ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION OF DRUG

ADME or pharmacokinetics is the quantitative study of drug movement in, through and out of the body.

ABSORPTION :

Passage or movement of drug from its site of administration into the blood stream is called absorption.

Except i. v. injection, the drug has to cross the biological membranes.

The different processes of drug absorption are -----

(i) Passive diffusion.
(ii) Filtration.
(iii) Active transport.
(iv) Facilitated diffusion.
(v) Pinocytosis.

(i) Passive diffusion :-

- In this the drug moves from the higher concentration to the lower concentration i.e. along with the concentration gradient, until the equilibrium is achieved.
- Highly lipid soluble drugs are absorbed by this process.
- It is a biodirectional process.
- This process is carried out without utilization of energy.

(ii) Filtration :

- In this, the drug pass through the aqueous pores in the membrane or through the paracellular space.
- Water soluble drugs with low mol. wt. less than 100 are absorbed by this process. Ex : H_2O, Urea.

(iii) Active transport :

- In this process, the drugs moves from lower to higher concentration i.e. against concentration gradient.
- Water soluble drugs, having large molecular size are absorbed.
- It involves a carrier system i.e. the drug molecule combine with specific component of the membrane (protein) i.e. carrier, to form complex and the complex dissociates from the carrier at another surface.
- This process utilizes energy.
- It is a rapid process as compared to passive transport.

(iv) Pinocytosis :

- In this, the cell – membrane forms a sort of invagination and surround the fluid, macromolecules but not the particulate matter from its surroundings.
- This process requires energy.
- This process plays an important role in unicellular organisms like amoeba.

(v) Facilitated Diffusion :-

- It is a rapid process than passive diffusion.
- Here, the drugs moves from higher to lower concentration.
- It involves the carrier system.
- It does not require energy.

FACTORS AFFECTING ABSORPTION OF DRUGS :-

1. Pharmaceutical factors.
2. Patient factors.

1. Pharmaceutical factors :

(i) Particle size of drug molecule :

The rate of drug absorption is inversely propotional to the particle size of drug molecule. i.e. If the particle size of a drug in the tablet or capsule is small then the absorption of drug is more than with larger particle size, and vice – versa.

(ii) Compression of tablet :

The rate of absorption is inversely propotional to the compression of tablet. i.e. If a tablet is highly compressed, then it will take more time for complete dis – integration and hence absorption, as compared to lightly compressed tablet. Hence the absorption is delayed.

(iii) Solubility of drug :-

Amorphos form of a drug is more soluble than the crystalline form.

Ex : Amorphos form of chloramphenicol palmitate have 10 times more bioavailability than crystalline form.

(iv) Ionization :

Ionized drug are absorbed poorly but un – ionized drugs absorbed rapidly, because the mucosal lining of G. i. t is impermeable to ionized form.

(v) G. i. transmit time :

Rapid absorption occur, if the drug is given on empty stomach, but certain irritant drugs are administered after food to minimize the gastric irritation.

(vi) Physical nature of the dosage form :

Solutions are absorbed rapidly than suspensions and suspensions are absorbed rapidly than solid dosage form.

(vii) Types of excipients used :

In case of sustained release preparation, the coating substance (excipients), controls the rate of drug release and hence absorption.

2. Patient Factors :

(i) Intestinal Motility :

Most of the drugs are absorbed from the intestine. Rate of absorption is inversely propotional to the intestinal motility. Increase in intestinal motility (as in diarrhoea) reduces the drug absorption.

(ii) Presence of Other substances in the G.i.t :-

The presence of food in the g.i.t affects the absorption of drug. The drug absorption may be increased, decreased or remains unaffected.

Ex :

1. The absorption of griseofulvin increases in the presence of food.
2. The absorption of tetracycline decreases in the presence of milk in the G.i.t .

(iii) Fast Pass Metabolism :

- It occurs in liver and intestinal wall.
- Some drugs after absorption from the intestine, metabolized at these two sites before entering systemic circulation. So it affects the bioavailability of drug.

