CHAPTER 1

GENERAL PHARMACOLOGY

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Ch.Id:-ASU/NSP/EB/HOP/2022/Ch-01

DOI: https://doi.org/10.52458/9789391842529.nsp2022.eb.asu.ch1

I. INTRODUCTION TO PHARMACOLOGY

Pharmacology: The study of drug interactions with living beings is referred to as pharmacology. It also provides information on the drug's history, source, physicochemical qualities, dosage forms, administration techniques, absorption, and distribution mechanism of action, biotransformation, excretion, clinical applications, and side effects.

Key Definitions

1. **Clinical Pharmacology:** Clinical trials are used to evaluate the pharmacological action of drugs, as well as the safe dosage range.
2. **Drugs:** Chemicals that modify the functioning of living creatures are known as drugs. Drugs are typically prescribed for disease diagnosis, prevention, control, or treatment.
3. Pharmacy is the science of identifying, selecting, preserving, standardising, synthesising, and distributing medicinal substances.
4. Pharmacodynamics is the study of the biological and therapeutic effects of drugs (i.e., "what they do to the body").
5. Pharmacokinetics is the study of a medication's absorption, distribution, metabolism, and excretion (ADME) ("what the body does to the drug").
6. **Pharmacotherapeutics:** It is concerned with the right selection and application of medications for illness prevention and therapy.
7. **Toxicology:** Toxicology is the study of toxins. Many medications can be poisonous in high dosages. Poisons are substances that have the ability to induce harmful, hazardous, or lethal symptoms in living things.
8. **Chemotherapy**: The action of medications on microbes, parasites, and cancer cells that live and reproduce in living creatures.
9. **Pharmacopoeia:** An official code including a selected list of established pharmaceuticals and medicinal preparations, as well as characteristics of their physical properties and tests for their identity, purity, and potency, such as the Indian Pharmacopoeia (I.P) and the British Pharmacopoeia (B.P) (B.P).

A. Drugs can be obtained from the following sources

1. Minerals- include liquid paraffin, magnesium sulphate, magnesium trisilicate, kaolin, and other minerals.
2. Animals- Insulin, thyroid extract, heparin, antitoxin serum, and so on.

3. Plants- Morphine, digoxin, atropine, castor oil, and other plants are examples.
4. Synthetic sources- Aspirin, sulphonamides, paracetamol, zidovudine, and other synthetic sources
5. Penicillin, streptomycin, and a variety of other antibiotics are used to treat microorganisms.
6. Genetic engineering: human insulin, growth hormone, and other hormones The bulk of medications currently utilised in therapeutics come from synthetic sources, despite the fact that they can come from any of the following sources.

II. PHARMACODYNAMICS

- This refers to how medications interact with target cells to change their function.
- Endogenous neurotransmitters, hormones, autacoids, and most medications work by attaching to specific receptors on the cell surface or inside the cell, such as adrenergic receptors, cholinoceptors, and insulin receptors.
- Aluminium hydroxide and magnesium trisilicate, which are used to treat peptic ulcer disease, work by neutralising gastric acid through a non-receptor method.

Lot of drugs are related to or contain chemical groups that are like naturally occurring chemicals and consist the ability to attach to a receptor, causing the receptor to respond or be blocked in one of two ways. A drug's affinity for a receptor is defined as its ability to fit onto that receptor. The capacity of a medicine to create an effect at a receptor is known as efficacy. Agonists have affinity & effectiveness, whereas antagonists have affinity but no efficacy or intrinsic activity.

An agonist is a substance that has the ability to stimulate a receptor and so mimics the endogenous transmitter. As soon as a drug binds to a receptor, it is referred to be an antagonist, and it inhibits the action of the endogenous transmitter (i.e. it will prevent the natural chemical from acting on the receptor). Since, most drug binding is reversible, the drug and the natural stimulation to the receptor will compete.

Chemical bonds (a) hydrogen bond (b) Vander Waals force (c) ionic bond (d) covalent bond are the forces that attract the drug to its receptor. The strongest link is covalent, and the drug-receptor combination is typically irreversible.

