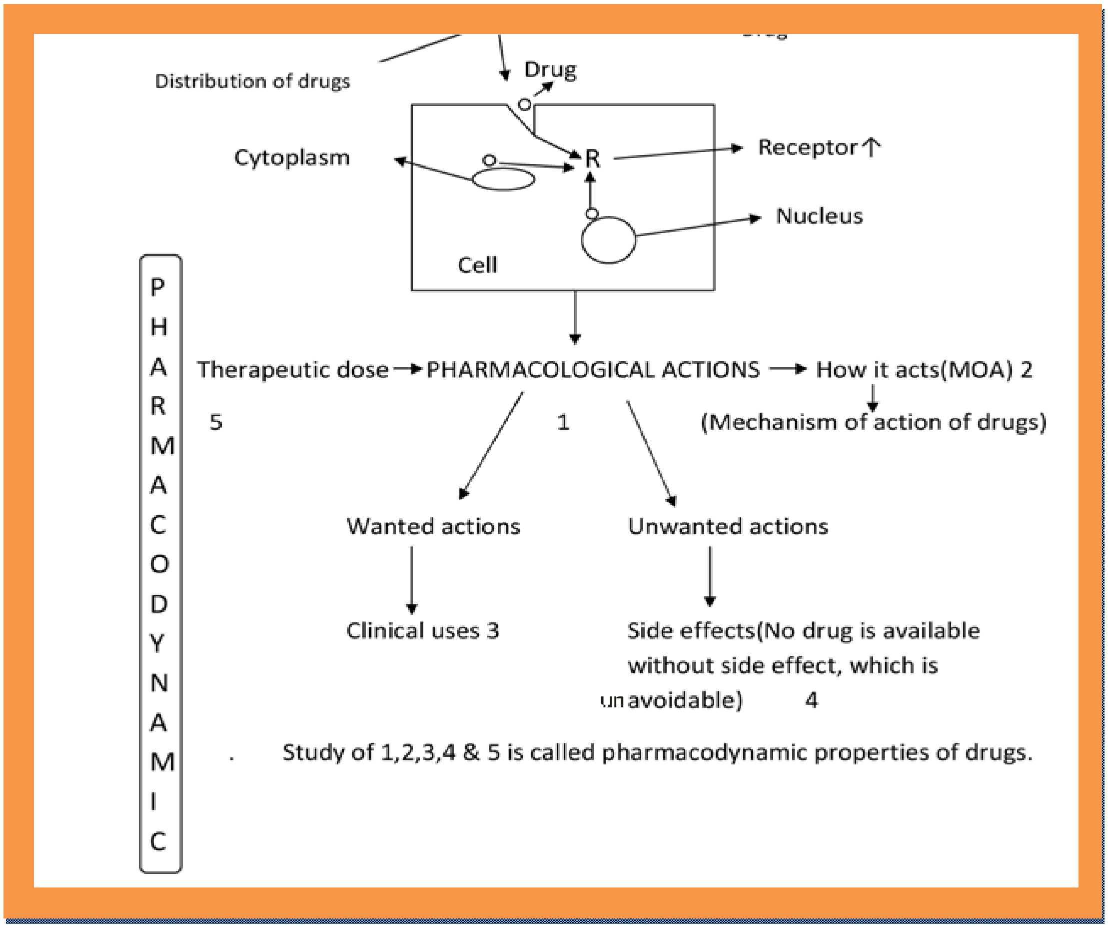


Fig. 02 : Pharmacodynamic

PHARMACOTHERAPHY: is the application of pharmacological actions in therapy (treatment).

PHARMACOVIGILANCE: Many rare adverse effects have been found out during the post marketing surveillance of the drugs. So, pharmacovigilance means continuous monitoring for unwanted effects of marketed drugs. It is the science related to the Detection, Assessment, Understanding and Prevention (DAUP) of adverse effects or any other drug related problems.

PHARMACOGENETIC: To study the genetic variation in drug metabolism or drug response (example: Haemolysis is common in the individual who is showing deficiency of Glucose 6 Phosphate Dehydrogenase (G6PDH). Example : Primaquine inhibit the enzyme G6PDH and cause haemolysis in the above said individual.

PHARMACOGENOMIC: Treatment of diseases by genetic material according to the gene mapping of the individual.

PHARMACOEPIDEMIOLOGY: It is the study of the use and effects of a drug in large population after its approval for clinical use. It is now well established. That the risk: benefit ratio of the drug can be ascertained only after the drug is used widely in the general population.

EXPERIMENTAL PHARMACOLOGY: It is the study of effects of drugs on intact animals or isolated tissues. It is also considered as 'preclinical study' (before conducting clinical study on human) of the drug.

CLINICAL PHARMACOLOGY: It deals with the protocols of clinical evaluation of new drug on healthy volunteers and patients. It also includes clinical trials of drugs (PHASE I, PHASE II, PHASE III and PHASE IV or post marketing surveillance).

CHEMOTHERAPHY: deals with the study of drugs in the treatment of infectious diseases (diseases caused by microorganisms like bacteria, fungi, virus, protozoa and helminths). Cancer treatment is also included in chemotherapy because the fast dividing cancer cells resemble microorganisms.

CHEMOTHERAPEUTIC AGENTS: Those drugs used either to kill or prevent the growth of microorganisms with minimum or no lethal effect to the human cells. This is called as 'magic bullet'. Paul Ehrlich, the Father of Chemotherapy has coined the term 'CHEMOTHERAPY'.

NOMENCLATURE:

A drug may be prescribed either by its GENERIC NAME / OFFICIAL NAME OR BY ITS BRAND NAME (PROPRIETARY NAME). But in Pharmacology, only the generic/ official name should be used, not the brand names (given different names by different manufacturers).

Official name / Generic name	Proprietary name / Trade name
(1) Paracetamol	Crocin, dolo-650
(2) Diazepam	Valium, Calmpose
(3) Zolpidem	Zolfresh
(4) Metronidazole	Flagyl
(5) Clotrimazole	Candid

COMPLIANCE: If a patient follows fully the doctor's prescription, then the patient compliance is good. If the patients do not follow strictly as per doctor's prescription or advice is called patient's poor compliance due to many reasons.

CHAPTER 2

Nature and sources of drugs

This will be also dealt at the time of explaining the individual drugs. It is briefly explained here.

Sources of drugs mean, from where the drugs have been obtained. Nature means, the chemical nature of the drug.

1. From Plants: Alkaloids (Atropine, Morphine), Glycosides (cardiac glycoside like digoxin)
2. From Animals: Pig (Insulin), Horse serum (Anti Serum), Human urine (Pregnant)-Gonadotropic Hormones.
3. From Microbes: (ANTIBIOTICS) Antibiotic is a drug that derived from the microorganisms and used either to kill or prevent the growth of **other** microorganisms Example: Ampicillin, Amoxicillin, Cephalosporins, Gentamicin etc.,
4. Synthetic: More than 90% of the drugs are synthetic in nature (manufactured in the drug industry)
5. DNA Recombinant technology: It is also one type of synthesizing the drugs. Large amount can be synthesized. Example : Humulin (very closely resemble human Insulin). A note about DNA recombinant technology: They are genetically engineered drugs. A desired gene is inserted into a very fast multiplying non-pathogenic strain of some bacteria e.g., E.coli-K12 by this method. This host cell will now produce large amount of the gene-directed proteins (DRUGS), which are required. E.coli, otherwise, does not synthesize these proteins. e.g., Humulin (a human Insulin synthesized by inserting proinsulin gene). Humulin is very closely resembles human Insulin.
6. Mineral Source: Ferrous sulphate (used in anaemia), Aluminium hydroxide (antacid).

CHAPTER 3 Routes of administration of drugs

Routes of administration of drugs is the method by which the drug is introduced into the body.

CLASSIFICATION OF ROUTES OF ADMINISTRATION OF DRUGS. (Fig.3)

Enteral	**Parenteral** **(par=away, enteral = GIT, away from GIT)**	**Topical**
1.Oral 2.Sublingual 3.Rectal 4.Buccal	1.Injections i)subcutaneous ii)intramuscular iii)intravenous iv)intradermal v)interathecal/epidural vi)intraarticular vii)intraarterial 2.Inhalational administration 3.Transdermal administration	1.Drops i)nasal, eye and ear drops) 2.Vaginal, urethral tablets 3.Dermal – gel, ointment

For local action: The drug need not be absorbed. But for systemic action, the drug should be absorbed (absorption means, entry of the drug into the blood stream from the site of administration)

ORAL ROUTE: The drugs are administered by swallowing from the mouth. This route is meant for both local and systemic actions.

Dosage forms: tablet, capsule, powder, liquid preparations.

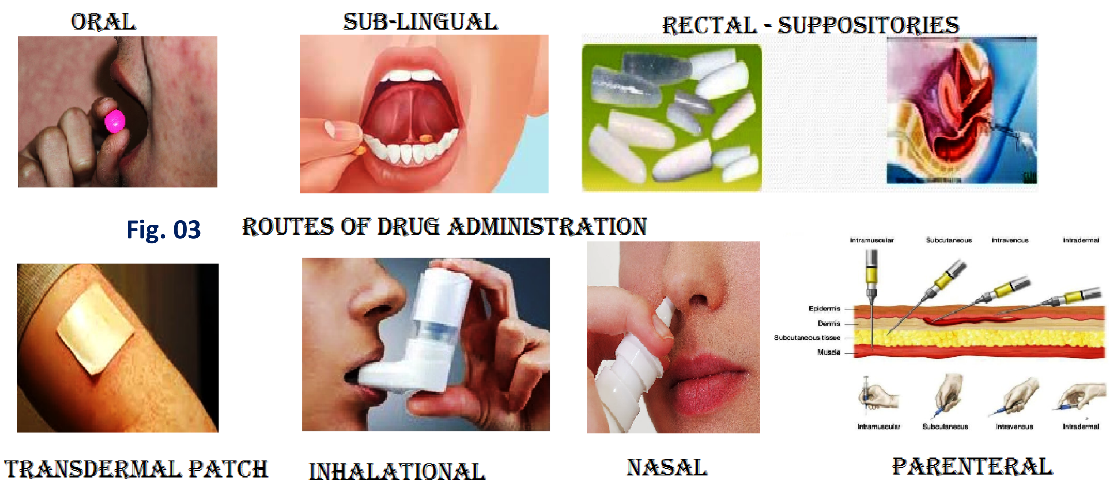


Fig. 03 ROUTES OF DRUG ADMINISTRATION

Advantages/merits of oral administration:

- Most common method.
- Very safe
- Self administration is possible.
- Non invasive
- Painless
- Economical, since sterilization and other procedure are not needed.

Disadvantages/demerits:

- Slow onset of action. Not suitable in emergency condition.
- Many drugs being polar are not absorbed (Gentamicin).
- The drugs which are destroyed by the gastric juice cannot be given by this route.
- The drugs which are having high first pass metabolism cannot be given by this route. (Example : GTN (Glyceryl Tri Nitrate)
- This route is not suitable in unconscious, noncooperative patients or in patients having severe vomiting.
- Unpalatable substances cannot be given by this route.

SUBLINGUAL ADMINISTRATION:

The drug is kept under the tongue mainly for systemic action. Example : Glyceryl Tri Nitrate (GTN)

Merits:

- This route is suitable for those drugs which have got high first pass metabolism, since this route bypasses liver (portal circulation) for the first time. The drug directly goes to the systemic circulation.
- Quick onset of action.

- Self administration is possible in case of emergency.
- The drug can be spit out as soon as action is over in order to avoid the side effects.

Demerits:

- Distasteful, irritant drugs cannot be given by this route.
- Higher molecular weight drugs like Insulin, Heparin cannot be given by this route, (otherwise it will be the best route for Insulin and Heparin).

RECTAL ADMINISTRATION for both local and systemic actions.

Drugs are administered through rectum. Dosage forms: suppository (conical shape) - Example : Dulcolax – (purgative in children). Liquids are administered with high pressure (enema). Example: Evacuant enema (soap water) is used to clear the GIT in case of emergency evacuation of bowel.

Merits:

- Useful in patients having severe nausea and vomiting.
- This route may be convenient in noncooperative children, (Diazepam suppository in febrile convulsion in children)
- It is alternate route for gastric irritant drugs.

Demerits:

- Inconvenient and embrassing to the patients.
- The drugs soil the clothes.
- Rectal inflammation is possible.
- Absorption is unreliable.

PARENTERAL ROUTES:

- Drugs are administered away from GIT (par= away, enteral=GIT) usually by injections or by inhalation.
- Injection → It is given by using needle and puncturing the skin. This route is preferred mainly for systemic action.
- Inhalation → The drug is administered through nose and mouth to the respiratory tract for local or systemic action.

INTRAMUSCULAR INJECTION:

Drugs are injected deep into the skeletal muscles.

Sites: Deltoid muscle, gluteal muscle of buttock (preferred for depot or long acting preparations of drugs).

Merits:

- Injections are suitable for those drugs which cannot be given by oral route. Injections are preferred, when quick action is required.
- Bioavailability is high (90 to 100%) after injection.
- Depot or long acting preparations are given by this route.

Demerits:

- Painful at the site of injection.
- Self administration is difficult.
- Expensive.
- Perfect aseptic conditions are required.
- Chances of abscesses or nerve damage at the site of injection is possible.
- Large volume cannot be given through this route.

SUBCUTANEOUS INJECTION:

The drugs are injected into the subcutaneous tissues of forearm, abdomen and thigh.

Merits:

- Self administration is possible.
- This is the best route for administering highly potent drug (among injections). Because of less blood supply, there will be slow absorption and hence less toxic. (Morphine, Insulin, Low molecular weight Heparin).
- Also depot preparation for prolonged action is given by this route (Example: Progesterone implant into the subcutaneous tissues for prolonged action as contraceptive).

Demerits:

- Only small volume can be given (maximum of 1 ml).
- Irritant drugs produce necrosis.
- Not suitable in shock as reduced blood circulation decreases the rate of absorption.

DERMOJET:

Subcutaneous administration of drugs with pressure (without needle). Useful for mass inoculation. No need for repeated sterilization.

INTRAVENOUS INJECTION (I.V.): (Slow administration of drugs into the vein is called as infusion)

Site: The drugs are injected into antecubital vein.

Merits:

- I.V. Injection is suitable for those drugs which cannot be given by oral route. I.V. injections preferred, when quick action is required.
- Bioavailability is 100%
- It is the best route in emergency.
- Large volume can be given (Example : IV infusion of Dextrose, Saline, Blood).
- For controlled dosage administration; (IV infusion of Oxytocin and IV General Anaesthetics).

Demerits:

- Painful at the site of injection.
- Self administration is difficult.
- Expensive.
- Perfect aseptic conditions are required.
- Chances of abscesses or nerve damage at the site of injection is possible.
- Necrosis and thrombophlebitis are common.
- Care should be taken that air should not enter into the vein (air embolism is fatal).
- Drugs of oily or suspension in nature (used for long action) cannot be given by this route.

INHALATIONAL ADMINISTRATION OF DRUGS:

The drugs are administered by inhalation through mouth and nose (through respiratory tract).

Example: Volatile general anaesthetics, Salbutamol in bronchial asthma, steroid (Beclomethasone) in bronchial asthma.

The drugs are administered and excreted through the same route.

Absorption is through alveoli (plenty of blood supply and also vast surface area). So the absorption is quick and there will be quick onset of action.

General anaesthetic dose is accurately monitored. (Fig.12)

TOPICAL ROUTES: Mainly for local action.

Example: Eye drops, Ear drops, Nasal drops, vaginal tablet, foam etc., Diclofenac sodium spray on skin is for systemic action (analgesic and anti-inflammatory actions).

CHAPTER 4
Dosage forms of drugs

In the modern days, the pharmacist is no longer required to prepare or to dispense the drugs for doctors' prescription. Drugs are now prepared and well packed by the pharmaceutical companies and supplied in various dosage forms and formulations for dispensing to the patients. The drugs are not administered as formulated Syrups, capsules, tablets or injections.

FORMULATION OF DRUGS

It is a recipe of drug preparation. It consists of active ingredients (the drug) and other substances like excipients, vehicles, flavouring agents and preservatives, with the quantity of each components.

DOSAGE FORM

It is the form (e.g., as tablet or capsule or injection or oral liquid) in which the above formulation of the drug can be administered to a patient.

EXCIPIENTS

Pharmacologically inert substances which are added to the pharmaceutical preparation either to add bulk of the tablet (active drug is extremely small in quantity) or to mask (or reduce) the unpalatable taste e.g., lactose, calcium lactate, starch etc.,

VEHICLES

These are the substances which are used to dissolve or suspend the drugs, in a pharmaceutical preparation, to make them suitable into usage form (as in ointments) or more palatable (as in liquids), e.g., sugar syrups, cherry syrup, gum acacia and petroleum jelly etc.,

CLASSIFICATION OF DOSAGE FORMS :

SOLID DOSAGE FORMS

POWDERS

These may be one drug or combination of drugs in a dried and finely powdered form intended for external use (e.g., dusting powders, boric acid) or for oral use (e.g., Aspirin powder).

