UNIT 2 GENERAL ACTION OF DRUGS-II

Structure

2.1 INTRODUCTION

In this unit, you will study about the various processes involved in the interaction between an externally administered substance and the human body. These processes have been divided into two categories: Pharmacodynamics, which pertains to the physiological and biochemical alterations produced in the body by the drug, and pharmacokinetics, which pertains with the was in which the body handles the drug.

Objectives

After studying this unit, you should be able to:

- explain the principles of pharmacodynamics and pharmacokinetics;
- the factors that affect drug action;
- explain the rational of fixed dose combination;
- the factors affecting dose-plasma concentration; and
- explain the precautions required during dose selection for an individual.

2.2 PHARMACODYNAMICS

Pharmacodynamics is the study of drug effects (biochemical and physiological) and their mechanism of action. When the drug reaches its site of action it has a pharmacological effect which may be responsible for an eventual therapeutic effect and also responsible for the adverse effects as well as some other effects which may be of no clinical importance.

2.2.1 Sites and Mechanism of Drug Action

The site of drug action means where a drug acts and mechanism means how the drug acts. Drug which act only at the site of application (i.e. localized region) are termed as local or topically acting drugs for example, ointments, paste, creams and certain other local preparations used externally produce only local effect. The local anaesthetics like lignocaine, procaine produce anaesthesia (local) in a localized region only.

The second type of action is systemic or general actions which produce their action after absorption, for example, general anaesthetics act centrally after absorption and often drugs like antibiotics, antacids, and so many other drugs acts systemically.

2.2.2 Effects of Drug Action

The drug may produce their effects by:

i) **Stimulation**

Stimulation is an increase in the selective activity of specialized cells, which increases the secretion from a gland.

ii) **Depression**

It is a reduction/decrease in the activity of specialized cells. For example barbiturates depress central nervous system.

iii) **Irritation**

It is the effect of drugs on the growth, nutrition and morphology of living tissues which induce a gross change in cellular function.

iv) **Replacement**

It includes certain drugs, which are used to replace some missing endogenous component of the body or when the production of endogenous components is reduced.

v) **Bactericidal and Cytotoxic Action**

The *bacteriostatic* activity which is inhibition of growth and multiplication of bacteria and *bactericidal* activity, which is bacterial death, is induced by certain types of antibiotics. Cytotoxic action is selective for invading cancer cells and altering them without affecting the host cells.

2.2.3 Factors Modifying Drug Action

The drug action can be modified either quantitatively (in which the action of drug is increased or decreased) or qualitatively (in which the type of response is altered). The factors are:

i) **Age:** In newborn infants, the renal filtration rate is immature, which takes 5 to 7 months to mature. Also, the hepatic drug metabolism capacity is also inadequate (that is why chloramphenicol can produce '*grey baby syndrome*'), and due to the higher permeability of blood brain barrier, certain drugs attain high concentration in the Central Nervous System.

The dose of a drug for children is often calculated from adult dose.

$$\text{Child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{Adult dose}$$

Children are more susceptible to special adverse effects of drugs and in the elderly, the renal function is on decline and doses of drugs have to be reduced.

ii) **Body size/weight:** The average adult dose refers to individuals of medium body build. For obese or lean individuals, doses of drug may be calculated by the formula:

$$\text{Adult dose} \times \frac{\text{Weight (kg)}}{70}$$

Dose can be calculated more accurately by body surface area (BSA).

$$\text{Individual dose} = \frac{\text{BSA(m)}^2}{1.7} \times \text{Average adult dose}$$

iii) **Sex:** Females require lower dose than males. Drugs given during pregnancy can affect the fetus. There are certain physiological changes that take place during pregnancy, which can alter the drug disposal.

iv) **Species and racial difference:** In animal species, rabbits are resistant to atropine and rat and mice are resistant to digitalis.

Among human beings, blacks require higher and Mongols require lower concentration of atropine and ephedrine to dilate their pupils.

v) **Genetics:** In certain individuals, the same dose may produce their effect 5-6 times more among others, which is due to their differing rate of drug metabolism.

vi) **Routes and time of administration:** The different routes of administration may affect the intensity of drug effect e.g. magnesium sulphate, when used orally acts as a purgative, in local application it relieves inflammation of wound or boil and when it is used intravenously it causes depression of central nervous system (CNS) and reduce seizures.

The time of administration can also affect drug response e.g. corticosteroids when taken in morning as single dose cause less adrenal-pituitary suppression.

vii) **Pathological conditions:** Several disease conditions also influence the drug disposal and action of drug. For example: bioavailability of drug (having first pass metabolism) is increased due to diminished liver function.

viii) **Tolerance:** Tolerance is a condition when there is a requirement of higher dose of a drug to produce a given response. **Tachyphylaxis** is the rapid development of tolerance in which there is a marked reduction in response even after repeated doses of a drug.

ix) **Drug resistance:** It is tolerance of microorganisms to inhibitory action of antimicrobials e.g. staphylococci to penicillin.

x) **Other drugs:** Drugs may modify the response to each other by pharmacokinetic or pharmacodynamic interaction between them.