(iv) Enterohepatic Circulation :

- Substances from small intestine are absorbed by passive transport and through portal system, they reach the liver, from where they enters the systemic circulation.
- From liver, they may be actively transported to small intestine through bile. In the small intestine these substances can also get reabsorbed again and the whole cycle gets repeated. This is called enterohepatic circulation.

Ex : Diazepam.

(v) Area of absorbing surfaces and local circulation :

- Drugs can be absorbed better from the small intestine than from the stomach because of the larger surface area.
- If the blood flow to the area is increased then the absorption is also increased. Hence massage or application of heat to the site of i.m. administration increases the absorption of drug.

DISTRIBUTION :

The conveying of drug throughout the body in the circulating blood, to reach the tissues of each organ is called distribution .

FACTORS AFFECTING DISTRIBUTION OF DRUGS :

a. Protein binding.
b. Specialized barriers.
   (i) Blood - Brain – Barrier (B – B – B)
   (ii) Blood – CSF Barrier.
   (iii) Placental Barrier.

(a) Protein Binding :

- After absorption, the drug circulates in the blood either in the free form or bound to plasma proteins. Drugs usually binds with the plasma protein i.e. albumin . This binding is reversible. The free drug in the blood can get distributed to various body fluids and tissues. In blood, when the free drug is distributed, there is release of drug from the drug - protein complex.
- The extent of plasma protein binding varies with types of drugs.
  Ex : Plasma – protein binding of dicumarols is 99 % and aminoantipyrine is 0 %.

- The drugs competes with each other for the binding sites on protein. So, free concentration of highly bound drugs can be increased by administration of other drug which has more affinity for binding sites.

ACCUMULATION :

Certain drug accumulated in some of tissue and affects distribution.

Ex : Calcium of teeth and bone, forms chelates with tetracyclines and impacts discolouration of teeth, so deformities of teeth are also increased.

Thus, tetracycline is not administered in growing children.

(b) SPECIALIZED BARRIERS :

In the body, some psysiological barriers are three which affects the distribution of drug.

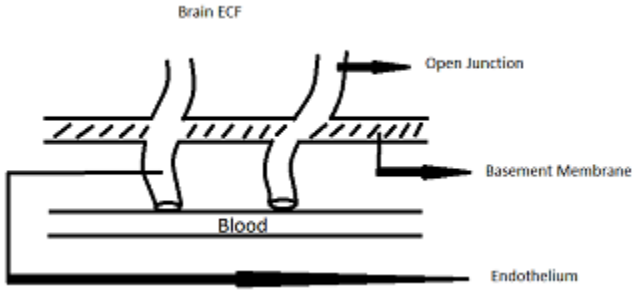
(i) Blood – Brain – Barrier :

- In capillaries of brain the endothelical cells are joined by tight intracellular junctions.

Certain cells of brain connective tissue e.g. astrocytes have long processes and form

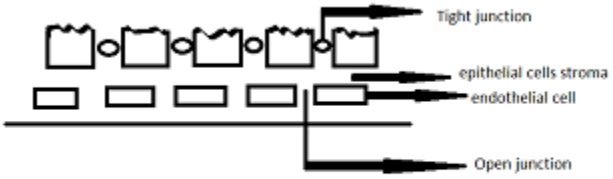
sheath close to the capillary endothelium.

- Hence the drug molecule in the plasma must diffuse through endothelial cells and astrocytic sheaths to enter into the extracellular fluid (ECF) of brain.
- Therefore the drug can enter into the brain ECF by passive diffusion.



(ii) Blood – CSF Barrier :

The CSF is separated from blood by the tissue of choroid plexus.



- The junction between endothelial cells are open but the junctions between choroidal epithelial cells are closed.

So, for entering into the CSF, the drug has to diffuse through choroidal epithelial cells.

(iii) Placental Barrier :

The barriers exist between maternal and foetal circulation is called placental barrier. This barrier is not an efficient barrier, hence foetus is exposed to some extent to all most of the drugs administered to the mother.

3. METABOLISM : (Biotransformation).

Bio – living organism.

Transformation – change.

- Alteration of a drug within a living organism is termed as " biotransformation ".