EFFERVESCENT POWDERS

Drug powders are mixed with sodium bicarbonate, citric acid or tartaric acid. If dissolved in water, they effervesce with release of carbon dioxide (e.g., Eno Antacid powder) and thus make the mixture more palatable and tasty. In tablet form it is called dispersible tablet, e.g., Disprin (dispersible Aspirin tablet).

GRANULES

These are small units of powder bound together by a binding agent (e.g., starch or alcoholic spray), e.g., Vitamin D_3 granules. Some of these granules can be dissolved in a specific volume of water to make a suspension for immediate oral use in children, e.g., Amoxicillin or Ampicillin dry syrup.

TABLETS

Drugs which are powdered or granulated form are compressed under heavy pressure into a round or oval shaped making them suitable for swallowing.

i) Ordinary Tablets

These are uncoated compressed tablets, e.g., Paracetamol tablets.

ii) Sugar-coated Tablets

These tablets are coated with sugar to avoid bitter taste of ingredients, e.g., tab, Chloroquine, tab. Metronidazole.

iii) Film-coated Tablets

A transparent film coating is done by gelatin or cellulose derivatives just to mask the unpleasant taste. But the tablet size or weight remains the same. E.g., Cefuroxime film coated tablet, Diltiazem film coated tablet etc.,

iv) Enteric-coated Tablets

Coating of the tablet is made by cellulose acid phthalate, shellac or keratin which are resistant to gastric acid but dissolve at intestinal alkaline pH. The active drug is protected from destruction by acidic pH. Gastric irritation is reduced, e.g., Diclofenac enteric coated tab Enteric coated enzyme preparation), Enteric coated Aspirin tablets.

v) Long acting tablets (retard tablets-R, sustained release tablets-SR)

Each unit of drug particles have individual coating with different types of inert resins so that each type of coating dissolves at different time intervals. Such tablets provide a steady and sustained release of the drug over a period of 10-12 hr and hence have a lesser side effects, e.g., Pot.chloride retard tabs, Diclofenac sod.sustained release tablet. Nifedipine retard tab. Controlled release drugs are most suitable for drugs of short $t_{½}$. Therapeutic failure can occur for life saving drugs such as Nitro glycerine controlled release capsules.

vi) Pellets

Drugs which are in sterile spheres prepared by compression of drug powders such as hormonal preparations. Used for subcutaneous depot implantation of the drugs which will be slowly released for a long duration . e.g., Testosterone pellets.

vii) Lozenges

It is a tablet form of drug prepared with sugar and resin, and is meant for chewing to provide local effects in mouth or throat e.g., various cough lozenges, throat smoothening agents.

Capsules

These are inert gelatin coated shells of suitable size, incorporating powdered drug and excipients meant for swallowing, e.g., Doxycycline cap., Amoxicillin cap., etc., Thick gelatin capsules are used to incorporate powder form of drug (e.g., Amoxicillin) while soft, thin gelatin capsules are used to incorporate oily drug (e.g., Vit E). The gelatin coating quickly dissolves in gastric juice and release the drug in the GIT.

a) Spansules

These are longer acting capsules, similar to long acting tablets., e.g., Iron formulations, Isosorbide dinitrate Spansules, Nitroglycerine Spansules. These are visible coloured drug granules inside a transparent capsule. These beads are impregnated with various resins which will dissolve at different time intervals.

LIQUID DOSAGE FORMS OF DRUGS

AQUEOUS SOLUTIONS

These are subdivided into the following forms:

i) Syrups

Drug(s) present in concentrated solution. Sugar or Sugar free liquids plus flavouring agents and permitted colours, e.g., Commonly used cough syrups, vitamin syrups.

ii) Solutions (Liquor)

These are aqueous solutions of therapeutic agents e.g., hydrogen peroxide solution, liquor ammonia and iodine solution.

iii) Linctus

Viscous syrupy liquid formulations consist of the drug and demulcents, like menthol. Linctus provides soothing effect in sore throat, e.g., cough linctus.

iv) Injections

These are sterile solutions or suspensions of the drug in appropriate solvent and preservatives which are meant for parenteral use, e.g., Injection Diclofenac, Injection Lignocaine. Some drugs are supplied as dry powders which should be dissolved in aqueous vehicles like water for injection e.g. Cephalosporins, Amoxycillin etc.,

a) Depot injection

It is a longer acting injectable preparation similar to long acting Tablets or Spansules, but in injection form. The drug is suspended in sterile oily base from which it is slowly released for a prolonged duration, e.g., Testosterone depot inj. Fluphenazine depot inj.

AQUEOUS SUSPENSION

i) Mixtures

Solid drugs dispersed homogeneously in water by suitable suspending agent (agar agar), e.g.,Milk of magnesia etc.,

ii) Emulsions

They are prepared by mixing two or more immiscible liquid medicaments by means of a suitable suspending agent (Gum acacia). One liquid serves as continuous phase in which the other liquid is dispersed uniformly in fine droplet form, e.g., cod liver oil emulsion, liquid paraffin emulsion. This preparation helps for better absorption of the drugs.

ALCOHOLIC SOLUTIONS

i) Spirits

These are 10% v/v solution of volatile essential oils plus alcohol and are used as flavouring agents, masking agents and to some extent as preservatives, e.g., spirit chloroform, spirit ammonia aromaticus,

ii) Elixirs

These are pleasantly flavoured solutions of a drug in sugar syrup or glycerol along with higher proportions of alcohol,e.g., vitamin B – complex elixirs, cough elixirs; but these preparations are now on the decline. Alcohol is used in elixir as a solvent for drugs that are not suitable for water alone.

iii) Tinctures

These are alcoholic extracts of plant drugs (10-20 w/v), e.g., tinct. belladonna . Many tinctures are used as flavouring agents, e.g., tinct.cardamom . and tinct. Zingibaris (in such cases drug contents many range from 20% to 50%). Hydroalcoholic solutions of inorganic substances known as tinctures, e.g., Tinct.iodine which is used as an antiseptic.

Drops

Used mainly in paediatrics. These formulations contain small quantity of concentrated solutions of drug (s), e.g., vitamin drops and enzyme drops. Eye/ear drops are also included in this category. These are sterile, isotonic buffered solutions of the drug. These are usually supplied in a vial with a dropper, e.g., Ciprofloxacin eye/ear drops, gentamicin eye/ear drops etc.,

Enema

Medicated liquid preparations for rectal route of administration with high pressure and are used for emergency evacuvation of bowel e.g., soap and water enema

DOSAGE FORMS FOR EXTERNAL USE

Liniments

Liquid medicaments to be rubbed on skin with friction. It contains drug (s) in a liniment vehicle (fixed oil or soap) and water or alcohol. One ingredient is usually incorporated with another medium (Capsaicin, camphor which serve as counterirritant). These are mainly used as pain relievers or as rubefacient (making skin red), e.g., liniment capsaicin, and liniment turpentine.

Lotions

Liquid medicaments used for local application but without rubbing. They are generally used as antiseptics, soothing agents, astringents and antipruritic agents, e.g., Permethrin lotion, zinc calamine lotion, povidone iodine scrub lotion.

Ointments

These are soft, semi-solid substances containing the drug in a greasy base (paraffin or wool fat), e.g., Povidine Iodine skin ointment and Silver sulfadiazine ointment. Some ointments are in a water miscible base (vehicle). Ophthalmic ointments are sterile medicated ointments for eye ailments, e.g., Ciprofloxacin eye ointment, Atropine eye ointment.

Paste

It is like an ointment with some adhesive material (like starch) or a foaming agent (like carboxymethyl cellulose),e.g., zinc oxide paste, etc.,

Plaster

It consists of a drug mixed in a resinous base spread over a muslin cloth. Some plasters are coated with water repellent film also. The preparation remains hard at room temperature but becomes sticky at body temperature. These are used for protective, analgesic and antiseptic action, e.g., Flurbiprofen plaster, belladonna plaster and Band-Aid.

Gels/ Colloidal aqueous Suspensions

The drug is dissolved in a liquid and then dispersed in soft gelatin. These are usually transparent preparations, e.g., contraceptive gels. The colloidal aqueous suspensions of hydrated inorganic substances used as antacids, e.g., aluminium hydroxide gel.

Inhalants

Liquid preparations of a drug which is meant to be inhaled as vapour. e.g., Eucalyptol, Menthol, tincture benzoin inhalation. The contents may be poured into a jug of boiling water and inhaled to relieve nasal or chest congestion. Solid powdered inhalants, e.g., Salbutamol, Budesonide are inhaled with the use of rotahaler, turbo spin inhaler.

Aerosols

The drug is dissolved in a liquid form is kept inside a cylindrical container (canister) and is then filled with a propellant gas (air or oxygen) under pressure. A compression at the valve releases the microfine drug through a tiny nozzle in the form of mist which is inhaled. If one compression releases a measured dose of drug ,then these are called as “metered aerosols”, e.g., Salbutamol metered aerosol, Budesonide metered aerosol.

Suppositories (rectal), Pessaries (vaginal) and Bougies (urethral)

The drug is mixed with any one of the incredients e.g., glycerine, gelatine, soap, paraffin, cocoa butter. These remain solid at room temperature but become soft and melt at body temperature. Suppositories are bullet shaped, pessaries are conical, while bougies (for both male and female urethra) are pencil shaped. For example: Bisacodyl suppositories and Clotrimazole vaginal pessaries.

Transdermal drug delivery system - Transdermal patch

These are adhesive patches, the drug is incorporated into a polymer (usually polyisobutylene) which in turn is bonded to an adhesive plaster. The drug is delivered at the skin surface by diffusion, by percutaneous absorption it enters into circulation. These preparations are designed to provide steady and smooth plasma concentration of the drug for a period ranging from 1-3 days from the site of their application (usually chest, abdomen, upper arm or mastoid region). Examples are transdermal patches of Nitroglycerin patch, Nicotine patch and Estradiol patch.

TARGETED DRUG DELIVERY SYSTEMS

To improve the drug delivery at the site of action and to reduce the systemic adverse drug reactions special drug delivery systems have been developed recently which have an added advantage of reduced dosage with prolonged drug action. Examples of targeted drug delivery systems are:

Ocuserts

These are thin elliptical microunits of drug in a reservoir from which the drug is slowly released through a semipermeable membrane by diffusion at a steady rate. e.g., Pilocarpine ocusert used in glaucoma, which is placed under the lower eyelid to deliver pilocarpine for a period of 7 days, thus avoiding cumbersome frequent administration of eye drops every day.

Progestaserts

Intrauterine contraceptive device to deliver progesterone into uterus. It is inserted into uterus which delivers progesterone uniformily at a specified rate for a period of one year.

Liposomal drug encapsulation for Intravenous Infusion

Liposomes are minute spherical vesicles of phospholipids containing an aqueous suspension . They can be artificially filled with soluble drug particles, which may be delivered to target tissues. Amphotericin (an antifungal drug used to treat systemic mycoses) is available in a liposomal formulation for intravenous infusion; the preparation is less nephrotoxic and better tolerated. The cost is high due to the manufacturing.

Prodrugs

This is a form of inactive drug which will be converted in the body to an active drug. These are used to overcome the pharmacokinetic disadvantage of bioavailability of the therapeutically very useful drug. For example: Dopamine is very useful in treating parkinsonism, but it does not cross blood-brain barrier (Fig.56). Levodopa, its prodrug, can cross BBB, which is then converted to dopamine in the CNS. Prodrug may also be used to provide longer duration of drug action, e.g., esters of penicillins get slowly hydrolysed in the body to provide slow and sustained release of penicillins (e.g., Procaine Penicillin – G and Benzathine Penicillin –G).

Computerised Miniature Pumps (Fig.06)

These are Computer programmed pumps to release drugs at a definite rate, either continuously as in the case of insulin pumps or intermittently in pulses as in the case of GnRH (gonadotrophin-releasing hormone) pumps. These pumps may also be synchronized with glucose sensor devices which release the desired dose of insulin as per the blood glucose level.

Monocclonal Antibodies (MAbs) as Drug Carriers

These are antibodies which are produced by a single antigenic determinant (epitope) and directed against that particular antigen are called “monoclonal antibodies”.

Large scale production of monoclonal antibodies against any specific antigen is now done by using “hybridoma technology”. Hybridomas are somatic cell hybrids, obtained by fusing a specific B-lymphocyte (forming antibody against a specific antigen) with a mouse myeloma (tumour) cell. The resultant hybridoma, therefore, retains the antibody forming capacity of the B-lymphocyte with an ability of the myeloma tumour cell to proliferate endlessly.

To generate these antibodies, the mouse myeloma cells are first grown in a culture deficient in hypoxanthine phosphoribosyl transferase (HPRT) enzyme so as to inactivate antigen and to prevent the subsequent formation of immunoglobulins (because a tumour cell itself has a specific antigen on its surface). These myeloma cells are then fused with B-lymphocytes, obtained from the spleen of mouse immunised with the desired antigen, in polyethylene glycol. The fused cells (hybridomas) are then placed in HAT medium and cloned.In HAT medium, only the hybridomas can be maintained endlessly in this culture and can continue to produce monoclonal antibodies (MAbs) which can be eluted and purified for clinical use.

However, totally humanised MAbs are the least antigenic. These are obtained either by recombinant DNA technology (by replacing a part of mouse gene sequence with human gene sequence) or by grafting of “complimentarity determining regions (CDRs)” of murine MAbs on human immunoglobulins framework.

The name of any monoclonal antibody ends with a suffix “mab”. The letter before “mab” indicates the source of the antibody e.g., “o” for murine (omab), “xi” for chimeric (ximab) and “zu” for human (zumab). The letters appearing before these words denote their therapeutic use, e.g., “tu” for tumour, “vi” for virus and “ci” for circulation. If there is no prefix then such a “Mab” is generally an immunomodulatory.

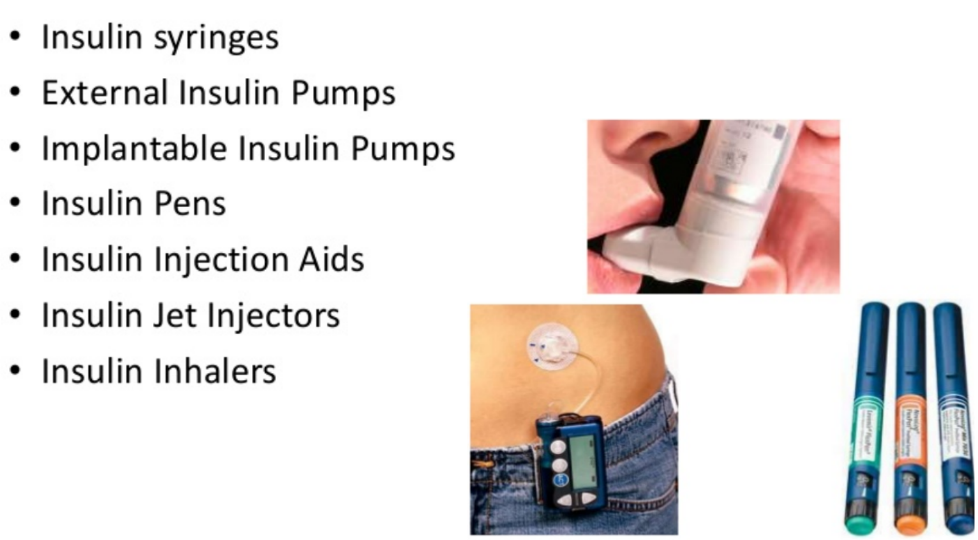
For example, muromonab – CD3 is a murine anti – CD3 monoclonal antibody which is used to prevent transplant rejections. Rituximab is a chimeric monoclonal antibody used to treat non Hodgkin’s lymphoma (tumour). Palivizumab is a Mab that binds to fusion protein of respiratory syncytical virus (RSV) and thus prevents RS-viral infections in airways. Abciximab is a chimeric Mab which binds to GP IIb/IIIa receptors present on activated platelets to prevent their aggregations and very useful in preventing platelet aggregation in coronary angioplasty.

Mechanism of action of monoclonal antibodies: MAbs bind with specific antigens (virus, grafted tissues and neutralize (kills virus, prevent graft rejection) and also neutralize the specific antigens like non-self antigen and prevent the destruction of non-self tissues), prevent antigen antibody reaction on mast cell and prevent the release of chemical mediators from mast cells.

Clinical uses of monoclonal antibodies:

1. As antiviral : Palavizumab- it neutralizes RSV (Respiratory Syncytial Virus) and inhibits its fusion with human cell membrane. It is used to prevent lower respiratory tract infections due to RSV.
2. As anticancer: i) Rituximab : Used in B-cell lymphoma, chronic lymphocytic leukaemia. ii) Epratuzumab (humanized): Used in Non-Hodgkin's lymphoma. iii) Alemtuzumab- Used in B- cell chronic lymphoid leukaemia and T- cell lymphoma.
3. As antiasthmatic: Omalizumab: Used in allergic type of asthma. It inhibits the binding of IgE with mast cells and suppressses IgE mediated release of bronchoconstrictor chemical mediators (Histamine/LTs)
4. As immunosuppressive agents: Muromonab-CD-3 (anti CD3). It depletes cytotoxic T-cell (CD8+Tc) Hence it is useful to prevent graft rejection in organ transplantation. It is also useful in autoimmune diseases, since it inhibits the antigen and antibody reaction, which prevent the destruction of non-self tissues.