SAQ 1

a) ________________ is the study of drug effects (biochemical and physiological) and their mechanism of action.

b) ___________________ is the rapid development of tolerance in which there is a marked reduction in response even after repeated doses of a drug.

c) Bioavailability of drug (having first pass metabolism) is ____________ in hepatic diseases.

d) ____________________ is tolerance of micro-organisms to inhibitory action of antimicrobials e.g. staphylococci to penicillin.

e) Define 'pharmacodynamics'.

2.2.4 Drug Receptors

The drug receptors are macromolecular sites which are situated on the surface or inside the effector cells with which specific agonist (ligand/drug) combines to produce its response. Antagonist prevents the action of an agonist on a receptor, but does not have any effect of its own (Fig. 2.1).

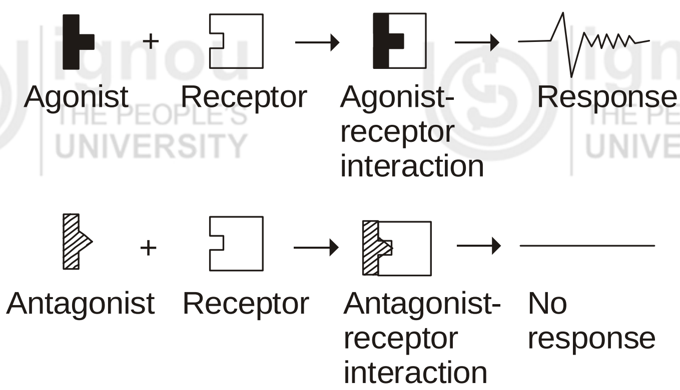

Fig.2.1: Drug-receptor interaction

The agonist completely fits (interact) with the receptor site to produce a pharmacological response and antagonist only partially fit with the receptor site and is unable to produce any pharmacological response, and also prevents the agonist from combining with the receptors.

The ability of a drug to get bound to a receptor is termed as the **'affinity of the drug'** for the receptor. The ability of the drug to produce a pharmacological response after its interaction with the receptor is known as **'intrinsic activity of the drug'**, it also determines the degree of receptor response. The agonists produce a maximal receptor response, partial agonists produce intermediate response and antagonists produce low, or no response.

2.2.5 Combined Effect of Drugs

Synergism

When two drugs are given simultaneously, and the action of one drug is increased by the other, they are treated as ***synergistic***. In the synergism, the drugs can have action in the same direction or when given alone, one may be inactive. Synergism can be additive or supradditive in nature.

Additive: When the effect of two drugs are in the same direction. For example when aspirin is combined with paracetamol the combined effect is analgesic/antipyretic.

Supradditive: In this the effect of combined therapy is greater than the individual effect of the one drug. For examples when sulfonamide and trimethoprim are combined for antibacterial action.

Drug Antagonism

Antagonism is when one drug decreases or inhibits the action of another. The antagonism may be ***physical*** in which the physical property of the drug can affect the absorption of another drug, ***chemical*** in which two drugs react chemically and form a biologically inactive compound or receptor antagonism, where one drug inhibits the binding of another drug with the receptor. On receptor basis, drug antagonism will be of two type's competitive and noncompetitive antagonism.

SAQ 2

a) In ______________ the effect of combined therapy is greater than the individual effect of the one drug.

b) What are receptors?

c) Define receptor antagonism.

2.3 PHARMACOKINETICS

Pharmacokinetics is the studies, which determines the rapidity and concentration of the drug in the body and its duration of appearance at the target organ, i.e. onset, time of peak action and duration of action and by these also determine the route(s) and frequency of administration of drug.

The bioavailability of any drug is defined as its rate and extent of absorption. This is mainly used to describe the biological availability of a drug from a preparation and is calculated/determined in terms of amount or rate of presence of drug in various body fluids like blood, urine etc.

The excretion of drugs has been known to take place through different routes like kidneys, skin, lungs and alimentary tract. Only few drugs are eliminated through skin and via lungs (only for volatile drugs like chloroform, ethyl alcohol, ether etc.). Drugs which are poorly absorbed are excreted in faeces. So kidneys serve as the primary and major organ for removal of most drugs, which is constituted by the microunits called 'nephron'.