A. Mechanisms of Receptors and Non-Receptors:

The majority of medications work by connecting with a cellular component known as a receptor. Some medications work by causing basic physical or chemical processes that don't require the interaction of any receptors.

B. Site of Drug Action:

A Drug May Act:

1. On the surface of cell,for instance: digitalis, penicillin, catecholamines
2. Inside the cell, for instance: anti-cancer drugs, steroid hormones.
3. Extracellularly, for instance: osmotic diuretics, plasma expanders.

C. Dose Response Relationship:

The accuracy of the relationship between the dose and the response relies on the the drug employed and biological object under observation. When a logarithm of dose as abscissa and responses as ordinate are constructed graphically, the "S" shaped or sigmoid type curve is obtained. The lowest concentration of a drug which draws a response is minimal dose, and the largest concentration of a drug after which further increase in concentration will not change the response to the maximal dose.

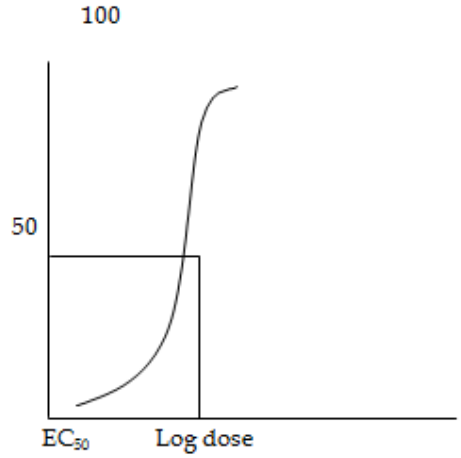


Fig 1.1: Log dose Response Relationship.

1. **Graded dose Effect:** As the dose administered to a single subject or tissue increases, the pharmacological response also increases in graded fashion up to ceiling effect.
    - It is used for characterization of the action of drugs. The concentration which is required to produce fifty percent of the maximum effect is referred as ED_{50} or EC_{50}.
2. **Quantal Dose Effect:** It is all or none response, the sensitive objects give response to small doses of a drug while some will be resistant and need very large doses.

The quantal Dose-Effect curve is often characterized by stating the median effective dose and the median lethal dose.

- **Median Lethal Dose or LD_{50}:** This is the dose (mg/kg), which would be expected to kill one half of a population of the same species and strain.
- **Median Effective Dose or ED_{50}:** This is the dose (mg/kg), which produces a desired response in 50% of test population.
- **Therapeutic Index:** It is an approximate assessment of the safety of the drug. It is the ratio of the median lethal dose and the median effective dose. Also known as Therapeutic Window or Safety.

$$\text{Therapeutic Index (T. I)} = \frac{LD_{50}}{ED_{50}}$$

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

Structural Activity Relationship

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

- Synthesis of new compounds with more specific actions and fewer adverse reactions
- Understanding the mechanism of drug action
- Synthesis of competitive antagonist

Slight change in the structure of the compound can alter the effect completely.

III. PHARMACOKINETICS

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

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

1. **Structure of biological membrane:** The outer surface of the cell covered by a very thin structure known as plasma membrane. It is consisted of lipid and protein molecules. The membrane proteins have many functions such as:

   i. Acting as carrier for transport of substances

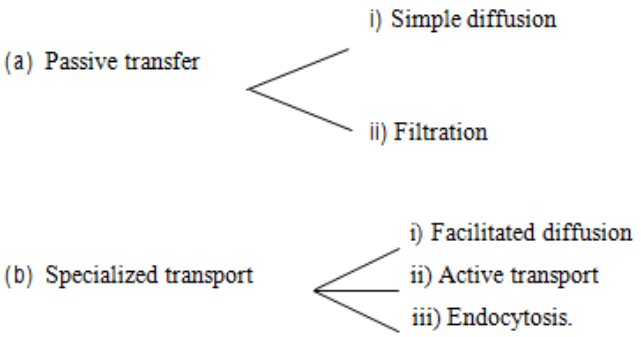
ii. Contributing structure to the membrane

iii. Acting as receptors

iv. Acting as enzyme

The plasma membrane is a semipermeable membrane allowing certain chemical substances to pass freely, for example, it allows water, glucose, etc. but it won't allow sucrose until it is converted into glucose and fructose.