Fig.05 Insulin Delivery Devices



(Fig.06)

Continuous subcutaneous insulin infusion (CSII) through pumps

-Most physiological method of insulin delivery

-Preferred in patients uncontrolled on multiple injections & those needing excellent control(pregnancy)

-Specially suitable for patients with risk of hypoglycemia, uncertain lifestyles,meal times.

❑Consists of insulin reservoir, program chip, keypad& screen. Insulin infused through plastic tubings connected to s/c inserted infusion set .

INSULIN DELIVERY – short acting insulin analogues like Aspart(lispro) used.

- Provides constant basal infusion of insulin & patient can activate pre-meal boluses.
- Pumps can be discontinued for short periods for activities like exercise
- Pump can be pre-programmed to compensate for nocturnal & early morning glucose fluctuation.

Advantages

- Rate of insulin absorption more predictable than multiple injections
- Risk of hypoglycemia less

Drawbacks

-Pump failure -→ketoacidosis

-Injection site abscess

CHAPTER 5 Biological membrane and the mechanism by which the drugs cross (transported) the membrane

Before going to the pharmacokinetic properties of the drugs, it is better to know how the drugs cross the biological membrane or are transported across the membrane.

The drugs are carried all over the body mainly through blood stream. The drugs enter into blood stream and leave the blood to reach the site of action on the cell membrane or into the cell. Two membranes are involved for the drugs to cross and reach the site of action. One is capillary endothelium and another one is cell membrane. Biological membrane is present in all those places.

Structure of biological membrane (Fig.07)

It is made up of lipid bilayers. On the surface of the membrane, water filled pores are present. There are also carrier proteins present on the cell membrane. On the cell membranes, some specialised cells are also present to transport the big molecular sized drugs by engulfing.

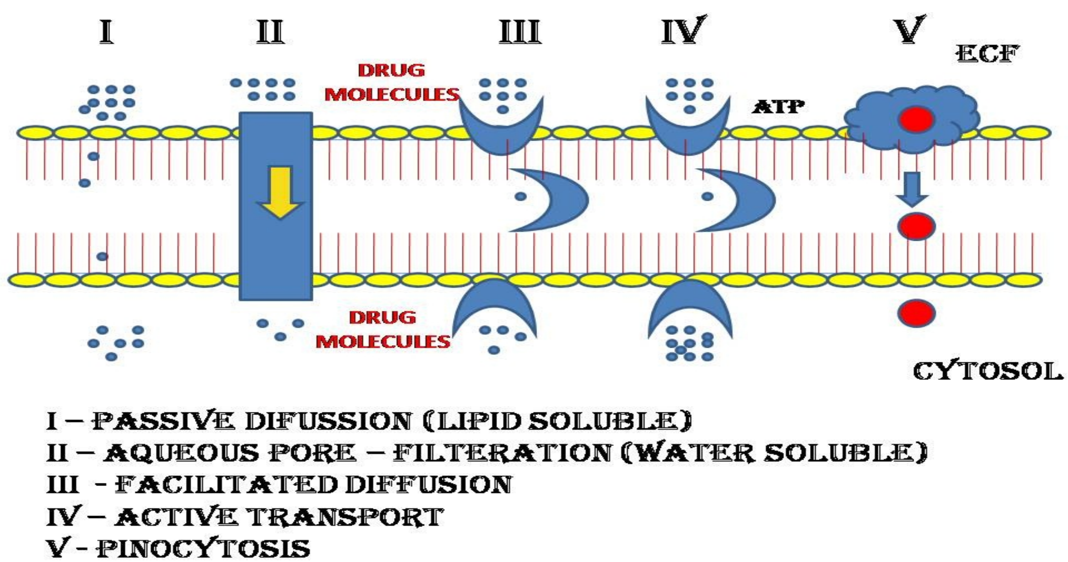


Fig.07 - STRUCTURE OF BIOLOGICAL MEMBRANE AND MECHANISM OF DRUG TRANSPORT

Mechanims of drug transport: (Fig.07)

1. Passive diffusion
2. Filtration
3. Carrier protein mediated transport:
   i) Facilitated diffusion
   ii) Active transport
4. Pinocytosis

1. Passive diffusion: It is the process by which the lipid soluble drugs dissolve in lipid layer of biological membrane and cross (move) from one end (from higher concentration of drugs) to the other end (lower concentration of drug) of the membrane till the concentration of the drug becomes equal on both sides. So in this process, the drugs move from higher concentration to lower concentration (along the concentration gradient).

- Only the lipid soluble drugs will cross by this process.
- No carrier protein or energy is needed for this transport
- Lipid soluble drugs are better absorbed, better penetrating BBB (Blood Brain Barrier) and better crossing all the cell membranes.
- This transport process depends on pH of the medium. i.e., pH dependent.
- All the drugs are either weak acids or weak bases
- Weak acidic drug in acidic medium→ unionized→ lipid soluble→ better diffusion→better absorbed/crossed. Example: Aspirin is a weak acidic drug and in the acidic medium of the stomach, it is unionized and better absorbed from stomach. Just opposite is for the weak basic drugs.

2. Filtration:

- Water soluble drugs will cross through aqueous pores present in the cell membrane.
- Drugs move from higher concentration to lower concentration like diffusion.
- No energy and no carrier protein is needed.
- It is not pH dependent. Filtration depends on the molecular size of the drug. If the molecular size of the drug is bigger than that of the pore, then the drugs will not cross. Only smaller molecular sized drugs are allowed to cross by filtration.
- The pore size of the capillary endothelium is 40 A^0. The pore size of renal capillary endothelium is the biggest. Hence, most of the drugs and metabolites except protein/protein bound drugs are filtered and excreted.

BBB (Blood Brain Barrier) and its CLINICAL SIGNIFICANCES: There is no pore in the endothelium of capillaries entering into CNS. So water soluble drugs will not cross BBB and reach CNS. Only lipid soluble drugs will cross BBB.

3. Carrier protein mediated transport

i) Facilitated Diffusion:

- Carrier protein is needed for the transport of drugs (the carrier protein combines with the drug and carries to the other end and leaves it there, comes back and takes another molecule of the drug and the process is repeated (ferry like transfer).
- Drugs move from higher concentration towards lower concentration like that of passive diffusion.
- Energy is not required.

ii) Active Transport:

- Carrier protein is needed for the transport of drugs.
- Drugs can also move from lower concentration to higher concentration (against concentration gradient).
- Energy is needed (obtained from ATP).

Example: Glucose transport to the peripheral tissues, Gentamicin enters into g^{-ve} bacteria by active transport only, α methyl dopa etc.,

4. Pinocytosis:

- Pino=I drink. Bigger molecules are engulfed.
- Cell engulfs bigger molecule in solution and transfers across the membrane. (Example :Insulin, which is a bigger molecular size is transported through BBB).

COMPARATIVE STATEMENTS OF EACH TRANSPORT:

Passive diffusion	**Active transport**
1. Drugs move from higher concentration to lower concentration (along concentration gradient, till the concentration become equal at both ends)	1. Drugs also move from lower concentration to higher concentration (against concentration gradient)
2. Energy is not required	2. Energy is required
3. Carrier protein is not required	3. Carrier protein is required
4. Lipid soluble drugs and all drugs acting on CNS will cross by this mechanism	4. Non lipid soluble and bigger water soluble drugs will cross by this mechanism
5. pH dependent	5. Not pH dependent

CHAPTER 6
Absorption of the drugs

Absorption of drugs means the entry of drugs into blood stream from the site of administration of drugs. It is possible by the drugs only after crossing the capillary endothelium. All the drugs cross the capillary endothelium and enter into venules (absorbed) and taken into the systemic circulation→to the heart→ reach all the body tissues through arterioles while cardiac out put. Remember, the capillaries (arterioles and venules) are important for absorption of drugs (through venules) and distribution of drugs (through arterioles) (Fig.08 and 09)

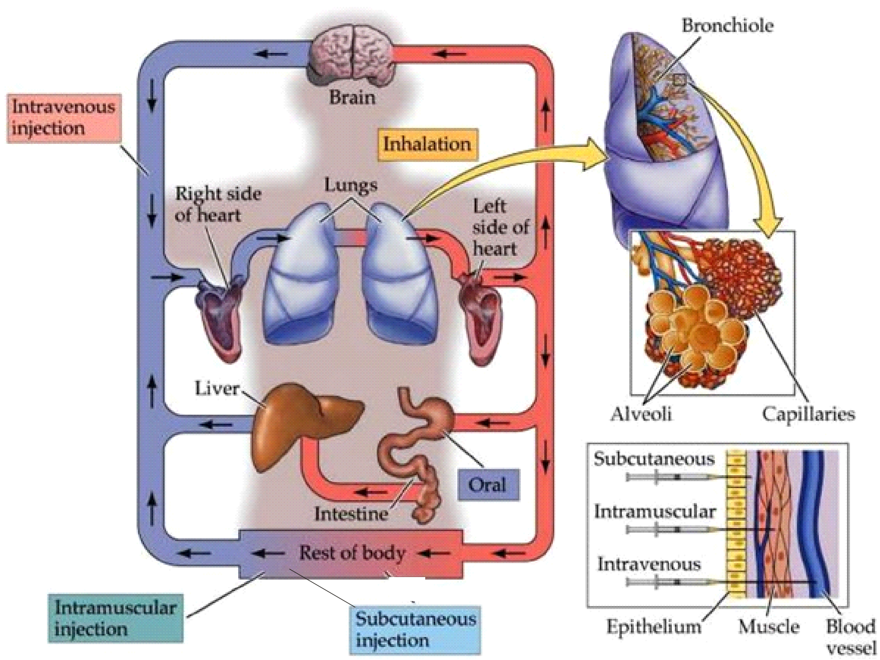
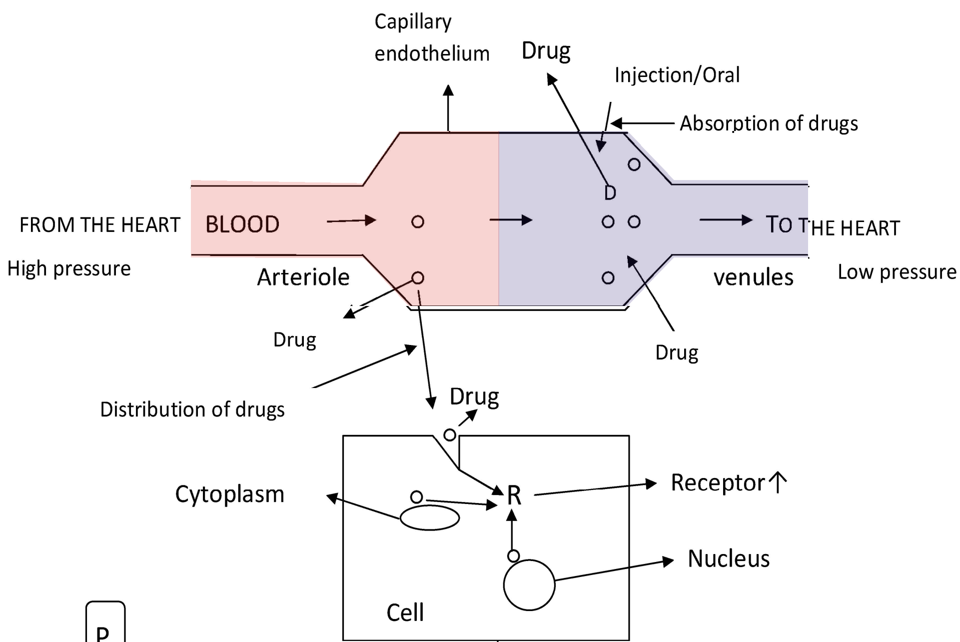


Fig. 08 Absorption of Drugs

Fig. 09 Absorption through capillary



PHARMACODYNAMIC

Therapeutic dose → PHARMACOLOGICAL ACTIONS → How it acts(MOA) 2

5   1   (Mechanism of action of drugs)

Wanted actions → Clinical uses 3

Unwanted actions → Side effects(No drug is available without side effect, which is avoidable) 4

. Study of 1,2,3,4 & 5 is called pharmacodynamic properties of drugs.

Absorption after oral administration: (Fig.10)

First the drug has to cross intestinal epithelium
↓
and then it has to cross capillary endothelium (capillaries supplying the villi)
↓
the drug now is absorbed (entered into blood stream)
↓
enters portal vein
↓
liver
↓
then reaches the systemic circulation
↓
venacava
↓
reaches the heart
↓
from there the drug is pumped out (by cardiac output) to
↓
arteries
↓
arterioles
↓
reaches all over the body tissues.

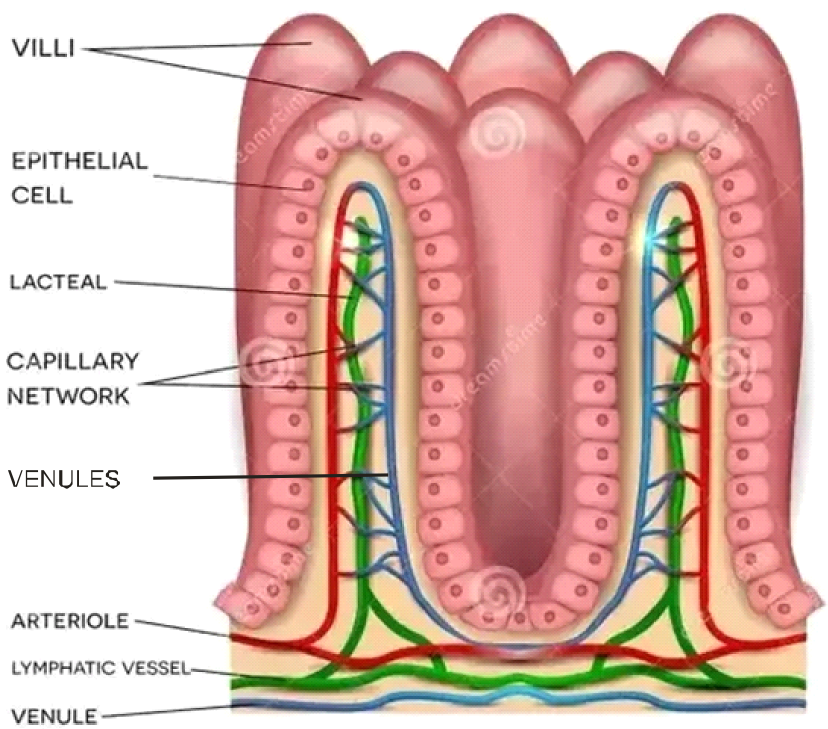


Fig. 10 Absorption of drugs after oral administration

The drugs are not absorbed or poorly absorbed after oral administration due to the following reasons:

1. If the drugs are in ionized form in the intestinal pH medium will become less lipid soluble and less or not capable of crossing the intestinal epithelium (villi) before reaching the capillaries, from where the drugs get absorbed and hence the drugs are poorly absorbed or not absorbed. (e.g., Gentamicin)
2. Certain drugs are degraded by gastric acid (Peniccilin - G) or by peptidase (Insulin), so they could not reach the intestine in sufficient concentration for absorption.
3. Some drugs form complexes and become bigger molecular size and not absorbed or poorly absorbed. Tetracyclines form complex with Ca++ (milk products) or antacids. Both the drugs are given two hours apart to prevent from forming complexes.
4. Certain drugs back diffuse into the intestinal lumen and hence poor absorption (Digoxin, Cyclosporine)

Absorption of drugs from sublingual

buccal mucosa
↓
buccal vein
↓
absorbed
↓
systemic circulation
↓
heart
↓
to all over body tissues through arterioles

parenteral injection
↓
cross the capillary endothelium
↓
absorbed
↓
systemic circulation
↓
heart
↓
to all over the body tissues through arterioles.