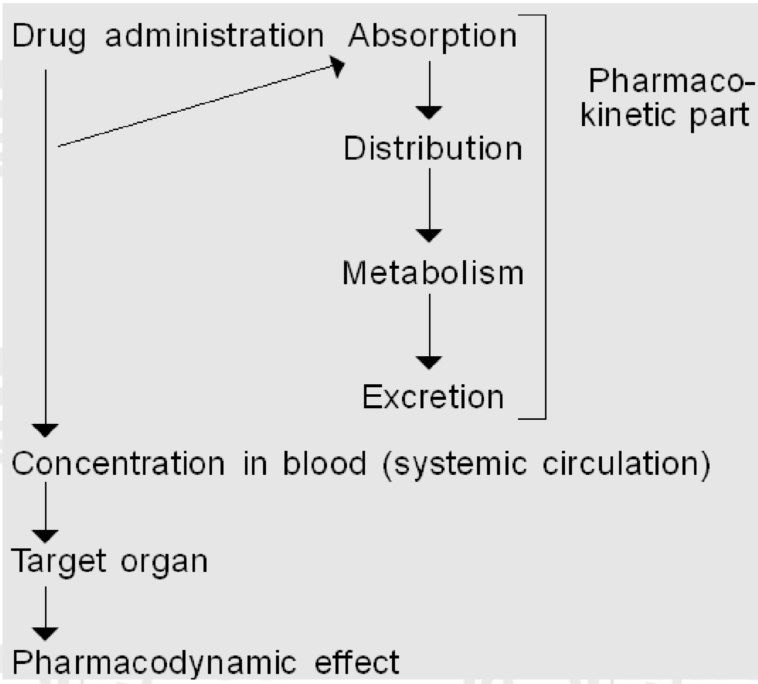

Fig.2.2: Various processes in pharmacokinetics

2.3.1 Absorption

Absorption is the entry of drug into blood via the biological membrane from the site/route of administration (as discussed in Unit 1).

Factors Affecting Drug Absorption

It is the study of factors influencing the extent and rate of absorption and release of a drug from its various physicochemical properties and dosage forms and the therapeutic response obtained after its administration.

The rate and total amount of drug absorbed is dependent upon many factors, which are:

Biological Factors

The biological factors which affect the drug absorption are:

Passage of Drug through Body Membranes: After a drug is administered in any form/route, it must reach the site of action and remain there for a particular period, so as to yield the desired effect. During their way to site of action, drug molecules have to cross one or more membranous barrier, which are lipoidal in nature, and having different sizes of pores. The substance with higher water partition coefficient values can penetrate through natural membranes easily as compared to those having lower value. The natural substances like amino acids, bile salts, glucose readily pass through body membranes even if their molecules are too large.

Site of Absorption: The site of absorption is mainly localized in mouth (for buccal administration), stomach, intestines or colon. Certain vasodilators (like nitroglycerine) and hormones which can penetrate the buccal mucosal wall will only be kept in buccal cavity or under the tongue. It provides rapid onset of action and prevention of gastrointestinal interactions. The absorption in stomach depends upon the gastric emptying, gastrointestinal motility and pH. For example, if benzylpenicillin if allowed to stay longer in the stomach, much of its activity is lost.

Presence of Food and Other Salts

Normally, the presence of food in the gastro-intestinal tract (GIT) reduces the rate of absorption of drugs like tetracycline, but on the other hand griseofulvin absorption is enhanced by giving it with fatty meals. Bile salts have favourable effect on the absorption of drugs mainly due to their surface activity.

Routes of Administration

The drugs are mostly given by oral route, which is considered already in previous sections. The other routes of administration of drugs in relation to absorption are being discussed here.

Parenteral administration: This route is applicable for drugs which are inactivated by gastrointestinal tract or absorption is poor when given orally or there is an urgency for fast response in small dose.

Inhalational administration: The absorption of drug takes places through lungs and the absorbing membrane is very thin and surface area is quite large. The lipid soluble drugs are readily absorbed from the nasal mucosa, as these drugs diffuse more rapidly.

Topical administration: It is employed for local action in the form of ointments, creams, jellies etc. for its antiseptic and local anaesthetic action. The lipid soluble drugs penetrate the skin easily and rapidly.

Rectal administration: The drug is also administered rectally in the form of suppositories and enema preparations which are absorbed from the colon.

Physico-chemical Factors

The physico-chemical factors affecting the absorption are lipid solubility, dissolution rate, salt from complexation, viscosity and drug stability in the GIT.

Lipid Solubility Dissociation Constant and pH: The drug solution of weak acid in the stomach (pH = 1.0; acidic) will be in more unionized form, which is more lipid soluble and gets more easily absorbed in the stomach. A solution of weak base in stomach is more ionized, and therefore is most unabsorbable e.g. quinine. The high pH in intestine favours the absorption of weak bases.