2. Passage of Drug Across Membrane.



(a) Simple Diffusion:

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

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

(b) Facilitated Diffusion:

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

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

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

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

1. Routes of drug administration:

a) From the alimentary tract:

i. **Buccal cavity**: e.g. nitrates

ii. **Stomach:** e.g. aspirin, alcohol

iii. **Intestine:** e.g. most of non ionized and ionized drugs.

iv. **Rectum:** e.g. rectal suppositories, bisacodyl laxatives.

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

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

b) From the Parenteral Route:

i. **Intradermal:** This is given into the layers of the skin e.g. B.C.G. vaccine

ii. **Subcutaneous**: Non-irritant substances are given into subcutaneous tissue For example: insulin

iii. **Intramuscular:** Soluble substances, mild irritants, suspensions and colloids can be injected by this route. These injections can be given to deltoid or gluteal muscle. This route is one of the more common routes e.g. multivitamins, streptomycin, etc.

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

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

iv. **Intravenous:** Drugs directly given into a vein, produce rapid action, no need of absorption as they enter directly into blood, can be given as

bolus e.g. furosemide, morphine, dopamine or as continous infusion e.g. fluids during shock or dehydration.

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

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

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

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

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

c) **Transcutaneous Route**

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

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

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

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

d) **Topical/ Local Route:** The absorption through skin is a passive process. The absorption occurs more easily through the cell lining e.g. dusting powder, paste, lotion, drops, ointment, suppository for vagina and rectum.

e) **Inhalation:** Drugs may be administered as dry powders, and nebulized particles when sprayed as fine droplets get deposited over the mucous membrane producing local effects and may be absorbed for systemic effects e.g. salbutamol spray used in bronchial asthma and volatile general anaesthetics.

2. Bioavailability

It is the rate and amount of drug that is absorbed from a given dosage form and reaches the systemic circulation following non-vascular administration. When the drug is given IV, the bioavailability is 100%. It is important to know the manner in which a drug is absorbed. The route of administration largely determines the latent period

between administration and onset of action. Drugs given by mouth may be inactive for the following reasons:

a) Enzymatic degradation of polypeptides within the lumen of the gastrointestinal tract e.g. insulin, ACTH.
b) Poor absorption through gastrointestinal tract e.g. aminoglycoside antibiotic.
c) Inactivation by liver e.g. testosterone during first passage through the liver before it reaches systemic circulation.

3. Factors Affecting Drug Absorption and Bioavailability:

a) Physico-chemical properties of drug
b) Nature of the dosage form
c) Physiological factors
d) Pharmacogenetic factors
e) Disease states.

a) Physico-Chemical Properties of Drug:

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

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

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

Acidic drugs: rapidly absorbed from the stomach e.g. salicylates and barbiturates. **Basic drugs**: Not absorbed until they reach to the alkaline environment i.e. small intestine when administered orally e.g. pethidine and ephedrine.

b. Dosage Forms:

i. **Particle size:** Small particle size is important for drug absorption. Drugs given in a dispersed or emulsified state are absorbed better e.g. vitamin D and vitamin A.

ii. **Disintegration Time and Dissolution Rate:** The rate of break up of the tablet or capsule into the drug granules. Dissolution rate: The rate at which the drug goes into solution.

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

c. Physiological Factors:

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

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

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

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

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

d. **Pharmacogenetic factors:** Individual variations occur due to the genetically mediated reason in drug absorption and response.

e. **Disease states:** Absorption and first pass metabolism may be affected in conditions like malabsorption, thyrotoxicosis, achlorhydria and liver cirrhosis.