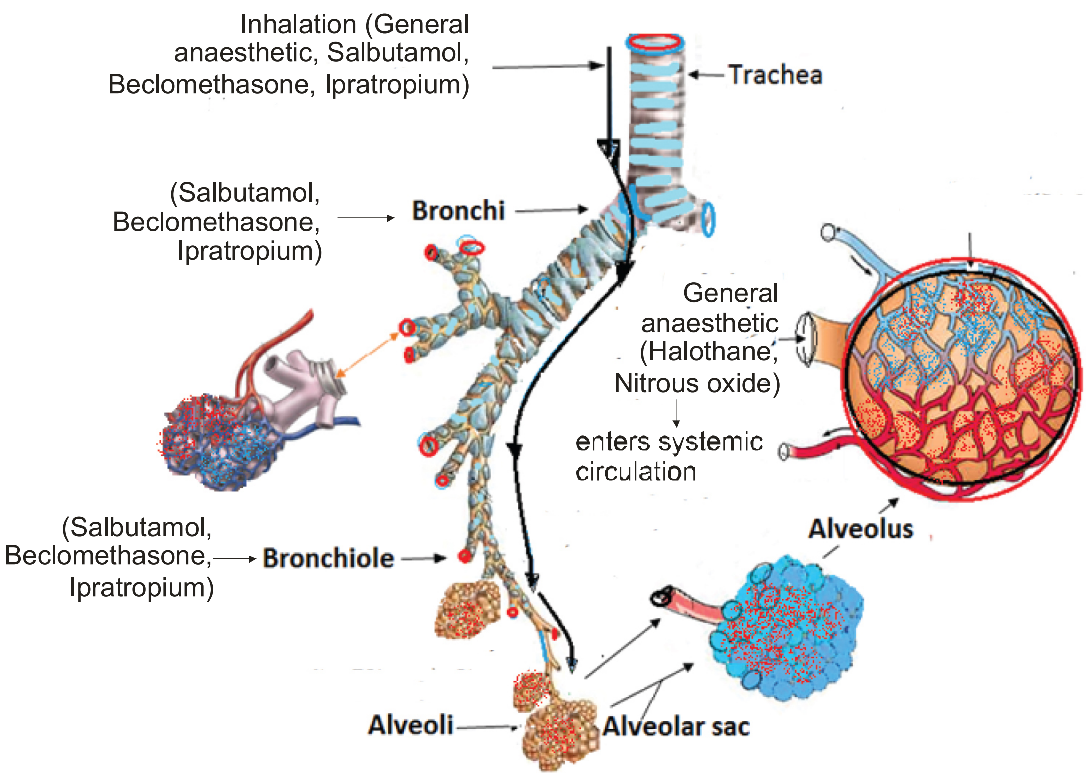
Absorption of drugs after injections:

The drugs which are not absorbed orally given by parenteral route for quick onset of action. The drug is injected (SC/IM) directly into the vicinity of capillaries. There is no need of crossing any other membrane except capillary endothelium, so there is quick onset of action. The drugs are also injected directly into the vein, hence there is no question of absorption and the onset of action is immediate.

Absorption after inhalation (via lungs): (Fig.11)

The lipid soluble drugs are administered in vaporized form (general anaesthetics), Salbutamol (aqueous solution spray) are absorbed (reach the blood stream) by crossing two membrane, first cross pulmonary epithelium/mucous membrane of trachea and lungs by simple diffusion and then capillary endothelium (now the drug enters into blood stream and hence absorbed). The absorption is rapid due to two reasons, 1. Vast surface area for absorption is available and 2. High vascularity for better absorption. As soon as the administration of the drug is discontinued, the drug back diffuses and is rapidly eliminated in the expired air. The control of the dose of general anesthetics accurately is possible.

Absorption of drugs after inhalation: (fig: 11A)



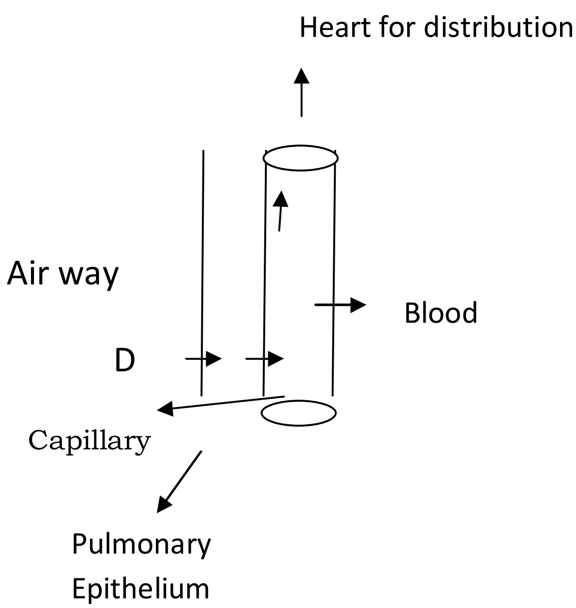
The drugs are administered through nose, mouth,respiratory tract. The drugs travel trachea→ bronchus → bronchioles→ alveoli→ capillaries → absorbed →systemic circulation.

For local action: (Fig.11A) Inhalation of Solbutamol, Iprotropium and Beclomethasone (all the drugs are used in bronchial asthma)→ reach the site of action directly only by crossing pulmonary epithelium (no need of absorption through capillaries). The action is quick.(hence systemic side effects are minimum). The inhalational Salbutamol produces less or no tremor, when compare to oral administration.

For systemic action: (Fig.11-B) The volatile General anaesthetics like Halothane will reach the alveoli quickly, crosses quickly and absorbed quickly through capillaries, which are plenty surrounding the alveoli, reach the site of action (CNS) through the systemic circulation quickly and produce the anaesthetic action quickly.

As soon as the drug administration is discontinued, the drug back diffuses from blood to pulmonary epithelium and crosses pulmonary epithelium and reaches airway and then exhaled (Rapidly eliminated in expired air).

The drugs are administered through inhaled air and excreted through exhaled air.



After Discontinuation:

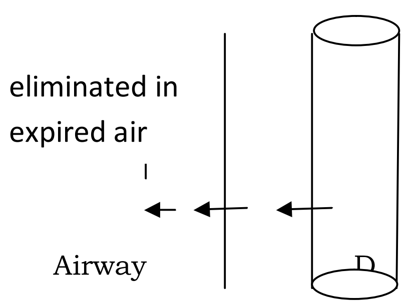


Fig. 11-B Absorption and elimination of drugs after inhalation

Note: The drug is absorbed through venules and distributed through arterioles.

Clinical significances of absorption of drugs:

- The drug has to be absorbed for systemic effect.
- Absorption of drugs from oral administration is through intestinal epithelium of villi and then capillary endothelium.
- If the absorption is faster, the action of drug will be faster (oral absorption-50-60%, IM, SC absorption is 90-95%. IV -100% absorption (where the drug directly comes to the blood circulation) and hence bioavailability.
- Absorption from SC inj. is slow when compared to IM inj. Hence the highly potent drugs like Morphine, Insulin, Low molecular weight Heparin are given by SC route. (Refer below)

Absorption of drugs from eye:

- After applying the eye drops, the drugs cross cornea and directly reach the site of action or after absorption through capillaries.

FACTORS INFLUENCING THE ABSORPTION OF DRUGS:

1. Liquid preparation is better absorbed than the solid.
2. Solubility; Lipid soluble drugs are better absorbed than water soluble drugs.
3. **Dissolution time:** If any drug dissolves in the GIT medium or at the site of parenteral administration faster, the absorption will be faster.
4. **Area of absorbing surface:** The absorption of drugs from the intestine is faster than from the stomach (the absorption surface of the intestine is larger than that of stomach). Larger the area of absorbing surface (alveoli), faster is the absorbtion of drug.
5. **Blood supply to the absorbing area:** more blood supply→ more absorption. Blood supply to the SC tissue is less than that of skeletal muscle. So less absorption from SC inj. than from IM inj. So potent drugs like Morphine, Insulin are given by SC route.
6. **Route of administration of drug:** Absorption is slower after oral administration. Absorption is faster after parenteral administration of drugs.
7. **GIT motility:** If GIT motility is faster, the contact time of the gastric content (which contains the drug) is less and the absorption is less from the intestine.
8. Presence of food will interfere with the absorption of many drugs. Drugs will be absorbed faster in empty stomach.
9. Vasoconstrictor like Adrenaline prolongs the action of local anaesthetic, Lignocaine by reducing its absorption from the site of administration.
10. Suspension of Penicillin G slows the absorption from the site of injection and prolongs the action of Penicillin G (Benzathine Penicillin G).

BIOAVAILABILITY:

Bioavailability is concentration of drug available at the site of action.

If more absorption of a drug, then there will be more bioavailability of that drug at the site of action.

Absorption is proportional to bioavailability.

All the factors influencing the absorption of drugs will also influence the bioavailability of drugs.

CHAPTER 7

Metabolism/ Biotransformation of the drugs

Both the terms are more or less similar, with slight difference.

Metabolism is a chemical alteration of drugs in which the active drugs are always converted into inactive metabolites.

Biotransformation is a chemical alteration of drugs in which the active drugs are converted into inactive form and active form also (inactive prodrug is converted into active drug inside the body).

L-Dopa (inactive prodrug) is converted to Dopamine (active form) in the liver and brain.

Active drug
↓
Metabolism
↓
Inactive drug →active drug → inactivation ← active metabolite ← active drug
↓ ↓
Excreted Prolonged duration

Sites of metabolism: LIVER, intestinal wall, kidney, plasma etc.,

LIVER: The most important organ for the metabolism of more than 90% of drugs.

Enzyme: Microsomal enzymes (CYP-450/Mixed Function Oxidases/Drug metabolising enzymes) are responsible for metabolism/degradation of drugs.

CYP-450 has got many isoenzymes (more than 15-20), which are present in smooth endoplasmic reticulum of liver. Microsomal enzyme are also present in the intestinal wall and kidney. The isoenzymes are represented as CYP-3A4 (metabolise around 60% of the drugs) and other isoenzymes will metabolise the rest of the drugs.

Non-microsomal enzymes present in mitochondria of liver cells, plasma, cytoplasm etc., are Mono Amine Oxidase, Cyclooxygenase, Acetylcholine esterase, Xanthine Oxidase etc., Liver microsomal enzymes (most) are subjected to induction or inhibition by many drugs and produce Drug-Drug interactions, which are clinically significant.

The metabolism of drugs take place by the following chemical reactions:

PHASE I : Oxidation, Reduction and Hydrolysis.

Oxidation: Chemical alteration of a drug by addition of Oxygen atom to the drug molecule or removal of Hydrogen atom from the drug molecule.

Reduction: Chemical alteration of a drug by addition of Hydrogen atom to the drug molecule or removal of Oxygen from the drug molecule.

Hydrolysis: Chemical alteration of a drug by the addition of water molecule.

PHASE II: (Synthetic reaction):

Conjugation (chemical alteration of a drug by combining with one of the body ligands)

Glucuronide conjugation (common form) is the addition of glucuronic acid to the drug molecule.

Example : Paracetamol, diazepam

N-acetyl conjugation- INH, Dapsone, OCP (Oral Contraceptive Pill)

Sulfate conjugation- corticosteroids

Aminoacid conjugation- Dopamine, Adrenaline

Enzyme induction: Some drugs increase the synthesis (not stimulation) of microsomal enzymes and increase their activity are called ENZYME INDUCERS.

Common enzyme inducers are: Rifampicin, Carbamazepine, Barbiturates, chronic smokers and chronic alcoholics, Griseofulvin etc., The common isoenzyme, induced by drugs is CYP3A4, which also metabolise more than 60% of the drugs.

Some of the common drugs metabolised by the same enzymes are Ritonavir, Macrolide antibiotics, oral contraceptives, Warfarin, Paracetamol etc.,

Clinical significances of enzyme induction:

1. The enzyme induces reduce the efficacy of many drugs because the metabolism of those drugs are increased. They also reduce the plasma concentration and lead to therapeutic failure of those drugs given along with enzyme inducers (including contraceptive failure for oral contraceptive pills).

2. They reduce the plasma concentration of antidiabetic and antihypertensive drugs. The dose adjustment will become difficult.

3. Plasma concentration of body Folic Acid and Vit D are reduced (due to increased metabolism) and lead to megaloblastic anaemia and osteomalacia.

4. Paracetamol poisoning in children: Paracetamol is metabolised into hepato toxic metabolite, N acetyl benzoquinoneimine. Enzyme inducers will increase the formation of the toxic metabolite. (Antidote is N-Acetyl cysteine) (Ref. Paracetamol)

5. Enzyme induction increases the synthesis of porphyrin, leads to precipitation of acute intermittent porphyria (hereditary) (abdominal pain, gastrointestinal and neurological disorders in susceptible individuals).

6. Enzyme inducers are not without Clinical uses : They are used in Cushing's syndrome (increase metabolism of Glucocorticoids). Also useful in kernicterus, the neonatal jaundice: (the enzyme inducers increase the foetal hepatic glucuronyl transferase enzyme activity, which conjugates the bilirubin to glucuronic acid and excreted, reduces the bilirubin concentration in plasma. Hence they are useful in kernicterus (Phenobarbitone).

Enzyme inhibition and the clinical significances:

1. The drug interaction due to enzyme inhibition is more dangerous than the enzyme induction.

Enzyme inhibitors are: Erythromycin, Clarithromycin, Valproic acid, Ketoconazole, Metronidazole, Omiprazole, Calcium Channel Blockers like Verapamil and Diltiazem, Ciprofloxacin (except Ofloxacin)

Toxicity of concomitantly administered drug is increased (increased bleeding for dicumarol) cardiotoxicity with Cisapride (banned). In these situations, the clinicians should assess the clinical status. If it is possible, an alternate drug to be prescribed. If it is not possible, the dose of the drug to be reduced according to the clinical conditions.

Factors affecting drug metabolism:

1. Drug-Drug interactions: Enzyme inducers increase the metabolism of some drugs, when given along with them and lead to therapeutic failure of those drugs. Whereas the enzyme inhibitors reduce the metabolism of many drugs given along with the enzyme inhibitors and increase their toxicity for the same therapeutic dose.

The clinicians should remember the enzyme inhibitors. As far as possible, it is better to avoid prescribing the enzyme inhibitors when given along with 2 or more other drugs.

2. Genetic variations: Some individuals have got fast acetylating enzyme, which metabolise Isoniazid faster and reduce its efficacy. Some individuals have got slow acetylating enzyme, which metabolise Isoniazid slower and increase its toxicity.

3. Age: The glucuronyl transferase enzyme is deficient or absent in the neonates. Chloramphenical, which is metabolised by glucuronyl transferase produces toxicity in the neonates (gray baby syndrome).

4. Diseases: Liver disease, hypothyroidism reduce the metabolism of many drugs and lead to drug toxicity in normal therapeutic dose.

5. Nutritional deficiency reduces metabolism of many drugs.

First pass metabolism:

After the oral administration, the drug reaches the liver first through portel vein before going to systemic circulation. Drugs are metabolised at that time.

Some drugs are metabolised faster and some drugs slower. This is referred as 'first pass metabolism'. The drugs which have got high first pass metabolism will not reach the site of action with desired therapeutic concentration after oral administration. There is no use of giving that type of drug orally. It has to be given parenterally. When the drugs are given parenterally, they bypass the liver **for the first time** and the drug directly goes to the systemic circulation and site of action before going to the liver.

Example: GTN (Glyceryl Tri Nitrate)

CHAPTER 8
Distribution of drugs

DISTRIBUTION OF DRUGS:

The drugs always move (transported) in the fluid medium only (Fig.12). From the heart, the drug (with blood) is pumped out (during C.O.P) to the arteries and then to arterioles, which carry the drug and deliver to all the tissues in the body (Fig.13).

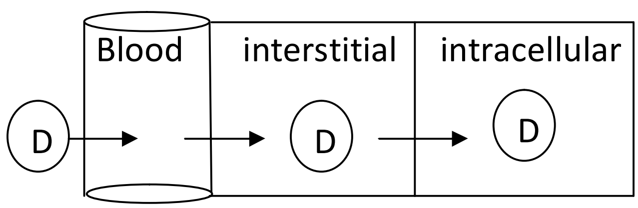


Fig.12 : Distribution of drugs in body fluids.

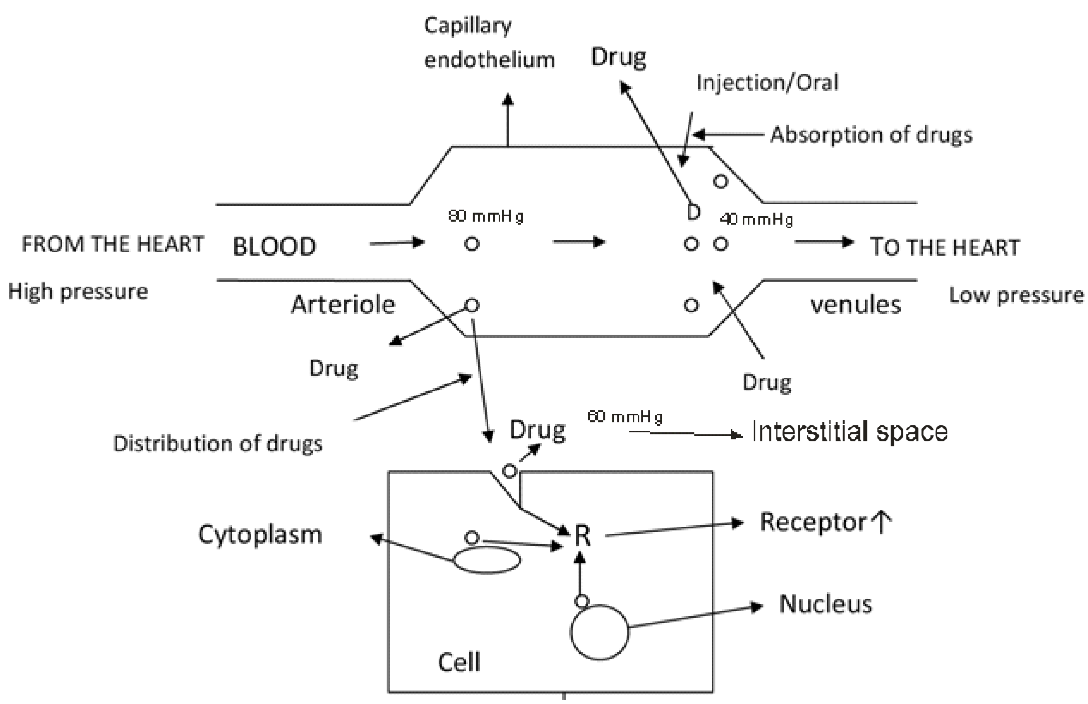
The drug crosses from arterioles →reaches interstitial fluid → reaches the receptors present on the cell membrane →and then the drug reaches intracellular to occupy receptors in the cytoplasm and in the nucleus.