Dissolution Rate: All the drugs in any solid dosage form or suspension when administered will first change into drug solution in body fluids. So, dissolution rate is important factor affecting the rate of absorption. When a drug is more rapidly or completely absorbed from solution, it is very likely that its absorption will be dissolution rate limited.

Viscosity

Viscosity limits the dissolution rate and thereby affect the rapid absorption e.g. aqueous solution of sodium salicylate is absorbed faster than its suspension form.

Pharmaceutical Factors

These factors are mainly related to the various dosage form of drugs. Their absorption depends upon their physical nature like aqueous solution, suspension, powder, tablets, capsules etc.

Aqueous Solutions: The aqueous solution are most quickly absorbed. But due to their poor stability, solubility limitation and packaging problems, most of the drugs are not designed in aqueous solution unless unavoidably needed in some specific preparations.

Solid Forms – Powders, Capsules, Tablets: When drug is given in the form of powder its absorption is largely dependent upon particle size, interaction with other diluents and dissolution rate. The micronized powder gives much higher concentration in blood as compared to ordinary powder and tablets. The absorption of capsule is also dependent on their type e.g. hard capsule and soft capsule. The hard capsule dissolves much more readily in gastrointestinal tract as compared to soft capsules. After swallowing, the tablet first disintegrates into granules and primary solid particles and then into solution by dissolution for absorption. The absorption of any tablets is dependent on its disintegration and dissolution time, which may be affected by adding certain pharmaceutical additive e.g. dissolution can be increased by increasing the starch content, binders can retard the dissolution as they delay disintegration.

Bioavailability

The bioavailability of any drug is defined as its rate and extent of absorption. This is mainly used to describe the biological availability of a drug from a preparation and is calculated/determined in terms of amount or rate of presence of drug in various body fluids like blood, urine etc.

It is also used to indicate a measurement of rate and relative amount of an administered drug in general circulation.

2.3.2 Distribution of Drug

After absorption, the drug may be distributed into various body fluids like intestinal fluid, trans-cellular fluids e.g. fluids in the gastrointestinal tract, cerebrospinal fluid, etc. Drug distribution depends on various factors.

Plasma Protein Binding

Most of the drugs are transported bound to nonspecific sites on plasma proteins, mostly to albumin. The binding is usually reversible and depends on the individual compound.

The binding of drugs to plasma proteins limit its concentration in tissue and glomerular filtration of the drug. Since only unbound drug is in equilibrium across membranes and this process does not immediately change the concentration of free drug in the plasma. The free drug is cleared from the plasma by the liver and kidneys, which is rapidly replaced by dissociation from plasma proteins and redistribution from the tissue.

Since, only unbound drug in the plasma is available for distribution. Therefore, higher the degree of protein binding, greater is the proportion which remains in the blood which makes the drug long acting, as bound fraction is not available for metabolism or conversion unless it is actively excreted by the liver or kidney.

Other drug reservoirs are cellular and fat reservoir. The accumulation of drug in the cells may be the result of active transport or binding. Many drugs are accumulated in muscle and other cells in higher concentration than in the extracellular fluids. Many lipid soluble drugs are stored in the neutral fat, and act as the important reservoir.

Redistribution

In general, the termination of drug effect is usually by metabolism and excretion, but it can also be due to the redistribution of drugs. The highly lipid soluble drugs when given intravenously or by inhalation route, the fat, muscle and tissue take up the drug (initially they are distributed in other organs like heart, kidney, brain etc.) by which the plasma concentration falls and drug is with-drawn for these sites. However, where the same drug is repeatedly administered, the drug action can be prolonged.

Blood Brain Barrier (BBB)

The capillary endothelial cells in the brain, small extracellular space, sheet of glial cells lining the capillaries and the myelin sheath together constitute the barrier, so called blood-brain barrier. The penetration of any drug through these barriers is dependent on their lipid solubility and ionization. Both barriers are lipoidal in nature and restrict the entry of non-lipid soluble drugs. Only lipid soluble drugs are able to penetrate and produce their action on central nervous system. The best example is levodopa in the treatment of parkinsonism. Dopamine (which is ultimately required in the brain) does not enter the brain but its precursor levodopa crosses the blood-brain barrier, changes into dopamine and produce their action.

Placental Barrier

The placental membranes are also lipoidal in nature and lipophilic drugs (also nonlipid soluble drugs to some extent) can easily cross the placental barrier. It is a contact between the foetal blood and the maternal blood.