4. **Bioavailability Curves**

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

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

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

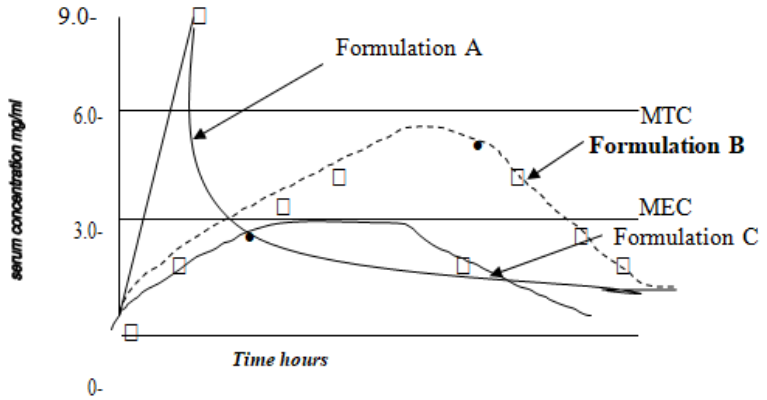


Fig 1.2: The plasma drug level curves following administration of three formulations (A, B and C) of the same basic drug.

MTC: Minimum toxic concentration

MEC: Minimum effective concentration

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

Formation B = Effect would last much longer and nontoxic

Formulation C = gives inadequate plasma level so therapeutically ineffective.

C. **Distribution of Drugs**

i. **Definition**: Penetration of a drug to the sites of action through the walls of blood vessels from the administered site after absorption is called drug distribution. Drugs distribute through various body fluid compartments

such as (a) plasma (b) interstitial fluid compartment (c) trans-cellular compartment.

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

Factors Determining the Rate of Distribution of Drugs

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

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

i) After I.V. administration plasma concentration falls sharply
ii) After oral administration plasma concentration rises and falls gradually.
iii) After sublingual administration plasma concentration rise sharply and falls gradually.

ISBN- 978-93-91842-52-9

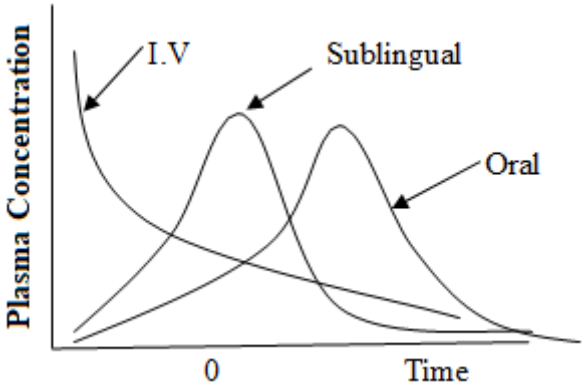


Fig 1.3: Plasma concentration of drug after different routes of administration.

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

4. **Physiological Barriers to Distribution**: There are some specialized barriers in the body due to which the drug will not be distributed uniformly in all the tissues. These barriers are:

    a) **Blood Brain Barrier (BBB)** through which thiopental sodium is easily crossed but not dopamine.

    b) **Placental barrier:** which allows non-ionized drugs with high lipid/water partition coefficient by a process of simple diffusion to the foetus e.g. alcohol, morphine.

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

D. Metabolism of Drugs:

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

Enzymes responsible for metabolism of drugs:

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

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

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

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

E. Excretion of drugs

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

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

Different routes of drug excretion

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

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

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

i) Glomerular filtration: It is a process, which depends on (1) the concentration of drug in the plasma (2) molecular size, shape and charge of drug (3) glomerular filtration rate. Only the drug which is not bound with the plasma proteins can

pass through glomerulus. All the drugs which have low molecular weight can pass through glomerulus e.g. digoxin, ethambutol, etc.In congestive cardiac failure, the glomerular filtration rate is reduced due to decrease in renal blood flow.

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

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

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

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

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

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

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

harmful effects in the baby such as ampicillin, aspirin, chlordiazepoxide, coffee, diazepam, furosemide, morphine, streptomycin etc.