The drug then stimulates the respective receptors present on the cell membrane, cytoplasm and nucleus and produces appropriate pharmacological actions.

The drug crosses the membranes in the distribution of drugs, depending on the medium of the fluid and characteristic features of the drugs (whether it is lipid soluble/water soluble, pH medium etc.,)

As a rule, all the lipid soluble drugs cross all biological membranes and reach intracellular structures (receptors).

Fig.13 Circulation of Drug in the body



(Fig.13) Fluid pressure in arterioles (80 mmHg) is high when compare to interstitial fluid pressure (60 mmHg) – Hence the fluid from the arteriole (along with drug) is pushed out (filtered) into interstitial fluid. The drug acts on the receptors, and then reaches venule side. Fluid pressure in the interstitial fluid (60 mmHg) is high when compare to that of venules (40 mmHg). So the fluid is pushed back (along with drug) to the venules from the interstitial fluid and taken to heart for further round of distribution. So, the drug is going on circulating in the body till it is completely excreted.

Clinical significances of protein bound drugs:

Some drugs have affinity towards protein (albumin) in the blood and bind to it. They are called as protein bound drugs. The percentage of protein binding varies from drug to drug

1. The protein bound drugs will be circulating only in the blood (due to their big molecular structure after binding with protein, they cannot leave the blood).
2. The protein bound drugs will be having equilibrium with free drug (bound drug $\rightleftharpoons$ free drug). Once the free drug concentration falls, then the protein bound drug will be dissociated to 'free drug', so the duration of the protein bound drug will be increased.
3. Protein bound drugs are pharmacologically inert.
4. Protein bound drugs do not cross BBB, placental barrier and are not metabolised or not excreted.

Fig.14A Warfarin (W) is highly protein bound to albumin, leaving a small fraction unbound and available for therapeutic activity.

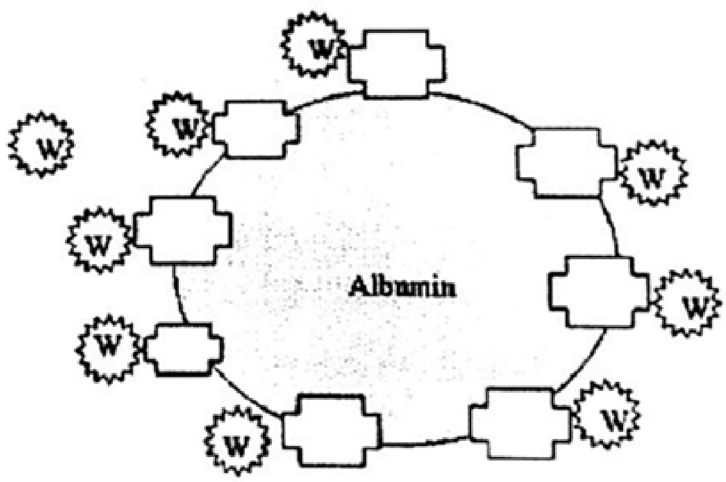
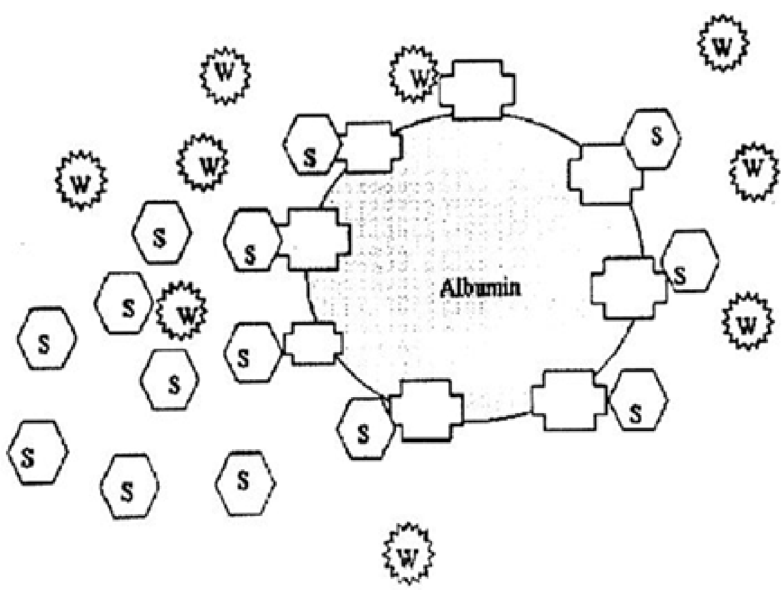


Fig.14-B The addition of the displacer drug salicylic acid (S) with a higher affinity for albumin and a higher serum concentration, displaces warfarin from the binding sites. A larger free fraction of warfarin with more biological activity occurs.



5. Drug interaction is common among the protein bound drugs. (Fig.14-A/14-B)

   Example: Basic drug displaces the basic drug from the basic sites. Like that the acidic drug also displaces acidic drug from acidic site. When both protein bound drugs are given together, the high affinity (towards protein) drug will displace the low affinity drug irrespective of the percentage of protein binding.

   Warfarin is HIGHLY protein bound (99%) but has WEAK affinity to the protein.

   Aspirin is WEAKLY protein bound (40%) but has HIGH affinity towards protein. So, Aspirin displaces warfarin from protein bound site.

   1% free drug of Warfarin is sufficient plasma concentration for action.

   When combined with Aspirin, which displace Warfarin from protein bound site and increases the free Warfarin level in the blood and the toxicity of Warfarin (bleeding). So this combination should be avoided (even the 1% free Warfarin release increases the blood concentration to double of Warfarin and hence the toxicity).

6. **Redistribution of drugs:** It takes place only for high lipid soluble drugs (Thiopentone). Thiopentone rapidly goes to brain and produces general anaesthesia action and immediately leaves the brain (short action). It gets deposited in the fatty tissues immediately, hence short duration of action of Thiopentone sodium. The short duration of action of Thiopentone is due to its rapid redistribution but not due to its increased metabolism or excretion. (the duration of action is 15-20 min.) If the surgery procedure requires more than 20 min, this drug cannot be repeated. Because repeated injection will lead to saturation of fat and once the fat gets saturated, the drug will leak out and plasma concentration of Thiopentone is increased and toxicity occurs (prolonged apnoea) If the surgical procedure requires more than 40 min, other IV general anaesthetic (Ketamine) can be preferred as repeated injection is possible to prolong the duration of action. Thiopentone sodium can be given as infusion in neurosurgery.

Factors influencing the distribution of drugs

1. Blood Brain Barrier (BBB) (Fig.15)

Lipid soluble drugs are better distributed including CNS (lipid soluble drugs cross BBB better) Unlike the capillary endothelium of peripheral blood vessels, the endothelium of brain capillary has got tight junction (No intercellular aqueous pores). Water soluble drugs do not cross BBB. And also one more glial cells are present over the capillary endothelium. This structure of the capillary endothelium makes it a tight barrier to many drugs. This structure is called BBB. Only lipid soluble and actively transported drugs will cross BBB.

The drug to produce actions on CNS must cross BBB.

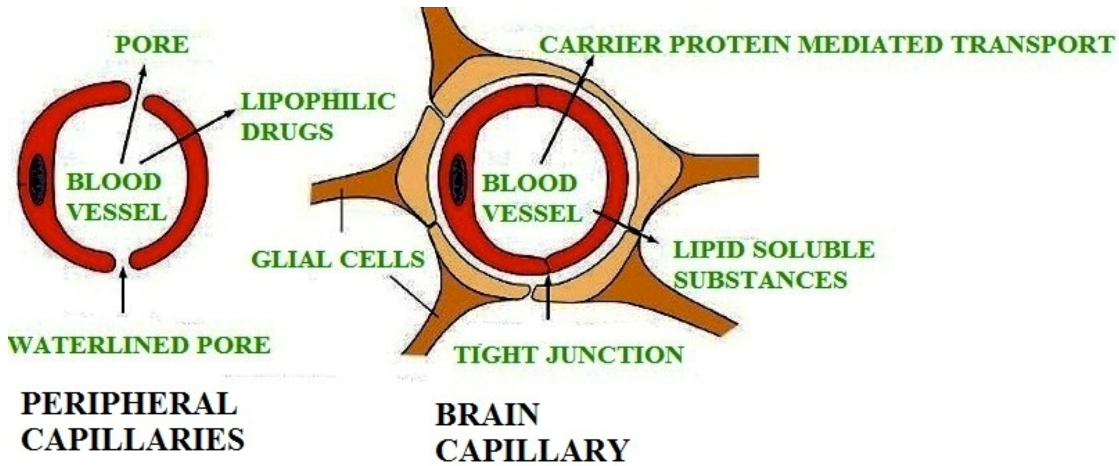


Fig.15 Blood Brain Barrier

2. CTZ (Chemoreceptor Trigger Zone). Even though it is situated in the CNS, it is not covered by BBB.

This anatomical structure is very much useful for the treatment of vomiting due to L-Dopa. Domperidone is given to prevent the vomiting due to L-Dopa without affecting the basal ganglia (antiparkinsonism action), since Domperidone does not cross BBB, but reaches CTZ, where it acts as antiemetic and does not reach Basal Ganglia. But metoclopramide, which cross BBB will produce antiemetic action as well as antagonising the anti-parkinsonism action of L-Dopa. (Ref. : Prokinetic agents under G.I.T.)

VOLUME OF DISTRIBUTION: (Fig.12) This is the volume of fluid, in which the active drug is distributed. The volume of distribution depends on apparent volume of distribution, which will be calculated as follows:

$$Vd = \frac{Total\ amount\ of\ drug\ administered\ IV\ (mg)}{\text{Plasma concentration of drug mg/ml}}$$

Vd= Apparent volume of distribution

The total body fluid is 40 L (approximate)

Plasma volume is 5 L

Interstitial fluid volume is 15 L

Intracellular fluid volume is 20 L

If the volume of distribution of a drug is 5 L and below, then the drug is distributed only in plasma (Heparin). The volume of distribution of Heparin is 5 L, that means, Heparin will be distributed only in the blood and act on blood.)

If the volume of distribution of a drug is 20 L, then the drug is distributed in plasma and in extra cellular fluid.

If the volume of distribution of a drug is 40 L, then the drug is distributed throughout the body fluid. If the volume of distribution is more than 40 L, then the drug is deposited in some organs.

CHAPTER 9 Excretion of drugs and kinetics of elimination

EXCRETION OF DRUGS: The process by which the drugs or their metabolites are eliminated from the body.

Organs of excretion: KIDNEY (through urine), skin (through sweat),mammary gland (through milk), GIT (through faeces), Liver (bile).

Kidney is the most important organ of excretion, through which more than 90% of drugs or metabolites are excreted.

Three processes are involved in the excretion of drugs through kidney.

Fig 16-A. Glomerular filtration

Fig 16-B. Tubular secretion

Fig 16-C. Tubular reabsorption

I. CLINICAL SIGNIFICANCES OF GLOMERULAR FILTRATION: (Fig.16-A) GFR is approximately 150 L. Many drugs are excreted in the active form. In normal kidney function, there won't be any problem for those drugs. But in renal failure, the GFR (Glomerular Filteration Rate) is low and so the elimination of the active drug is reduced and plasma concentration is increased and hence the toxicity of the drug.

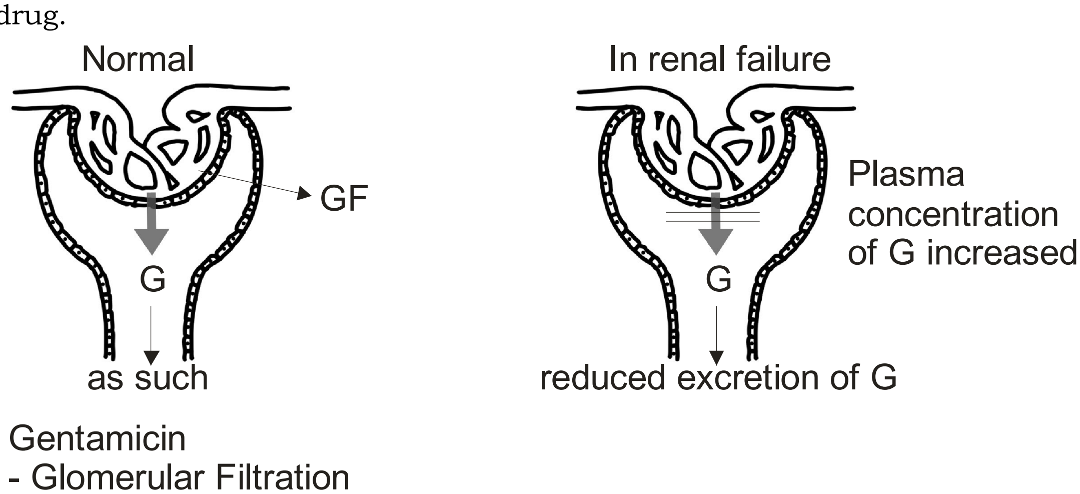


Fig. 16A Glomerular filtration

Precautions: Those drugs which are excreted in active form (Gentamicin) should be avoided in renal failure. If not possible, then the dose is proportionately reduced on the basis of creatinine (renal) clearance. Take it for granted, the creatinine clearance in normal is 100 ml/min. If the creatinine clearance is 50% (for the drug in question), then the dose of the drug should be 50% of the normal dose. Like this the dose of the drug is to be calculated.

$$Dose\ of\ the\ drug\ (in\ question) = \frac{Normal\ dose\ x\ creatinine\ clearance\ of\ drug\ ml/min}{\text{Normal creatinine clearance 100 ml/min}}$$

II. Clinical significances of tubular secretion: (Fig.16-B)

1. Frusemide and Thiazides are secreted into the proximal tubule in active form and reach the site of action in the renal tubule to produce diuretic action.

2. There will be competition between drugs excreted through tubular secretion. Example : Ampicillin and Probenecid are secreted through the same sites. When those drugs are given together, Probenecid will inhibit the secretion of Ampicillin and increases the concentration of Ampicillin in the plasma, which is very much needed in the treatment of Gonorrhoea (To achieve high concentration in plasma, oral high dose of Ampicillin is needed, which will produce intolerable side effect like diarrhoea). So in the treatment of gonorrhoea both Probenecid and Ampicillin (normal dose) are given.

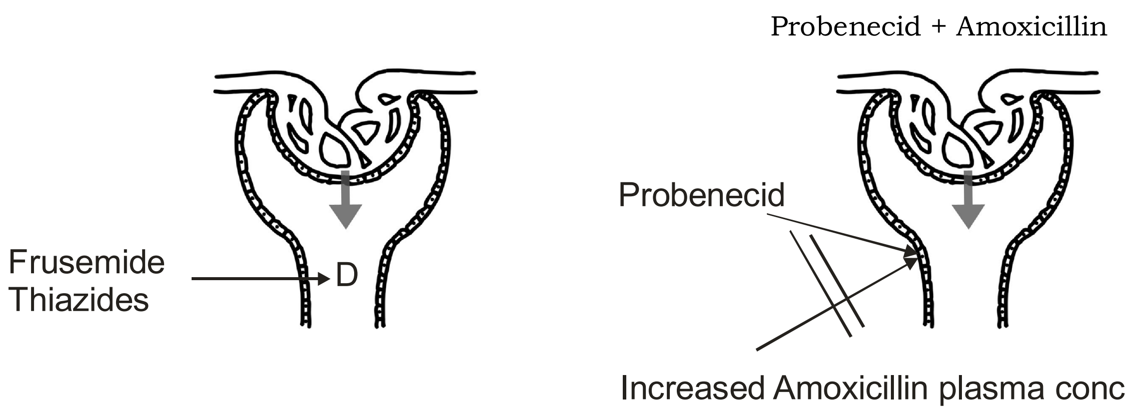


Fig 16-B. Tubular secretion.

Frusemide and Thiazides are secreted in active form into the proximal tubule to reach the site of action. Probenecid inhibits the secretion of Amoxicillin and hence the concentration of Amoxicillin is increased in the plasma.