2.3.3 Metabolism of Drugs

Metabolism of drugs means chemical alteration of the drug in the body i.e. drugs are converted to their metabolites that are more polar than the parent compound. Most drugs, are hydrophilic drugs and are not biotransformed and are excreted unchanged e.g. streptomycin, neostigmine etc. The most lipid soluble drugs are readily absorbed from the filtrate by diffusion through renal tubular cells. Thus, the enzymatic biotransformation of drugs to more polar and less lipid soluble metabolites enhances their excretion and reduces their volume of distribution. The primary site of drug metabolism is liver. The other organs like kidney, intestine, lungs and plasma are also involved in drug metabolism.

Factors affecting drug metabolism

i) **Age:** In general, infants and older (human or animals) tend to be more sensitive to the action of the drugs. The impairment of drug metabolism in the new born infants usually results from a diminished capacity to deactivate drugs and consequently to more prolonged pharmacological action and to increased toxic reactions.

ii) **Nutrition:** Protein or calcium deficiency impairs drug metabolism in animals, due to decreased activity of the microsomal enzymes of the liver. The sleeping time by hexobarbitone is increased as a result of prolonged protein malnutrition.

iii) **Disease conditions:** Patients with liver disease may exhibit an increased sensitivity of many drugs. Patients with obstructive jaundice, hepatitis, cirrhosis shows reduce ability to synthesize glucuronide and sulfate conjugates.

iv) **Hormonal effects:** The hormones of adrenal glands, thyroid and pancreas exert various effects on the metabolism of drugs. Administration of ACTH, adrenaline or thyroxine impairs the hepatic microsomal metabolism of drugs.

v) **Genetic Factor – Species Differences:** Species differences in the metabolism of drug may be due to the difference in the rate of metabolism or in their metabolites difference. Certain drugs have been found safe and non-toxic in animals, but when they were tested in human beings severe toxic effects were observed. For example, when sulfanilamide was tested in dog it was found safe and non-toxic, but when it was administered to human being, certain toxic effects like the hematuria, renal failure were observed.

2.3.4 Excretion of Drugs

The excretion of drugs has been known to take place through different routes mainly kidneys, skin, lungs and alimentary tract. Only few drugs are eliminated through skin and via lungs (only for volatile drugs like chloroform, ethyl alcohol, ether etc.). Drugs which are poorly absorbed are excreted in faeces.

i) **Renal Excretion:** The kidneys serve as the primary and major organ for removal of most drugs, which is constituted by the microunits called 'nephron'. Three major processes that are involved in the excretion of drugs through kidneys are: glomerular filtration, tubular secretion and passive diffusion.

ii) **Pulmonary Excretion**

Volatile lipophilic substances like volatile general anaesthetics, ethyl alcohol, paraldehyde are excreted by the lungs. These volatile substances and certain gases that enter the body through the respiratory tract in the form of aerosol are excreted by this route.

iii) **Biliary Excretion**

Certain drugs are excreted in urine only in small amounts but appear in high concentrations in the bile for example, erythromycin, novobiocin, tetracycline, phenolphthalein etc. The abnormality or any disease related to liver may impair bile secretion which can lead to the accumulation of these drugs

Certain drugs that are secreted by the liver into the bile and then to small intestine are not eliminated out through the faeces, so that the drugs will re-enter the blood that perfuses the intestine and again carried to the liver (repeatedly reabsorbed from the intestine and re-excreted in the bile) and thereby prolongs the action by the so called '***enterohepatic circulation***'.

iv) **Excretion in Other Body Fluids**

Sweat and Saliva: The excretion of drugs through sweat and saliva is primarily dependent upon the diffusion of the non-ionized, lipophilic form of the drug across the epithelial cells of the glands. The compounds like lithium, potassium iodide and heavy metals are present in these secretions.

Milk: The excretion of drugs into the mother's milk will depend upon the amount of drug in blood, its lipid solubility and the extent of its active excretion. A highly lipid soluble drug should tend to accumulate in milk fat. As milk has a lower pH (6.5), the basic drugs are more concentrated in it. The drugs which are excreted in milk include sulfonamides, penicillin, tetracycline and other antibiotics, morphine, lithium, antithyroid drugs, antineoplastic agents, radioactive iodine etc.So these drugs should be avoided or breast feeding should be suspended in lactating mothers as these drugs have effect on the infants.

SAQ 3

a) ________________ is the entry of drug into blood via the biological membrane from the site/route of administration.

b) The ____________________ of any drug is defined as its rate and extent of absorption.

c) Volatile lipophilic substances like volatile general anaesthetics, ethyl alcohol, paraldehyde are excreted by the __________________.

d) What is the blood brain barrier?

e) Define pharmacokinetics.

2.4 ADVERSE DRUG REACTIONS / DRUG TOXICITIES

Adverse drug reaction may be defined as 'any response to a drug which is noxious (injurious) and unintended, and which occurs at doses of an appropriately given drug used in man for prophylaxis, diagnosis or therapy excluding therapeutic failures.'