Clearance of a drug

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

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

C_t = total clearance

C_h = hepatic clearance

C_r = Renal clearance

IV. THEORETICAL PHARMACOKINETICS

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

Half life: Half life ($t_1/_2$) of a drug is the time taken for the concentration of drug in the blood or plasma to decline to half of original value or the amount of drug in the body to be reduced by 50%. It has two phases i.e half-life of distribution and half-life of elimination. A half-life value can be readily determined for most drugs by administering a dose of the drug to a subject, taking blood samples at various time intervals and then assaying the samples., For example if a blood level of drug A is 8.6 mg/ml at 10 minutes and 4.3 mg/ml at 60 minutes, so the half – life of that drug is 50 minutes. In most of the cases the rate of disappearance of a drug from the body is reflected in the rate of lowering of its plasma concentration following a single intravenous dose, the plasma concentration of the drug is focused to fall exponentially. With drugs whose elimination is exponential, the biological half – life is independent of the dose, the route of administration and the plasma concentration. It depends on VD as well as on the metabolism and renal excretion of the drug.

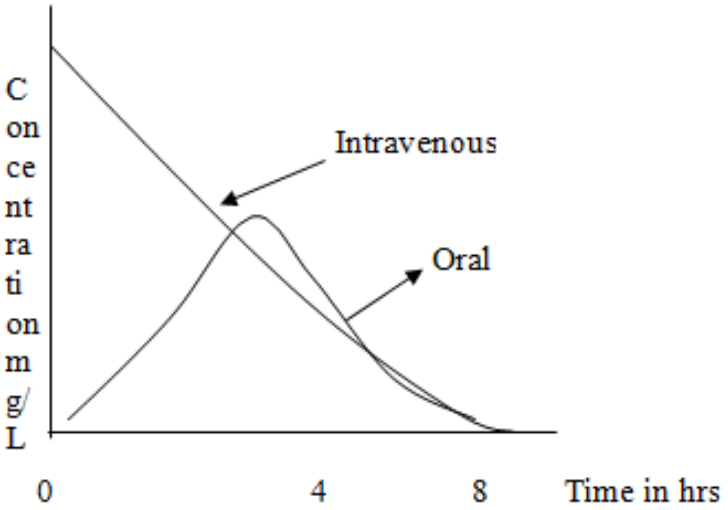


Fig 1.4: Exponential curves of plasma concentration following oral and intravenous drug administration.

Order of Kinetics

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

First Order

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

Zero Order Kinetic

It is independent of the amount of drug present at the particular sites of drug absorption or elimination. Few drugs follow this process e.g. ethanol, phenytoin. Here constant amount of the drug is eliminated in each equal interval of time. On repeated

administration of drug after certain stage it goes on accumulating in the body and leads to toxic reactions.

Steady State Plasma Concentration

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

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

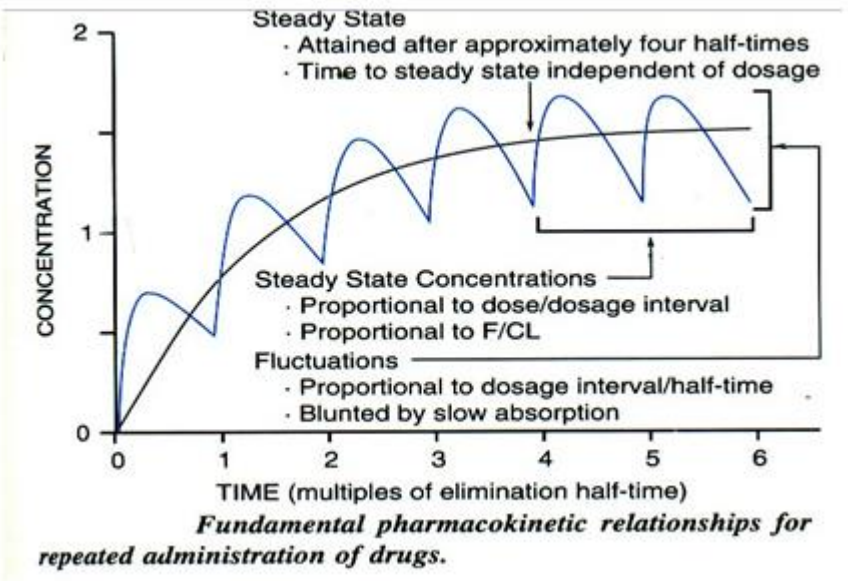


Fig 1.5: Steady state plasma concentration of a drug after repeated administrations.