III. Clinical significances of tubular reabsorption: (Fig.16-C)

Active drugs are not normally reabsorbed except few drugs like Phenobarbitone in poisoning, where the active Phenobarbitone is filtered and reabsorbed, being lipid soluble. Only lipid soluble drugs are reabsorbed and the plasma concentration is increased.

Phenobarbitone poisoning: Active drug appears in the urine. Phenobarbitone is a acidic drug. In the acidic urine, it gets unionized (lipid soluble) and reabsorbed and poisoning will be aggravated. To quicken the excretion of Phenobarbitone, the urine should be alkalanized by giving IV sodium bicarbonate. In the alkali medium of urine, Phenobarbitone gets ionized and will not be reabsorbed and then excreted. In the same way the basic drugs poisoning, the urine should be acidified by giving IV Ammonium chloride/Ascorbic acid.

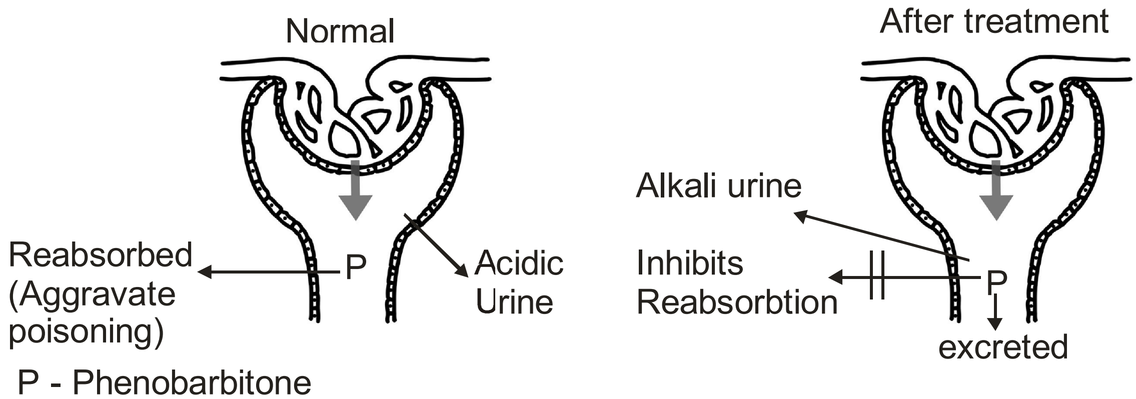


Fig 16-C. Tubular Reabsorption

Phenobarbitone in Alkali urine gets ionized, not reabsorbed and excreted.

Excretion of drugs through milk secretion: Many drugs are secreted in the milk in active form. In that adult dose it may produce toxic effects in the infants (breast feeding). Breast feeding should be avoided when the mother takes drugs that are excreted through milk. The breast feeding mother should consult the doctor before taking any drug.

Clinical significances of biliary excretion and enterohepatic circulation:

1. The drugs which undergo enterohepatic circulation prolong the duration of action of drugs.
2. From the liver→ OCP (Oral Contraceptive Pill) is secreted into the intestine through bile → In the intestine it is deconjugated by the intestinal bacterial flora into active form → reabsorbed back to liver. If the bacterial flora is inhibited by Ampicillin → prevent the deconjugation of OCP and back to liver → excreted in the faeces →↓ (reduce) plasma concentration of OCP → therapeutic failure (failure of contraception).
   Ampicillin or any other antibiotics that suppress the bacterial flora should not be given with OCP.

KINETICS OF DRUG ELIMINATION

The rate and the pattern of drug elimination follows any one of the following kinetics:

1. First order kinetic.
2. Zero order kinetic
3. Mixed order kinetic

1) First order kinetic :

Majority of the drugs obey First order kinetic

Here a CONSTANT FRACTION (PERCENTAGE) of the drug is eliminated at unit time. If the concentration of the drug is increased in the plasma, there is proportionately increase in the elimination

For example:

If plasma concentration of a drug declines at a rate of 50% per hour.

$$100\ \mu g/ml \xrightarrow[1\ hr]{50\%} 50\ \mu g/ml \xrightarrow[1\ hr]{50\%} 25\ \mu g/ml \text{ and so on}$$

If the plasma concentration of the drug is doubled, then the elimination will be as follow

$$200\ \mu g/ml \xrightarrow[1\ hr]{50\%} 100\ \mu g/ml \xrightarrow[1\ hr]{50\%} 50\ \mu g/ml$$

Here the plasma half life is not increased and remains CONSTANT, irrespective of the increase in the plasma concentration of the drug. In this kinetic, it needs approximately 5-6 half lives for complete elimination of the drug.

2) Zero order kinetic:

In this kinetic, a constant or fixed QUANTITY (AMOUNT) of the drug is eliminated per unit time. Say for example 50 μg/ml in unit time (not 50%/ml in unit time) is eliminated.

If the initial plasma concentration is 100 μg/ml and 50 μg/ml is eliminated per hour, then the elimination will be as follow:

$$100\ \mu g/ml \xrightarrow[1\ hr]{50\ \mu g} 50\ \mu g\ /ml \xrightarrow[1\ hr]{50\ \mu g} \text{Nil}$$

If the plasma concentration is increased to double, then the elimination will be as follow:

$$200\ \mu g/ml \xrightarrow[1\ hr]{50\ \mu g} 150\ \mu g/ml \xrightarrow[1\ hr]{50\ \mu g} 100\ \mu g\ /ml$$

Here the plasma half life is increased to 2 hrs, not constant.

3) Mixed order kinetic:

Low dose obey first order kinetic

High dose obey zero order kinetic.

Some drugs obey this kinetic of elimination. For example: Warfarin, Digoxin, Aspirin etc.,

CHAPTER 10 Plasma half life

PLASMA HALF LIFE AND ITS CLINICAL SIGNIFICANCES:

The time taken for a drug to be reduced to half of its original concentration in plasm is referred as 'plasma half life –$t_{1/2}$'

1. If higher the plasma half life, longer the duration of action of drugs.
2. Dose interval depends on the plasma half life
3. Normally, after a single therapeutic dose, approximately 4-5 plasma half lives are needed for drugs following first order kinetic to eliminate the drug completely from the body. If the drug concentration is 100 mg at the beginning, then

1st half life 100 mg to 50 mg

2nd half life 50 mg to 25 mg

3rd half life 25 mg to 12.5 mg

4th half life 12.5 mg to 6.25 mg

5th half life 6.25 mg to 3.8 mg

6th half life 3.8 mg to 1.8 mg

Plasma half life of some important drugs

1. GTN – 1 hr (shorter duration of action)
2. Digoxin – 10 days (longer duration of action)

It is needed to calculate the loading and maintenance dose for digoxin

Factors affecting plasma half life

i) Protein binding of drug: Drugs binding to plasma proteins increases the plasma half life and hence the duration of action. (warfarin sodium)

ii) Entero-hepatic circulation: Drugs undergo enterohepatic circulation increases the plasma half life and hence increases duration of action.

iii) Faster the metabolism of drugs – will have the shorter plasma half life and shorter duration of action.

iv) Faster the excretion of drugs – will have the shorter plasma half life and shorter duration of action..

Biological half life – it is the time required for total amount of the drug in the body to be reduced to half.

Biological effect half-life – it is the time required for the biological effect (pharmacological action) of the drug to be reduced to half.

Example: Hit and run drug like Gentamicin – the bacteriocidal effect (biological effect) will persist for long time even after the excretion of drug which is called as Post-antibiotic effect.

CHAPTER 11 Methods of prolonging the duration of action of drugs, therapeutic index

METHODS OF PROLONGATION OF DURATION OF ACTION OF DRUGS:

I. By slowing the absorption of drugs:

1. Oral
   i. Sustained release (SR) formulation – examples: Diclofenac sodium, Nifedipine – each unit of drug particles have individual coating with different types of inert RESINS. So that each type of coating dissolves at different time intervals. Such tablets provide a steady and sustained release of the drug over the period of 12-24 hrs (long duration of action) and have a lesser side effects.
2. Parenteral : To prolong the duration of action of drugs, there are given as follows
   i. Oily suspension - By reducing the solubility (Procaine + Penicillin).
   ii. By increasing the particle size of the drug – Insulin Zinc Suspension.
   iii. By reducing the systemic absorption due to vasoconstriction – Adrenaline + Lignocaine
   iv. By increasing the protein binding capacity of the drug – the drug is slowly released from the protein binding site (by reducing the absorption) and hence prolong the duration of action of drugs ex: Protamine + Zinc + Insulin.
   v. Transdermal patch – GTN - the drug is incorporated into the adhesive patch, which is fixed on the skin. The drug is slowly released and absorbed which prolongs the duration of action of drugs.
   vi. Transmucosal (ocusert) – Pilocarpine ocusert, which is kept in eye. The drug is slowly released and absorbed which prolongs the duration of action of drugs.

II. Distribution – refer protein bound drugs - warfarin

III. By inhibiting metabolism
   a. Anticholinesterase – (Ref: Neostigmine)
   b. Cilastatin + imipenem (Ref : Imipenem)

IV. By reducing excretion – Probencid + Ampicillin, Probencid + Amoxicillin (Fig.16B)

Probenecid competitively ↓ (inhibits) the secretion of Ampicillin and amoxicillin → ↑ (increases) the concentration of those drugs in the plasma, which is very much useful in the treatment of gonorrhoea. The high concentration of Ampicillin in the plasma cannot be achieved for the treatment of gonorrhoea by giving high oral dose, since it produces intolerable diarrhoea). So, Ampicillin (in normal therapeutic dose) is combined with Probenecid only for the treatment of gonorrhoea.

Therapeutic index

Therapeutic Index is the ratio between ED_{50} (the dose effective in 50% of the animal) and LD_{50} (the dose effective to kill 50% of the animal)

$$\text{Therapeutic Index} = \frac{LD_{50}}{ED_{50}}$$

LD = Lethal dose
ED = Effective dose
Clinical significance
The higher the therapeutic index, the safer is the drug.
The drug is considered to be safe if the T/I is above 1.

Digoxin, lithium are having low margin of safety and hence they are highly toxic, if there is a slight increase in plasma concentration.

CHAPTER 12

Pharmacodynamic - Mechanism of action of drugs

PHARMACODDYNAMIC (dynamic=power) is the power of the drugs, which include the pharmacological actions and the mechanism of actions of drugs (how drugs act?).

Types of pharmacological actions:

1. Stimulant action: Stimulation of particular tissues/organs; CNS stimulants, cardiac stimulants to produce excess action.

2. Depressant action: Inhibition of particular tissues/organs: CNS depressants, cardiac depressants etc., to produce less action.

3. Irritant action: Irritation of particular tissues/organs → Bisacodyl and Senna produce purgative action by their irritant action on intestinal smooth muscles.

4. Counterirritant action: Turpentine oil, menthol (Iodex).They are used in headache and muscular pain. They irritate the skin. The irritant impulses and pain impulses are carried by the same nerve fibre. Here the irritant impulse will compete with the pain impulse and prevent the pain impulse passing through the nerve and the individuals feel skin irritation and forget the pain impulse.

5. Action on microbes: There is static action or cidal action on microbes. Static means drugs that inhibit the growth and multiplication of microbes. Cidal action means that drugs kill the microbes.

6. By replacement action: In adrenal insufficiency (Hydrocortisone), Insulin in Type-1 Diabetes Mellitus.

7. By modifying the immune status: Immunosuppressive drugs in autoimmune diseases.

Mechanism of actions of DRUGS (HOW DRUGS ACT?)

1. **Physical properties :** Drugs may act due to their physical properties: Osmotic diuretic- Mannitol, Osmotic purgative- Magnesium sulphate (ref: diuretics and purgatives)

2. **Reduction in surface tension :** Reduce surface tension of the bacterial cell membrane and cause damage to bacterial cell membrane and bacteria will die(Cetrimide- Antiseptic action)
3. **Chemical properties :**
   i) Neutralization : Antacids neutralize the acid and useful in hyperacidity.
   ii) By chelation : Chelating agent in heavy metal poisoning (ref: chelating agents)
4. **Mechanism of action** through enzyme: i) by inhibiting the enzymes – Anticholinesterases inhibit cholinesterase enzymre and potentiate the action of ACh in the body. ii) Allopurinol inhibits the enzyme xanthine oxidase and inhibit the synthesis of uric acid (used in gout)
   iii) ACE (Angiotensin Converting Enzyme) inhibitors inhibit the enzyme ACE and produce fall in BP and they are used in hypertension (ref: Antihypertensive drugs)
5. **Radio isotopes:** ^{131}I destroys thyroid gland and is useful in throtoxicosis. (Ref: Radioactive Iodine)
6. **Radio opacity:** It is also called as contrast media, used for diagnostic purpose by visualizing the blood vessels (by organic Iodide), GIT (by Barium meal) etc.,
7. **Adsorption** is, the surface absorption. i) Kaolin adsorbs bacteria and toxin, used in non- specific diarrhoea.
8. **Demulcent:** Pharyngeal demulcent act by soothening the pharynx and used in cough.
9. **Electrical charge:** Heparin by its strong electro negative charge combines with clotting factors with strong electro positive charge and neutralize (inhibit) them to produce anticoagulant action.
10. **Through receptors:** Receptor mechanism is very important, because most of the drugs act through their respective receptors. The drugs stimulate /inhibit the receptors and produce pharmacological actions.

Receptor is a macromolecular, active site present on the cell membrane or intracellularly. The receptors are specific in binding the drug. The drug and receptor are considered as 'lock' and 'key'. One particular key only opens the particular lock. Likewise, one particular drug can combine only with particular receptors (ACh-muscaranic and nicotinic receptors, Insulin with Insulin receptor, Glucocorticoids with glucocorticoid receptors).

- Receptor proteins are synthesized by the cells
- Receptors have definite life span, after which the receptors are degraded and new receptors are synthesized by the cells.
- Receptors are present on the cell membrane, in the cytoplasm or in the nucleus.

Functions of receptors:

1. Recognition and binding of ligand

2. Propagation of message

For the above functions, the receptor has two functional domains (sites)
1. A ligand binding domain – the site to bind the drug molecule (affinity of the drug)

2. An effector domain – which undergoes a change to propagate the message (intrinsic activity of the drug)

Drug + receptor → drug receptor complex →pharmacological action

There are thousands of receptors present in the body.

Example of receptors: Muscaranic receptors, Nicotinic receptors, α receptors, β receptors etc.,

Affinity: The ability of the drug to bind with the receptor to form drug-receptor complex. Like key (drug) enters into key hole (receptor) of the lock.

Intrinsic activity: The ability of the drug to stimulate the receptor. Like the key (drug) opens the lock (stimulate the receptor) after entering into the key hole (receptor) of the lock.

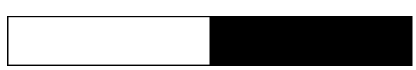
Drug + Receptor → DR complex → Pharmacological actions

Agonist: is a drug which has got both affinity towards the receptor and intrinsic activity (stimulate the receptor). Example: ACh, Adrenaline, Histamine etc.,

A	IA
Affinity	Intrinsic activity

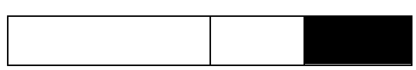
Antagonist: is a drug which has got only affinity to the receptor but no intrinsic activity.

Example: Atropine, α - adrenergic blockers, β - adrenergic blockers etc.,



Only Affinity No intrinsic activity

Partial agonist/antagonist: is a drug which has got affinity but has got submaximal intrinsic activity. Example: Pentazocine.



Affinity Submaximal intrinsic activity

Up regulation of receptor: The number of receptors are increased. Sudden withdrawal of β adrenergic blockers, increases the number of receptors causes an exaggerated response to agonist (rebound hypertension, exaggerated angina pectoris).

Down regulation of receptors: Due to repeated administration of an agonist, there is reduced response for the same dose. This may be due to less number of receptors are available for action. This is termed as 'tolerance' Example : GTN (Glyceryl Tri Nitrate), Hypnotics, etc., produced tolerance.

Drug+ Receptor complex → Drug Receptor complex → stimulate receptor → stimulate second messenger → affect various enzymes → transport of ions across cell membrane. If Na+ enters into the cell,then there will be stimulant action. If Cl^{--} enters into the cell, then there will be inhibitory action.