Metabolism is the chemical changes of drugs within the living system.

- Metabolism tends to make, the less polar lipid soluble substances to more polar water soluble substances. Hence, they can be excreted easily.

Sites Of Biotransformation :-

The most active tissue per unit weight for biotransformation is liver. Other minor sites are kidney, placenta, intestine, plasma, lungs, skin, testics etc.

Metabolism usually carried out by enzymes resulting in their activation, inactivation or modification.

1. **Activation :**

- Few drugs are inactive as such and requires conversion in the body to one or more active metabolites. Such drugs are called pro – drug.

Ex : Levodopa (Pro – drug) —Metabolism→ dopamine (active metabolite)

- Some drugs are active as such and after metabolism, the metabolites are also active.

Ex : codeine (active drug) —Metabolism→ Morphin (active metabolites)

2. **Inactivation :**

In this, most of the drugs and their active metabolites are render inactive or less active.

Ex : Chloramphenicol.

3. **Modification :**

Hexamine is metabolized is urinary tract at an acidic pH to formaldehyde and ammonia. Formaldehyde exerts an antibacterial action in the urinary tract.

BIOTRANSFORMATION REACTIONS :

The reactions can be classified into the following 2 types -----

(A) Non – synthetic / Phase – I reaction.

(B) Synthetic / Phase – II / configuration reaction.

(A) Nonsynthetic Reaction :

- Here the metabolites obtained may be active or inactive
- The different non – synthetic reactions are -------
  - (a) Oxidation.
  - (b) Reduction.
  - (c) Hydrolysis.

(a) Oxidation :

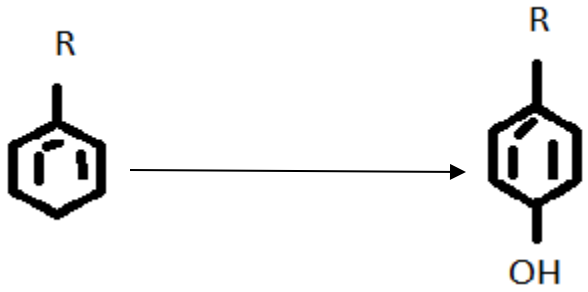
All the reaction are carried out by the enzymes of smooth endoplasmic reticulum of hepatic cells.

Various oxidation reactions are ------

(i) Hydroxylation.

(ii) Oxygenation (oxidative deamination, oxidative dealkylation).

(i) Hydroxylation :



(Phenobutazone) (Oxyphenbutazone)

(ii) Oxygenation :

- Oxidative deamination :

$R - CH - (NH_2) - CH_3 \longrightarrow R - C - CH_3 + NH_3$

(Amphetamine) (Phenylacetone)

- Oxidative dealkylation :

$R - O - CH_3 \longrightarrow R - OH + HCHO$

(codeine) (Morphin)

$R - R' N - CH_3 \longrightarrow R - R' - NH + HCHO$

(Diazepam) (Oxazepam)

But, a mitochondrial enzyme called mono – amino oxidase (MAO) causes oxidative deamination of substances like adrenalin, 5 – hydroxyl tryptamine (5 – HT) And tyramin etc.

5 – HT $\xrightarrow{MAO}$ 5 – hydroxyindole $\xrightarrow{\text{Aldehyde dehydrogenase}}$ 5 – hydroxyindole acetic acid.

N.B – The drugs may be oxidized by more than one mechanism and for the same drug, the mechanism may differ from species to species.

(b) REDUCTION :

The drug which contain disulphide (S = S) azo (N = N) or nitro (- NO_2) group can be metabolized by this pathway.

e.g. Disulphiram (S = S) $\longrightarrow$ Diethyl dithiocarbamic acid.

Prontosil $\longrightarrow$ Sulfanilamide.

(N = N)

Chloramphenicol $\longrightarrow$ Aminochloramphenicol.

(- NO_2)

(c) HYDROLYSIS :

The drugs which contain ester or amide group in their structure are metabolized by this pathway. These usually carried out by the enzyme " esterase " and " amidase " etc., which hydrolyse the drug molecule by taking up a molecule of water.