Adverse drugs reactions are not rare and have increased in number, which may be due to irrational use of multiple drug therapy, availability of most of the drugs as OTC (over the counter) i.e. without prescription and self medication by the patients.

Adverse effects can be based on the pharmacodynamics of the drug i.e. ***side effects*** (occur at therapeutic dose of the drug), ***toxic effects*** (occurs at overdose or poisoning) and ***drug withdrawal symptoms*** (i.e. withdrawal of narcotic drugs) and secondly, the effects which are individual to individual like drug allergy (hypersensitivity to drugs), idiosyncracy. Other types are ***teratogenicity*** (drug causing foetal abnormalities), ***carcinogenicity*** (drug causing cancer), ***iatrogenicity*** (drug induced diseases).

Side Effects: **T**hese are undesirable and unavoidable pharmacological effect of the drug, which occur at therapeutic dose. These unwanted effects of many drugs are based on their pharmacological actions.

Toxic Effects: **T**oxic effects develop due to excessive pharmacological action of drug, which may be due to overdose or continuous use of drug for prolonged period. The overdose toxicity occurs when the high dose of drug is required for the specific treatment or the drug is taken accidentally or with the intention of suicide. The effects are predictable and dose related.

Hypersensitivity (Drug Allergy): **D**rug allergy is a cell-mediated immune reaction producing symptoms, which are unrelated to the pharmacological effects of the drug. It results from previous sensitization to the drug itself or a particular chemical with similar structure.

Teratogenicity: **T**eratogenicity is derived from the word 'teratos' mean 'monster.' teratogens may act directly on the foetus, e.g., thalidomide and anticancer drugs act directly on the foetus, or act indirectly on placenta e.g., vitamin a, 5-ht.

It is clear that the major foetal damage occur by drug when it is taken in early pregnancy (i.e. first 2-9 weeks when organogenesis takes place.)

The teratogenic drugs can affect different stages of pregnancy i.e.

- At fertilization and implantation stage (i.e. conception to 3 weeks).
- Organogenesis period (3 to 9 weeks), and
- In growth and development period (i.e., after 9 weeks).

Carcinogenicity: **C**ertain drugs affect the genes and structural changes in the chromosomes. The drugs that cause cancer are called as carcinogenic drugs, for example, oral contraceptives increase the incidence of benign liver tumors, vaginal adenocarcinomas in the female offsprings of women who have taken stilboesterol during her pregnancy for abortion purpose.

Idiosyncrasy: **I**t is genetically determined abnormal reactivity to a drug. The abnormal reactions to the drug are precipitated sometime because of genetically determined total absence or reduced activity of some enzyme in the body of the recipient.

Poisoning: **P**oison is a substance which endangers life due to its toxic reaction/poisoning on certain vital functions in the body. The poisonous substances may be the toxins, very high doses of drug, industrial chemicals/gases, house- hold chemical like insecticides-ddt, bhc, etc. For the treatment of poisoning, a selective antidote (which antagonizes the action) may be given.

Management of Poisoning: Some general guidelines have been given for the management of poisoning. These guidelines are aimed at prevention of further exposure to the poisonous substance, alleviation of the symptoms of poisoning and maintenance of the vital body functions. The guidelines can be summarized as follows:

- Maintain a clear airway/adequate ventilation (for inhaled poisons).
- Washing the eyes and other surface of the body (for local poison entering from the surface).
- Gastric lavage (with hypertonic saline solution, apomorphine injection for ingested poison).
- Activated charcoal (to bind the unabsorbed drug) 10-30 g in suspension in 200 ml water.
- Identify the poison and specific antidotes should be given.
- Maintenance of blood pressure and other related body function by fluid infusion, pressor agents, depending upon the condition of the patient.

- The nonspecific antidotes are also given, for example anticonvulsants in convulsions.
- Forced diuresis by furosemide, mannitol etc. and altering the urinary pH– increasing the pH of urine favours ionisation of acidic drugs like salicylates, phenobarbital etc. whereas reducing the pH favours ionisation of basic drugs like pethidine, amphetamine etc.
- Haemodialysis and haemoperfusion which is a passage of blood through a charcoal or adsorbent resin column may be instituted, depending upon the patient's condition.

2.5 RATIONAL USE OF DRUGS

Rational use of drugs means using drugs which are safe and effective. These drugs should be available at reasonable prices and could be stored conveniently. The drug should be the appropriate drug for the disease, should be administered at the right dose for the right period of time. Following factors lead to irrational prescribing.

I. **A large number of commercial preparation:** There are large number of commercial preparations available in the market. It is difficult for the physicians to make a rational choice from the wide range of drugs available. However, by applying sound criteria for selection the most appropriate drug could be chosen.