Receptor mediated mechanism are of four types: (Fig.17A, 17B)

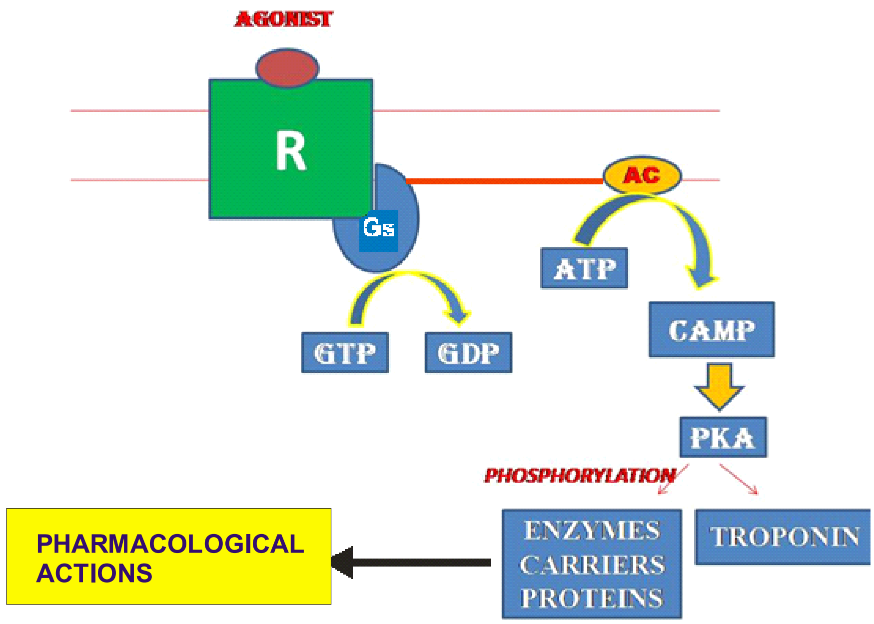
1. Ion channel receptors.
2. G-protein coupled receptors.
3. Enzyme kinase linked receptor
4. Enzyme as receptor.

1. Ion channel receptor: These receptors are present on the cell membrane and are coupled directly to an ion channel (also known as ligand gated ion channel) open only when the receptor is occupied by an agonist (Ca++, Na+, K+, Cl-) Channel blockers act by closing the channels, blocking the ion movement and produced antagonist action to the agonist.

2. G-protein coupled receptors (Fig.17A): These are membrane bound receptors which are coupled to the effector system (enzyme/channel) through GTP binding proteins called G-protein
Examples: Muscarinic receptor, adrenergic receptor, dopaminergic receptor etc.,
Gs = stimulatory, stimulate adenylyl cyclase.
$G_{i=}$ inhibitory, inhibits adenylyl cyclase.
G_o= inhibits Ca++ channel
Through adenylyl cyclase, c-AMP path way:

Agonist occupies and stimulates receptors
↓
Activation of G-protein
↓
activation of adenylyl cyclise
↓
accumulation of intracellular second messenger, c-AMP
↓
stimulate protein kinase
↓
alter the functions of many enzymes, ion channels, transporters
↓
increased contractility of heart, impulse generation, relaxation of smooth muscles etc.,

Fig.17A G-Protein mediated mechanism of drugs



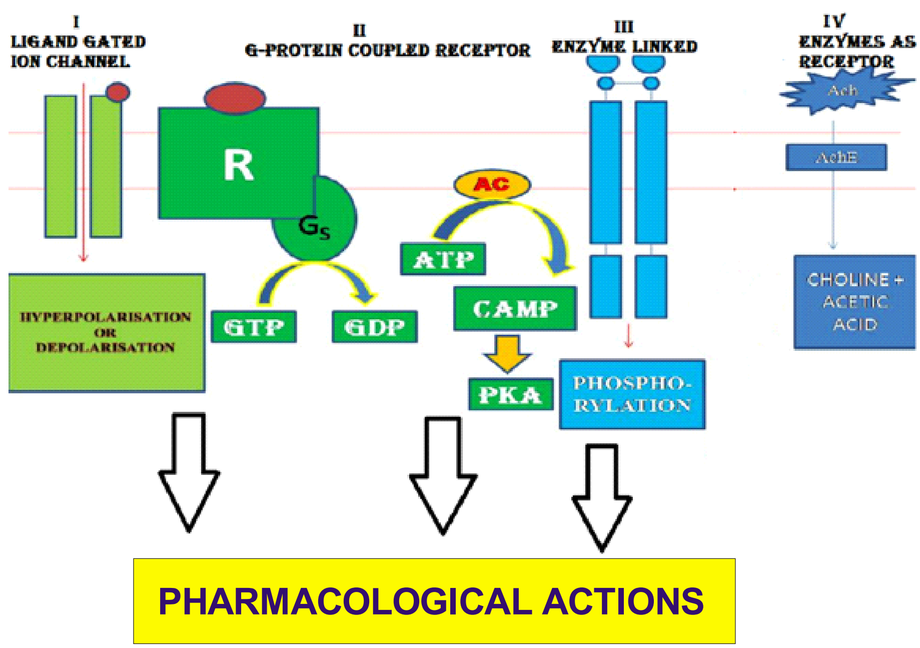


Fig.17B Receptors mediated mechanism of drugs

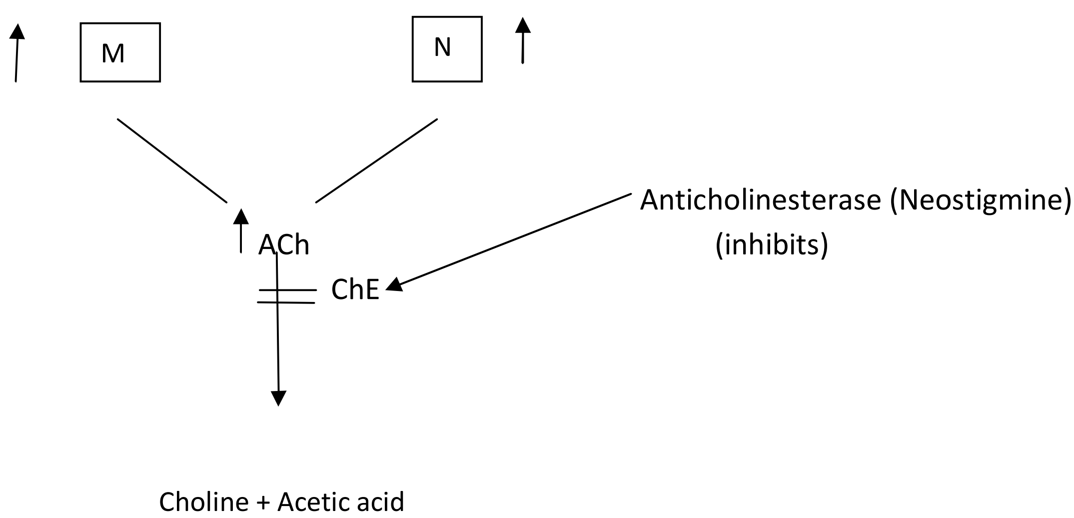
3. Enzyme kinase linked receptor (Fig.17B): These receptors are directly linked to tyrosine kinase. These are the receptors that are ligand(agonist) activated transmembrane enzymes having catalytic activity.

Example: Insulin receptor.

Insulin binds with receptor → stimulate tyrosine kinase → responsible for various cellular effects

4. Some enzymes act as receptor for drug and endogenous substrate. (Fig.17-B/17-C)

Example: Cholinesterase is considered as receptor for endogenous substrate, ACh. ACh occupies the receptor in the enzyme and degraded into choline and acetic acid. Anticholinesterase like Neostigmine inhibits the enzyme and prevents the degradation of ACh and hence increases the concentration of ACh at muscarinic and nicotinic sites in the body to produce muscarinic and nicotinic actions.



ChE – Cholinesterase

Fig.17C Enzyme acts as receptors

CHAPTER 13

Fixed dose drug combination

The fixed dose drug combination is, the combination of two different drugs in a single pharmaceutical formulation.

As a rule, if two drugs to be combined in a single pharmaceutical formulation, they should have approximately same plasma half life.

1. Cotrimoxazole : It is the combination of Sulfamethoxazole (plasma half life is 10 hrs) and Trimethoprime (plasma half life is 11 hrs)
2. L-dopa(plasma half life is 1.7 hrs) and Carbidopa (Plasma half life is 2 hrs)
3. Augmentin : Amoxicillin and clavulanic acid

The examples of Fixed-Dose drugs combination

(1) Sulfamethoxazole + Trimethoprim (cotrimoxazole)
400 mg + 80 mg
800 mg + 160 mg (DS) Double strength

(2) Levo dopa + Carbidopa (Syndopa)
250 mg + 25 mg
100 mg + 10 mg

(3) Amoxacilin + Clavulamic acid (Augmentin)
250 mg + 125 mg

(4) Neostigmine + Atropine in the treatment of myasthenia gravis
15 mg + 1 mg

The ratio of the doses depends on the volume of distribution of the drug.

Advantages of the combination

1. Patience's compliance is good
2. Enhanced effect of the combination (Ref: Cotrimoxazole)
3. Reduced side effect (Neostigmine and atropine)
4. Increased bioavailability (Ref: L-dopa)

Disadvantages of the combination:

1. It becomes difficult to confirm the toxicity is due to which drug.
2. If desired/needed, it is very difficult to alter the dose of individual drug

Thus, the therapeutic aim should be clear that the patient is in need of that combination

CHAPTER 14 Factors modify the drug effects

FACTORS MODIFYING THE DRUG EFFECTS:

There are many factors modify the effects of drugs either qualitatively or quantitatively.

First you write the factors and then explain.

1. Age
2. Sex
3. Body weight/body surface area
4. Route of administration of drugs
5. Time and place of administration of drug
6. Combination with other drugs
7. Tolerance and tachyphylaxis
8. Pathological states (diseases)
9. Pharmacogenetics
10. Teratogenicity
11. Substance abuse.
12. Drug interaction
13. Drug resistance

1. Age: The adult dose in children will produce toxic effect. The dose for a child is to be reduced and calculated as follows:

   i) Young's formula: Child's dose $= \frac{\text{Age in years}}{\text{Age+12}}$ X Adult dose

   ii) Dilling's formula: Child's dose $= \frac{\text{Age in years}}{20}$ X Adult dose

2. Body weight and BSA (Body Surface Area): At the same age, there may be lean or fatty children. So this calculation is somewhat dependable.

$$\text{Child's dose} = \frac{\text{Weight of child (lb)}}{150} \text{ X Adult dose}$$

3. Sex: There is variation in drug actions in men and women- Alpha methyl dopa, clonidine will cause loss of libido in men. Female oral contraceptives are effective only in females. α-adrenergic blockers produce impotence only in male.

4. Route of administration of drug: Change of ROA (Route of Administration), will change the effects of drugs either qualitatively or quantitatively.

   Parenteral administration will produce more potent action than that of the oral for the same dose (quantitative change).
   Magnesium sulphate – oral – purgative | qualitative change
   Magnesium sulphate -- parenteral-CNS depressant | ”

5. Time and place of administration: Hypnotics in noisy surroundings or in day time do not produce full effect.
6. Combination of drugs:
   i) Additive action: The combined effect of the drugs is equal to the addition of the individual drug effect. (1+1=2)

ADDITIVE EFFECT : Both act at the same site .

Ibuprofen ↓ Paracetamol ↓

INHIBITION OF PROSTAGLANDIN SYNTHESIS

↓ ↓

Analgesia + Anal gesia +

Analgesia ++

   ii) Synergism: The combined effect of the drugs is more than the addition of the individual effect of drugs (1+1= >2)

SYNERGISTIC EFFECT : Both act at different sites.

Sulphamethoxazole → Bacteriostatic, Limited Antibacterial Spectrum, +

Trimethoprim → Bacteriostatic, Limited Antibacterial Spectrum, +

Sulphamethoxazole + Trimethoprim → Bacteriocidal, Widened Antibacterial spectrum, +++

iii) Potentiation: The combined effect of the drugs is more than the addition of the individual effect of drugs. But here one drug is pharmacologically inert. (1+0=>2)

POTENTIATION : (Ref: Fig: Mechanism of action of Anti-cholinesterases)

Ach	Neostigmine	Ach + Neostigmine
↓	↓	↓
Skeletal Muscle Contraction	No Action (Pharmacologically inert)	Sk. Muscle Contraction (Neostigmine potentiates the action of Ach)
+	0	+++

iv) Antagonism

If the combined effect of two drugs is less than that of the sum of the effects of two individual drugs, then it is called as drug antagonism.

There are 4 mechanisms by which one drug may oppose the action of another.

1. Chemical antagonism
2. Physiological antagonism
3. Biological or pharmacokinetic antagonism
4. Pharmacological (Pharmacodynamic) antagonism

I. Competitive antagonism

i) Reversible (equilibrium)

ii) Irreversible (non-equilibrium)

II. Non-competitive antagonism

1. Chemical antagonism: One drug will antagonize the effect of another drug by chemical reaction.

i). Antacid – alkalies (Aluminium hydroxide, Magnesium trisilicate) – neutralize the acid in the treatment of hyperacidity.

ii). Chelating agents – chelating agents combine with heavy metals to form non-toxic soluble complex.

2. Physiological antagonism: Two drugs produce opposite effect on the same physiological system acting at **different** receptors

Example:

i). Histamine acts on H_1 receptor in the blood vessels which lead to vasodilatation, while Adrenaline acts on α_1 receptors on the blood vessels and cause vasoconstriction.

ii). CNS stimulants and CNS depressants

3. Biological or pharmacokinetic antagonism: One drug antagonizes the effect of another drug due to pharmacokinetic properties

Example:
i). Decreases absorption of one drug by another drug → Tetracyclines + Ca^{++} salts ii) Increased metabolism of one drug by another drug → reduce the efficacy (Rifampicin (Enzyme inducer) + Warfarin). The enzyme inducer reduce the anticoagulant effect of warfarin.

4. Pharmacological antagonism (Pharmacodynamic antagonism) – antagonism between two drugs by acting on the **same** receptor.
i) Reversible competitive → ACh + Atropine - antagonize each other by acting on muscarinic receptor, depending upon the concentrations.
→ Morphine + Naloxone - antagonize each
other by acting on μ receptors
ii). Irreversible competitive → antagonist binds to the receptor strongly by covalent bond and cannot be easily replaced by agonist, even in higher concentration of agonist.
Adrenaline + Phenoxybenzamine on α_1 receptor.

7. Tolerance and Tachyphylaxis: Reduced response to the normal dose of the drug due to repeated administration of that drug.

Types of tolerance:

1. Natural tolerance – Black races tolerant to mydriatics
2. Acquired tolerance(common)-tolerance due to repeated administration of drugs
   - i) Pharmacokinetic tolerance: due to pharmacokinetic properties (reduced absorption, increased metabolism, increased excretion etc.,)
   - ii) Pharmacodynamic properties: The tissue at the site of action is less responsive to the normal dose of a drug (Alcohol, Barbiturates, opioids etc.,)
   - iii) Cross tolerance: Tolerance among the drugs with related chemical structure (Example : Benzodiazepines). If the individual is tolerant to one drug in the BDZ group, he will be tolerant to all other drugs in that group.
   - iv) Tachyphylaxis: Acute tolerance (tolerance develops within hours)- due to the down regulation of receptors or due to the exhaustion of storage, which is released by the drug for action. Example : Ephedrine, Amphetamine

8. Pathological states (diseases): In liver diseases and in hypothyroidism, the metabolism of drugs is reduced and the toxicity of many drugs increased.

9. Genetic factor

Pharmacogenetic : The effects of the drugs vary from individual to individual due to variation in genetic materials in the body. Pharmacogenetic deals with the study of the variation in the effects of drugs due to genetic factors variation (genetically determined abnormal responses to drugs)

Example

(1) Deficiency of G6PDH (Glucose 6-Phosphate Dehydrogenase) - G6PDH is essential for the integration of cell wall of RBC. If there is deficiency of Glucose 6-Phosphate Dehydrogenase due to genetic factor, the cell wall of RBC becomes weak and the RBC will burst which will lead to haemolysis. Primaquin, Dapsone inhibit G6PDH. These drugs will easily produce haemolysis (anaemia) in the individual having deficient G6PDH. These drugs are also contraindicated in pregnancy, because in the foetus there is deficiency of G6PDH. So there will be haemolysis in foetus.
(2) Atypical pseudocholinesterase: Pseudocholinesterase degrades succinylcholine in the body. Atypical pseudocholinesterase is formed due to genetic variation in some individual. The Atypical pseudocholinesterase is not capable of degrading succinylcholine. Hence the concentration of succinylcholine is increased in plasma and lead to toxicity like prolonged apnea.
(3) Rapid and slow acetylator status: The acetylation enzyme degrades INH. In slow acetylator the INH produces toxicity like peripheral neuritis. In fast acetylator the therapeutic effect of INH is reduced.
(4) Acute intermittent porphyria : precipitated by enzyme inducers is due to genetic defect, which increase porphyrin synthesis. There will be accumulation of porphyrin, which is called as porphyria, characterized by neurological, gastrointestinal and behavioural abnormalities.
(5) Pharmacogenomic : Ref. Gene therapy

10. Teratogenicity (Ref : Adverse effects of drugs)
11. Substance dependence

Substance dependence will affect the effects of drugs. Some substances produce euphoria (pleasurable effects or feeling of well being) and hence some individual would like to experienc that effect (not on medical ground), will start taking the drug repeatedly. The repeated use of that particular substance will lead to

dependence of that substance in that individual. Example: coffee, cigarette, LSD, marihuana, alcohol etc.,
Psychological dependence: If any individual depends on a particular substance (not on medical ground) psychologically (not compulsorily) is called psychological dependence. Even if he stops taking that substance, there won't be any harm to that individual.
Physical dependence: On the contrary to psychological dependence, the individual depends on the substance compulsorily, without which he will experience some unwanted (harmful) effects like withdrawal syndromes. The body undergoes physiological changes to adapt itself to the continued presence of the drug in the body. Stopping of the drug will lead to rebound increase of the physiological changes, which the individual experience as withdrawal syndromes (irritation, palpitation, sweating, tremors, dysphoria, etc.,) like that of sudden withdrawal of β-adrenergic blockers or sudden withdrawal of anti-epileptic drugs will lead to rebound increase in epilepsy symptoms called as status epilepticus.
Example: Opioids, barbiturates, alcohol in heavy use – (severe)
And overuse of LSD, marihuana – (mild) withdrawal syndromes are seen.