Ester + water $\xrightarrow{\text{Esterase}}$ PABA + Diethylamino ethanol.

Procainamide + H_2O $\xrightarrow{\text{Amidase}}$ PABA + Diethylamino ethylamine.

Hydrolysis occurs in liver, intestine, plasma and other tissues.

(B) SYNTHETIC REACTIONS :

- This is a synthetic process, by which a drug or it's Phase – I metabolite is combined with an endogenous substance generally derived from carbohydrate or aminoacid to form various conjugates.
- The conjugates so obtained are polar, highly ionized organic acid, which are easily excreted in urine or bile.
- Large molecules (M . W > 300) are eliminated in the bile, where are smaller molecule (M . W > 300) are excreted in urine.
- Conjugation invariably results in inactivation of the compound.
- Such reaction have high energy requirement.
- The various synthetic reactions are --------
  - (i) Glucoronide conjugation reaction.
  - (ii) Glycine conjugation reaction.
  - (iii) Acetylation Reaction.
  - (iv) Methylation Reaction.
  - (v) Sulfate conjugation reaction.

(i) Glucuronide Conjugation Reaction :

- Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid.
- Glucuronic acid is derived from glucose. Here glucuronic acid is the conjugating agent.
- Drug glucuronides excreted in bile, can be hydrolysis by bacteria in the gut and the liberated drug is reabsorbed and undergoes the same fate. This enterohepatic circulation of the drug also prolongs its action.

(ii) Glycine conjugation Reaction :-

Salicylates and other drugs having carboxylic acid group are conjugated with glycine.

e.g. Salicylic acid ⟶ Salicyluric acid.

(iii) Acetylation :

Compounds having amino or hydrazine residue are conjugated with the help of Acetyl co – enzyme – A

e.g. Isoniazide —Acetyl transferase⟶ Acetyl isoniazide.

(iv) Methylation :-

The amines and phenols can be methylated. Here methionine and cysteine act as methyl donor.

Ex : Adrenaline, histamine, nicotinic acid etc.

(v) Sulfate conjugation Reaction :

The phenolic compounds and steroids are sulfated by sulfokinase.

Ex : Chloramphenicol, adrenal & sex steroids.

Factors Modifying Biotransformation :

(1) Inhibitors :-

Drug metabolizing enzymes can be inhibited by compounds like SKF 525 A. Such compound decreases the metabolism of drug and hence in turn increases the duration of action.

e.g. Quinidine is metabolized by cytochrome P3A4 and inhibited by CYP_2D_6.

(2) Stimulators :

The activity of drug metabolizing enzymes can be increased by certain drugs.

Ex : In the presence of Phenobarbital, the metabolism of hexobarbital is increased.

(3) Age :

Metabolism of drugs is poor in young children because of poor development of drug metabolizing enzymes.

Ex : Lack of glucuronyl transferase for the inactivation of chloramphenicol.

(4) Sex :

Females have less ability to metabolise drugs.

(5) Species :

Rabbits can metabolise atropine due to the presence of atropinase. But since humans lack this enzyme, it is toxic to humans but non – toxic to rabbits.

(6) Genetics :

Deficiency of drug metabolizing enzymes can be inherited.

e.g. Primaquine produces haemolysis in individual lack of Glucose – 6 – phosphate dehydrogenase enzyme.

(7) Body temperature :

Increase in body temperature increases the drug metabolism, where as decrease in body temperature decreases the drug metabolism.

4. EXCRETION :

- Excretion is the passage out of systemically absorbed drug.
- Drugs except the volatile general anaethetics are usually excreted by a route other than that of absorption.
- The principal organ of excretion is kidney. Excretion also occur by lungs, salivary glands, sweat, milk, intestine, biliary system etc.

(a) Excretion through kidneys :

- The kidney is responsible for excretion of water soluble substances.
- The total renal clearance of a drug is influenced by the rate of glomerular filtration, active tubular secretion and passive diffusion i.e. tubular reabsorption.