II. **Physician's decision making process:** The knowledge about the pharmacological properties of the drugs, an ability to deal with demanding patient and aggressive drug promotion by pharmaceutical companies all influence the prescriber. An up-to-date knowledge about drugs and the ability to deal with the patient and the pharmaceutical companies will make it easier for the doctors to select the right formulation.

   The rational use of drugs can be accomplished by applying the following approach:

   a) **Patients' problem:** Try to find an explanation for the patients' problem. Take a detailed history of the illness and the drug history of the patient.

   b) **Diagnosis:** An accurate diagnosis is a prerequisite for rational therapy.

   c) **Therapeutic objectives:** This should be arrived at from the prognosis of the disease or relieving a symptom or preventing a disease or a combination of these.

   d) **Selection of drug treatment (drug):** The approach towards selection of a drug treatment is divided into two phases:

      i) Determine the options available to treat a health problem. Sometime simple advice may be all that is necessary and drug therapy may not be needed.

ii) Evaluate the drugs on the basis of the following criteria:

Efficacy, safety, suitability, cost, ease of administration and storage requirements.

e) **Start the treatment:** Describe the drug and start drug administration. Inform the patient about the beneficial effects as well as side effects of the drugs and how to deal with.

f) **Result of treatment:** The results of the drug therapy should be assessed periodically.

2.5.1 Rational Prescribing

Rational prescribing is to prescribe drugs to treat a particular health problem effectively and safely at an affordable cost. Therefore selection of a drug to treat a particular disorder should be based on a systematic approach towards its rational use.

I. Selection of a drug: If a drug is really needed to treat a health problem, then its selection involves the following steps:

i) Accurate diagnosis is the prerequisite for rational therapy. However, if a tentative diagnosis is made due to the limited local resources, then it should be reviewed in the light of response to the therapy.

ii) Select group of drugs effective to treat the particular health ailment.

iii) Compare the effective groups of drugs and then select a drug on the basis of following criteria:

Efficacy: Efficacy of a drug is not only based on pharmacodynamic but also on pharmacokinetic parameters, which have special importance in certain situations where onset and duration of drug effect is to be considered.

Safety: Drug with fewer serious side effects in normal doses should be preferred.

Suitability: Dosage forms should be such that it does not only guarantee the desired effect but can also be handled easily by the patient and due consideration should be given for contraindications and interactions.

Cost: More expensive dosage forms may be an important factor for non-compliance. So, the cost factor should be considered while selecting a drug. The less expensive drug treatment may be preferred.

Storage conditions: If all other things are equal then the drug which can be stored more easily should be selected.

II. Monitoring of treatment: The treatment can be monitored by the following methods:

i) Passive monitoring: Information is given to the patient regarding the possible side effects with the necessary cautions. The patient is therefore well informed and able to do his monitoring.

ii) Active monitoring: Make another appointment for active determination of relief or side effects due to drug therapy.

Knowledge about the drugs are constantly changing. New drugs are introduced in the market and more information about existing drugs appear constantly. Therefore the doctor has to keep themselves updated.

SAQ 4

a) _________________use of drugs means using drugs which are safe and effective.

b) _________________ are undesirable and unavoidable pharmacological effect of the drug, which occur at therapeutic dose.

c) ___________ are effects that develop due to excessive pharmacological action of drug, which may be due to overdose or continuous use of drug for prolonged period.

d) Define adverse drug reactions.

e) What is rational use of drugs?

2.6 SUMMARY

- Pharmacodynamics is the study of drug effects (biochemical and physiological) and their mechanism of action.
- The different types of drug action can be classified as Stimulation, Depression, Irritation, Replacement, Bactericidal and Cytotoxic Action
- Tolerance is a condition when there is a requirement of higher dose of a drug to produce a given response.
- The drug receptors are macromolecular sites which are situated on the surface or inside the effector cells with which specific agonist combines to produce its response.
- When two drugs are given simultaneously, and the action of one drug is increased by the other, they are treated as synergistic.
- Entry of polar substances into the CSF is limited by the presence of the Blood Brain Barrier (BBB).
- Most of the drugs are excreted from the body through the kidneys or the liver.
- Teratogenicity is the property of a drug (if ingested by a pregnant woman) to bring about physical or physiological derformities in the developing foetus.

2.7 TERMINAL QUESTIONS

1. What are the different types of drug actions?
2. What is synergism?
3. Define bioavailability.
4. What is drug redistribution?
5. What are the different types of adverse drug reactions?
6. What do you understand by teratogenic drugs?

2.8 ANSWERS

Self Assessment Questions

1. a) Pharmacodynamics b) Tachyphylaxis c) Increased d) Antimicrobial Resistance e) Pharmacodynamics is the study of drug effects (biochemical and physiological) and their mechanism of action.