Substance abuse is misuse of the substances for pleasurable purpose (not on medical ground)

12. Drug interaction (ref: drug interactions)
13. Drug resistance : Many organisms develop resistance to drugs due to repeated administration of drugs (ref: chemotherapy-drug resistance)

CHAPTER 15 Adverse drug effects

Adverse Drug effects:

Adverse effects of a drug is unwanted pharmacological actions in therapeutic or in over dose.

They are of two types

TYPE – A –PREDICTABLE	TYPE B -UNPREDICTABLE
Insulin-(hypoglycaemia)	(allergy, idiosyncrasy)
(drug related)	(patients related)

Type A Predictable:

1. Side effects are unwanted effects of a drug in THERAPEUTIC DOSE
2. Toxic effects are unwanted effects of a drug in OVER DOSE
3. Poisoning means that a drug endangers the life by affecting the vital functions like respiration and BP.
4. Drug intolerance: Some persons are hyperactive to a drug (Chloroquine in therapeutic dose will produce nausea and vomiting But in some it produces excess vomiting for the same therapeutic dose)
5. Teratogenicity: The drug is capable of producing foetal abnormalities, when given to pregnant women is called 'teratogenicity'

Possible mechanism of teratogenicity:

i) direct effect on differentiation of foetal tissues (Vit A analogue, Isotretinoin).

ii) they interfere with placental oxygenation or supply of nutrients in the foetal tissues.

iii) the drugs may act directly on some specific foetal organs to produce their damage (antithyroid drugs will produce hypothyroidism in foetus). Folic acid is to be given to minimise the teratogenic effect.

The damage of foetus depends upon at which stage of development the drug is given to pregnant women.

1. Fertilization and implantation (from conception to 17 days)- failure of pregnancy, which is often unnoticed.
2. Organogenesis (18^{th} day to 55^{th} day of gestation)- It is the most vulnerable period, where deformities are produced.
3. Growth and development (56^{th} day onwards)-The developmental and functional abnormalities can occur in this period (ACE inhibitors can cause hyperplasia of organs, specially lungs and kidneys. NSAIDs (Non Steroidal Anti Inflammatory Drug) will cause premature closure of ductus arteriosus in the foetus.

Some drugs cause abnormalities in foetus when the drugs are given to pregnant women.

1. Thalidomide – phocomelia (absence of limbs)
2. Phenytoin – cleft palate
3. Antithyroid drugs – Foetal Hypothyroidism
4. Tetracyclines – abnormalities in bone and teeth
5. Morphine – respiratory depression in foetus
6. Chloramphenicol – Gray baby syndrome

Example of some safe drugs in pregnancy:

1. Insulin in diabetes mellitus
2. Heparin as anticoagulant
3. Pethidine as abstetric analgesia
4. G^{+ve} infection – Ampicillin, Amoxicillin
5. In hypertension – α – Methyldopa, Hydralazine
6. In schizophrenia – Atypical antipsychotic drugs
7. In epilepsies – Newer antiepileptic drugs

6. Carcinogenicity and mutogenicity: carcinogenicity is the ability to produce cancer. Mutogenicity is the ability to mutate DNA and so GENE (alter the structure). This leads to alteration of particular protein structure → abnormalities, including development of cancer (Estrogen can cause breast cancer)

Drug → free radicals are released → reactive and damage different cellular structure including DNA molecule → mutation of gene → cancer. However, the carcinogenic effect of a drug is not proved completely. But sometimes the drugs have to be used (Estrogen in osteoporosis. To prevent the development of cancer due to Estrogen, it is combined with Progesterone.)

7. Photosensitivity: i) Phototoxic and ii) Photoallergy

8. Substance dependence (ref: substance abuse)

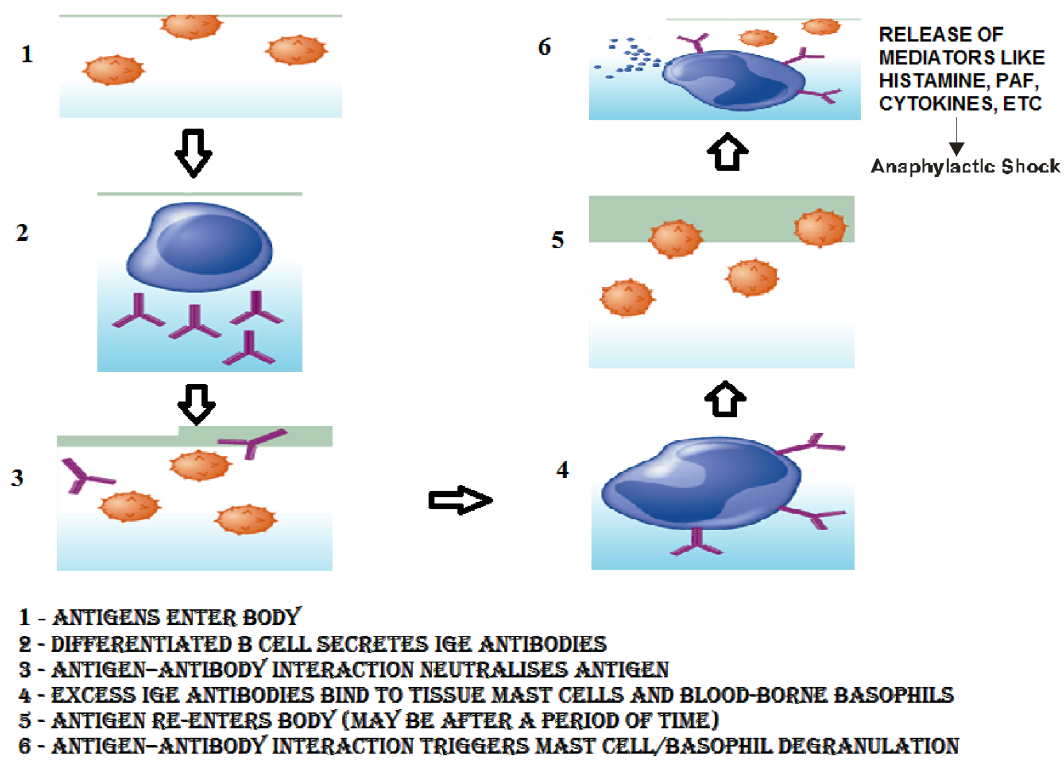
9. Drug withdrawal symptoms: (Acute adrenal insufficiency is due to sudden withdrawal of Glucocorticoids and unstable angina is due to sudden withdrawal of β adrenergic blockers)

Type b (unpredictable reactions)

I. Allergy: is a hypersensitive reaction to drugs.

1. Type I (immediate type reaction)- Example : Anaphylactic shock (Fig.18). Mechanism: The drug (allergen) sensitizes in the body → antibodies are produced → when the drug is introduced for the second time into the body → antigen and antibody reaction takes place on mast cells → degranulation of mast cells → release of mediators like Histamine, PAF, SRS-A, kinins etc., All are powerful bronchoconstrictors and vasodilators (fall in BP) → Anaphylactic shock and death.

Fig. 18 Type I Hypersensitivity Reaction



Treatment: Adrenaline, (IM inj. 0.5 ml of 1 in 1000) which is a powerful bronchodilator and vasoconstrictor (rise BP). This is the only drug simultaneously dilate the bronchi and rise BP and save the life.

2. Type II (Cytotoxic reaction)- haemolysis, thrombocytopenia, SLE (Systemic Lupus Erythematosus).
3. Type III (Arthus reaction): large antigen-antibody complexes → bind with a complement and precipitate on vascular endothelium and resulting in vasculitis (serum sickness, lymphadenopathy and joint pain are common clinical signs) Stevens-johnson syndrome is another manisfastation.
4. Type IV (delayed type hypersensitivity): Unlike the previous 3 types, it is 'T' cell mediated (CMI). Example: contact dermatitis

II. Idiosyncrasy: It is genetically determined abnormal reaction to a drug. Few drugs produce uncharacteristic reactions in some. (Example : Barbiturates in some individual cause excitement. Normally Barbiturates are CNS depressant). Quinidine in some causes cramps, purpura, asthma and vascsular collapse.

CHAPTER 16

Evidence Based Medicine (New drug development)

In the recent times new drugs are introduced in a rapid pace and the usage of older drugs becomes declining. The medical students must know how the newer drugs are developed? and also the various steps involved in the development of new drugs. Drug development has become a tedious, complex, prolonged and highly expensive procedure. Approximately new drug development from the initial stage takes 10 years and costs 500-1000 million US dollars.

Drug invention approaches :

1. Exploration of natural resources is still an important avenue for the new drug development. Opium, Cinchona, Digitalis, Belladonna, newer antimalarial Quinghaosu (artemisinin) are outstanding examples of plant sources. Animal sources such as Adrenaline, Thyroxine, Insulin, Antisera etc., and minerals like Iron, Calcium etc., are important medicines derived from natural resources.

2. Synthetic drugs 3. Molecular modelling 4. Biotechnology using DNA recombinant technology. 5. Gene therapy. These are the important new drug invention approaches adopted.

Preclinical Studies:

After identifying a suitable compound it is tested on animals to establish the pharmacological profile before introducing to human beings. Generally experiments are carried out in mouse, rat, guinea pig and then on larger animals. The following are the tests performed in animals screening tests, tests on isolated organs, animal models of human disease,toxicity tests etc., The aim of preclinical study is to determine the safety of the drug. Toxicity tests such as acute toxicity, subacute toxicity, chronic toxicity, reproductive and Teratogenicity, mutagenicity, carcinogenicity etc., are done.

EVIDENCE BASED MEDICINE:

Earlier, a new drug was introduced for treatment of diseases only based on experience by clinicians' observation Only herbals are used as medicine. But now a days, drugs are manufactured in large quantities. For that evidence based medicine replaced the experience based medicine. That means, a new drug is introduced into treatment only after confirmed by evidence based medicine.

Evidence based medicine is the process of systematically finding, evaluating and using contemporary research findings as the basis of clinical decisions. Therapeutic evaluation of a drug includes clinical studies which are basically clinical trials (testing the test drug on human) healthy human volunteer and diseased.

Clinical trials :

The suitable compound selected based on the animal study will be approved by the regulatory authorities as "investigational new drug" (IND) licence. This drug is formulated into suitable dosage form and undergoes the 4 phases of clinical trial. Standards for the design, ethics, conduct, monitoring, auditing, recording and analyzing data and reporting of clinical trials are laid down by Good Clinical Practice (GCP) guidelines by International Conference of Harmonization (ICH). National agencies such as ICMR in India also framed ethical guidelines for clinical trials. This provides accurate data and results which are credible. The rights of the subjects, integrity and confidentiality of trial subjects are protected as per the Helsinki Declaration of the World Medical Association.

First the inclusion and exclusions criteria to be decided depending upon the clinical trial drug

Exclusion criteria: 1. Generally the elderly persons, pregnant ladies, children, patients suffering from any other diseases

Others are included in the trial, depending upon the drug trial

There is every possibility of bias either by participants or by investigators in favour of or against the test drug. To minimise the bias, the following procedures are followed:

1. Randomization: The subjects are allocated to either group using a preselected random number table or computer programme, so that any subject has equal chance of being assigned to the test or the control group.
2. Blinding: This refers to concealment of the nature of treatment (test or control) from the subject (single blind), or both the subject and the investigator (double blind) For this purpose, the two medications should appear similar in appearance and taste. The randomized controlled double

blind trial is the most credible method of obtaining evidence of efficacy, safety or comparative value of treatment.

3. End point: The primary and secondary (if any) end points (cure, degree of improvement, symptom relief etc.) of the trial must be specified in advance.

CONSENT LETTER:

A letter of consent is written (in English or local language known to the volunteers) is a legal document, which binds both the parties (drug firm or clinicians who is handling clinical trial and volunteers, who is willing to participate in the drug trial)

The consent letter contains the following rules and regulations like,

1. The letter discusses the possible risks, side effects the volunteers encounter if he/she does agree to push through the clinical trial procedure.
2. Adequate compensation is to be given to volunteer in case of death (to the family) or any disability the trial causes.
3. The duration of validity of consent letter should be specific periods.

The consent letter should be signed by concerned parties before starting the clinical trials.

Following are the 4 phases of clinical trials with characteristics of each phase.

Phase I : Human Pharmacology and safety

The administration of drug in human is done by qualified clinical pharmacologist/ trained physician. There must be adequate facility to monitor vital functions and handle any drug related emergencies. Subjects are healthy volunteers. The number of patients are from 20-80. Starting from low dose increased to optimum effective dose. Safety, tolerability and adverse drug reactions and vital signs are monitored. Human pharmacokinetic parameters of the new drug is recorded.

Phase 0 : (microdosing) This new method is introduced to reduce time and cost of the drug development process.FDA also encouraging novel cost cutting approaches in new drug development. Microdosing human study is undertaken before phase -1 trial. Very low doses about 1/1000 of the estimated human dose administered to the healthy volunteers and pharmacokinetic studies done using sophisticated instruments such as Accelerated mass spectrometry (AMS) with radiolabelled drug or LC –Tandem mass spectrometry (LC-MS-MS).These studies yield very good pharmacokinetic information.

PHASE I	PHASE II	PHASE III	PHASE IV
First in Human (Healthy volunteers)	First in patient	Multi centre Trial	Post-marketing Surveillance
1-100 participants	50- 500 participants	Few hundred to few thousand participants	Many thousands of participants
Healthy volunteers Occasionally advanced or rare disease	Patient-subjects receiving experimental drug	Patient-subjects receiving experimental drug	Patients in treatment with approved drug
Open label	Randomized and controlled (Can be placebo-controlled) may be blinded	Randomized and controlled (Can be placebo-controlled)or uncontrolled, may be blinded	Open label
Safety and Tolerability	Efficacy and dose ranging	Confirm efficacy in larger population	Adverse events, compliance, drug-drug interactions
Months- 1 year	1-2 years	3-5 years	No fixed duration
U.S dollars 10 million	U.S. dollars 20 million	U.S.dollars 50-100 million	-No fixed rate
Success rate : 50%	50%	25-50%	--

Phase II: Therapeutic exploration and dose ranging

Conducted by physicians who are trained as clinical investigators. Involves 100-500 patients. Primary aim is to study the therapeutic efficacy, dose range and ceiling effect of the drug. Generally carried out in 2-4 centres. Mostly it is a controlled randomized study.

Phase III : Therapeutic confirmation and Comparision

These are randomized double blind comparative trials conducted in a large group of patients 500-3000 by several physicians in many cetres. The goal is to establish the efficacy of the drug in comparision with the existing therapy. Safety and tolerability also are also assessed in a bigger population. Indications and guidelines for therapeutic usage are formulated. "New drug application" (NDA) is submitted to licensing authority once it is accepted, approval will be given for marketing.

Phase IV : Post marketing surveillance

After the drug has been marketed and used in general population, through practicing physicians, data are collected regarding efficacy, acceptability, and adverse effects of the drug. Uncommon, idiosyncratic advesre reactions ,drug interactions are detected. Patterns of drug utilization and other indications of the drug may be found out in this phase. Special groups clinical trials such as children, elderly, pregnant/lactating women may be undertaken at this stage to establish the safety of the new drug.

CHAPTER 17 Therapeutic drug monitoring

THERAPEATIC DRUG MONITORING
(Monitoring of plasma concentration of drugs)

Measurement of plasma drug concentration for some drugs is needed to know about their efficacy and the patient's compliance. So that appropriate adjustments in the dosage regimen can be made.

For example : In grand mal epilepsy, the plasma concentration of anti-epileptic drugs should be measured periodically and the plasma concentration of that drug should be kept within the necessary range throughout the treatment.

The plasma concentration of valproic acid in grand mal epilepsy should be kept between 80-100 mg/ml to prevent the attack of epilepsy.

Therapeutic drug monitoring (TDM) is particularly useful in the following situations:

1. Drugs with low margin of safety
   Example: Digoxin, antiepileptic drugs, lithium
2. To check patient's compliance
   Example: Anti psychotic drugs, antidepressent drugs
3. In case of poisoning to know how much severe.
4. Potentially toxic drugs used in the presence of renal failure.
   Example: Aminoglycoside antibiotics.

Monitoring of plasma concentration is of no value for

1. Drugs with irreversible action – Anticholinesterase
2. 'Hit' and 'run' drugs like Gentamicin, Mono amino oxidase inhibitors.
3. Drugs activated in the body – Levo dopa
4. Drugs whose response is easily measurable – anti hypertensive, antidiabetic, oral anticoagulants etc.,