For some drugs, the effects are difficult to measure, toxicity and lack of efficacy are both potential dangers, and/or the therapeutic window is narrow. In these circumstances doses must be adjusted carefully to a desired steady- state concentration by giving loading and maintenance doses. Loading dose: The loading dose is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly. Maintenance dose: To maintain the chosen steady-state or

target concentration, the rate of drug administration is adjusted such that the rate of input equals to rate of loss.

V. DRUG SAFETY AND EFFECTIVENESS

A. Factors Modifying the Dosage and Action of Drugs:

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

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

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

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

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

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

c) **Body Weight:** The average dose is mentioned either in terms of mg per kg body weight or as the total single dose for an adult weighing between 50-100kg. However, dose expressed in this fashion may not apply in cases of excessively obese individuals or those suffering from edema, or dehydration nutritional

factors can sometimes alter drug metabolizing capacity and this should be kept in mind in malnourished patients.

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

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

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

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

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

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

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

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

a) Using age of the child the dose will be

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

b) Using body weight of the child it will be

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

e) Disease state: Some antimicrobial agents penetrate the cerebrospinal fluid well across the normal meninges while other antimicrobials penetrate well only when the meninges are inflammed (meningitis) e.g. sulphonamides, metronidazole, chloramphenicol, isoniazid and rifampicin penetrate well through the normal

meninges and other antimicrobial agents like benzyl penicillin, ampicillin, tetracycline, streptomycin, gentamicin and cephalosporin penetrate only when the meninges are inflammed.

Acute or chronic liver diseases markedly modify the rate and extent of biotransformation of drugs. The t1/2 of chlordiazepoxide and diazepam in patients with liver cirrhosis is greatly increased with corresponding prolongation of their effects. Cardiac disease by limiting blood flow to the liver may impair disposition of those drugs whose biotransformation is flow limited e.g. imipramine, isoniazid, lignocaine, morphine and propranolol. Similarly renal and pulmonary diseases may modify the biotransformation of drugs like insulin or isoprenaline. Excretion of drug is impaired in chronic renal disease.

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

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

g) Drug Interactions: It is usual for patients to receive a number of drugs at the same time. It is a phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another drug(s). A drug interaction may result in beneficial or harmful effects and may be classified into:

a) Pharmaceutical Drug Interactions: Serious loss of potency can occur from incompatibility between an infusion fluid and a drug that is added to it. For example diazepam if added to infusion fluid there will be a precipitate formation loss of therapeutic effect.

b) Pharmacokinetic Drug Interactions

1) Interaction During Absorption: Drugs may interact in the gastrointestinal tract resulting in either decreased or increased absorption.

For example

Tetracycline, Calcium, Decreased absorption of tetracycline.

2) Interaction During Distribution: A drug which is extensively bound to plasma protein can be displaced from its binding sites by another drug or displacement from other tissue binding sites.

For example:

i. Sulfonamide can be displaced by salicylates from plasma proteins and it leads to sulfonamide toxicity.

ii. Quinidine displaces digoxin from binding sites in tissues and plasma and leads to digoxin toxicity.

3) Interactions During Biotransformation: This can be explained by two mechanisms:

i. Enzyme induction.

ii. Enzyme inhibition.

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

For example:

Warfarin (Anticoagulant), Barbiturate (Enzyme Inducer), Decreased Anticoagulation. Enzyme Inducers: Rifampicine, Phenytoin, Sulfonamides, etc.

(ii) Enzyme inhibition: By this the biotransformation of drugs is delayed and is a cause of increased intensity, duration of action and some times toxicity. For example: Warfarin, Metronidazole (enzyme inhibitor), Haemorrhage.