2. a) Synergism b) The drug receptors are macromolecular sites which are situated on the surface or inside the effector cells with which specific agonist (ligand/drug) combines to produce its response c) Receptor antagonism is the phenomenon where one drug inhibits the binding of another drug with the receptor.

3. a) Absorption b) Bioavailability c) Lungs d) The capillary endothelial cells in the brain, small extracellular space, sheet of glial cells lining the capillaries and the myelin sheath together constitute the barrier, so called blood-brain barrier e) Pharmacokinetics is the study, which determines the rapidity and concentration of the drug in the body and its duration of appearance at the target organ.

4. a) Rational use b) Side effects c) Toxic effects d) Adverse drug reactions can be defined as ‘any response to a drug which is noxious (injurious) and unintended, and which occurs at doses of an appropriately given drug used in man for prophylaxis, diagnosis or therapy excluding therapeutic failures’. e) Rational use of drugs is the use of an appropriate drug for a disease, administered at the right dose for the right period of time.

Terminal Questions

1. The different types of drug action are as follows:

   i) Stimulation

   Stimulation is an increase in the selective activity of specialized cells, which increases the secretion from a gland.

ii) Depression

It is a reduction/decrease in the activity of specialized cells. For example barbiturates depress central nervous system.

iii) Irritation

It is the effect of drugs on the growth, nutrition and morphology of living tissues which induce a gross change in cellular function.

iv) Replacement

It includes certain drugs, which are used to replace some missing endogenous component of the body or when the production of endogenous components is reduced.

v) Bactericidal and Cytotoxic Action

The *bacteriostatic* activity which is inhibition of growth and multiplication of bacteria and *bactericidal* activity, which is bacterial death, is induced by certain types of antibiotics. Cytotoxic action is selective for invading cancer cells and altering them without affecting the host cells.

2. When two drugs are given simultaneously, and the action of one drug is increased by the other, they are treated as ***synergistic***. In the synergism, the drugs can have action in the same direction or when given alone, one may be inactive. Synergism can be additive or supradditive in nature.

Additive

When the effect of two drugs are in the same direction. For example when aspirin is combined with paracetamol the combined effect is analgesic/antipyretic.

Supradditive

In this the effect of combined therapy is greater than the individual effect of the one drug. Example: Sulfonamide and trimethoprim (well known preparation 'Septran') as antibacterial.

3. The bioavailability of any drug is defined as its rate and extent of absorption. This is mainly used to describe the biological availability of a drug from a preparation and is calculated/determined in terms of amount or rate of presence of drug in various body fluids like blood, urine etc. It is also used to indicate a measurement of rate and relative amount of an administered drug in general circulation.

4. It is a method of termination of drug action. The highly lipid soluble drugs when given intravenously or by inhalation route, the fat, muscle and tissue take up the drug (initially they are distributed in other organs like heart, kidney, brain etc.) by which the plasma concentration falls and drug is with-drawn for these sites. However, where the same drug is repeatedly administered, the drug action can be prolonged.

5. Adverse drug reaction is an undesired or unintended effect of the drug, occurs at dose normally used by human being. Adverse drug reaction may be defined as 'any response to a drug which is noxious (injurious) and unintended, and which occurs at doses of an appropriately given drug used in man for prophylaxis, diagnosis or therapy excluding therapeutic failures.'

   Adverse drugs reactions are not rare and have increased in number, which may be due to irrational use of multiple drug therapy, availability of most of the drugs as OTC (over the counter) i.e. without prescription and self medication by the patients.

   Adverse effects can be based on the pharmacodynamics of the drug i.e. ***side effects*** (occur at therapeutic dose of the drug), ***toxic effects*** (occurs at overdose or poisoning) and ***drug withdrawal symptoms*** (i.e. withdrawal of narcotic drugs) and secondly, the effects which are individual to individual like drug allergy (hypersensitivity to drugs), idiosyncracy. Other types are ***teratogenicity*** (drug causing foetal abnormalities), ***carcinogenicity*** (drug causing cancer), ***iatrogenicity*** (drug induced diseases).

6. Teratogenicity is derived from the word 'teratos' mean 'monster.' Teratogens may act directly on the foetus, e.g., thalidomide and anticancer drugs act directly on the foetus, or act indirectly on placenta e.g., vitamin A, 5-HT. It is clear that the major foetal damage occur by drug when it is taken in early pregnancy (i.e. first 2-9 weeks when organogenesis takes place.) The teratogenic drugs can affect different stages of pregnancy i.e.

   - At fertilization and implantation stage (i.e. conception to 3 weeks).
   - Organogenesis period (3 to 9 weeks), and
   - In growth and development period (i.e., after 9 weeks).