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

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

For example

Penicillin (antibiotic), Probenecid (antigout drug), and Increases the duration of action of penicillin (Both drugs excreted through tubular secretion).

C. Pharmacodynamic Interactions

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

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

i.e. A + B = AB

For example:

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

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

i.e. AB > A + B

For example: Trimethoprim+sulfamethoxazole

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

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

For example: Antagonism between acids and alkalis.

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

For example: Acetylcholine and atropine antagonism at muscarinic receptors.

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

For example: Acetylcholine and papaverine on smooth muscle. Acetyl choline and decamethonium on neuromuscular junction.

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

For example: Acetyl choline causes constriction where as adrenaline causes dilatation of pupil.

Importance of Drug Antagonism

1. Correcting adverse effects of drugs
2. Treating drug poisoning.

For example: Morphine with naloxone, organophosphate compounds with atropine.

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

h) Repeated Administration and Drug Cumulation:

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

To avoid cumulation.

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

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

i) Drug Tolerance:

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

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

For example: Ephedrine, Amphetamine and Nitroglycerine Which Produce Tachyphylaxis on Repeated Administration.

j) Emotional Factors.

For example: Placebo Response.

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

B. Adverse drug reactions:

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

For example: Hypotension following antihypertensive drugs. Hypoglycaemia following insulin.

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

The adverse effects are

1) Side effects
2) untoward effects
3) allergic reactions
4) idiosyncratic reactions
5) teratogenic effects.

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

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

2) Untoward Effects: Untoward effects develop with therapeutic dose of a drug. They are undesirable and if very severe, may necessitate the cessation of treatment. e.g: Diarrhoea with ampicillin and potassium loss with diuretics.

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

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

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

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

5) **Teratogenic effect:** Some drugs given in the first three months of pregnancy may cause congenital abnormalities and are said to be teratogenic. The best known example is thalidomide which results in early easily recognizable abnormalities such as absent or grossly abnormal limbs. Other drugs with teratogenic potential are androgens, steroids, anti convulsants, anti neoplastic drugs, cortisone, lithium, pencillamine, tricyclic antidepressants and warfarin.

V) DEVELOPMENT AND EVALUATION OF NEW DRUGS:

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

Scientists all over the world are in a continuous effort to develop new drugs although drug development is an extremely technical and enormously expensive operation. Among the contributors to new drug development, pharmacologists are more concerned in evaluating "new chemical entities" (NCE). Synthesis and evaluation of thousands of NCEs are usually necessary for new drugs to be introduced in the market. Research and development of new drugs have been done under strict government regulations which have greatly increased over the past couple of decades.

Drug development comprises of two steps.

a) Preclinical Development
b) Clinical Development

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

i. Random synthesis
ii. Structure activity relationship (SAR)
iii. Biochemical and pharmacological insight and

iv. Chance finding.

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

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

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

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

a) Pharmaceutical study covers stability of formulation and compatibility of the NCEs with other tablet or infusion ingredients.
b) Pharmacological study includes further chronic toxicological study in animal, initially animal metabolic and pharmacokinetic study. When studies in animals predict that a NCE may be useful medicine i.e. effective and safe in relation to its benefits, then the time has come to put it to the test in man i.e. clinical trial.
c) Studies on human or Clinical Trial:

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

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

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

Phase - III: Full scale evaluation of treatment comparing it with standard treatment is done in this phase. It involves randomised control trials on 250 to 2000 patients and is done in multiple centres. Information from all studies are received by the "Committee of

safety of medicines" (CSM). If the drug is satisfied by the CSM, the product license is issued then the drug is marketed.

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

Questions

i. Explain the various routes of administration of drug and write down the merits and demerits of parenteral administration route..

ii. What do you mean by bio-availability and explain the different factors that affect drug absorption.

iii. Define the following:
   a. Half-life of a drug
   b. Steady state plasma concentration
   c. Adverse drug reactions

iv. Describe about the factors that modify drug action.

v. What are the different types of drug interactions?

ISBN- 978-93-91842-52-9