- **Glomerular filtration :**

All non – protein bound drugs presented to the glomerulus in filtered and plasma protein and drugs attached to plasma proteins are retained in the blood.

Thus, glomerular filtration of a drug depends on its plasma protein binding and renal blood flow.

- **Tubular Secretion :**

In the proximal convoluted tubule, certain drugs are actively transported from plasma into the filtrate.

When two drugs are secreted into tubule by same mechanism, one will inhibit the tubular secretion of other.

e.g. probenecid decrease the tubular secretion of penicillin and hence it's excretion.

- **Tubular Reabsorption :-**

- This depends on lipid solubility and ionization of the drug at the existing urinary pH.

- Lipid soluble drugs filtered at the glomerulus back diffuse in the tubules, but non – lipid soluble and highly ionized drugs are unable to do so.

(b) Excretion through intestine :-

Some substances which are not fully absorbed from the GIT are excreted in the faecus.

e.g. purgatives like senna, cascaria etc.

(c) Excretion through lungs :

- Volatile anaesthetics and gaseous inhalants are eliminated by lungs, irrespective of their lipid solubility.
- Drugs like paraldehyde and alcohol are excreted through lungs.

(d) Excretion through skin :

Heavy metals like lead, arsenic, mercury are excreted through skin. On prolonged administration, arsenic gets incorporated in the hair follicles and used for detection of arsenic poisoning.

(e) **Excretion through Milk :**

More lipid soluble, less protein bound basic drugs enters breast milk by passive diffusion.

Ex : Diazepam, barbiturates, chlorpromazine etc.

(f) Excretion through Saliva & tears :

Certain drugs like iodide and metallic salts are excreted in the saliva. Lead compounds deposited as lead sulphide produce blue lining of gums. Excessive salivation is a frequent symptom of chronic heavy metal poisoning.

e.g. pot – iodide, heavy metals etc.

GENERAL MECHANISM OF DRUG ACTION

Pharmacodynamics : (What the drug does to the body)

It deals with the study of biochemical and physiological effects of drugs and also their mechanism of action.

Mechanism of Action of Drug :

It is the process by which the chemical agent induces a change in pre – existing physiological function of the living organism.

Effect of Drug :

- The series of events occurs after drug action is called as effects of drugs.
- The drug effects are of 2 types ------ (1) Primary (desired) effect.
  (2) Secondary effect.

Site Of Action :

The location inside or outside the body, where the drug produces it's effect is called site of drug action.

1. Drugs may produce localised effects on certain cells, tissues, organs etc. or generalized effects on most cells of the body.'
2. Drugs may act ---
   (i) Extracellularly e.g. osmotic diuretics.
   (ii) On the cell surface e.g. penicillin.
   (iii) Intracellularly. E.g. Anticancer drugs.

Mechanism of drug Action

It can broadly divided into 2 groups ------

(i) Mechanism of action due to physical and chemical properties.
(ii) Mechanism of action due to biological properties.

I. MECHANISM OF ACTION DUE TO PHYSICAL AND CHEMICAL PROPERTIES :

(1) Physical mass :

Agar produces a purgative effect because it absorbs water, when administered orally, and swell in size and this initiates peristalsis.

(2) Smell :

Volatile oils like peppermint oil are usually mask the unpleasant smell of mixtures.

(3) Taste :

Compounds with bitter taste reflexly increases the flow of Hcl in stomach and improve appetite. These substances are called bitters.

e.g. Chirata.

(4) Adsorption Property :

- Magnesium trisilicate acts as an antacid by adsorbing Hcl in the stomach.
- Adsorbents like activated charcoal and kaolin adsorb the toxins or poisons in the g.i.t and inhibit there absorption.

(5) Osmotic activity :

- Magnesium sulphate produces purgative effect due to osmosis.
- Mannitol produces diuretic effect due to osmosis.

(6) Demulcent effect :

Syrup are pharyngeal demulcents in the treatment of cough.

(7) Radioactivity :

Radioactive isotopes used for the treatment of cancer produces there effect by emitting ionizing radiation.

e.g. ^{131}I in hyperthyroidism.

(8) Acidity and alkalinity :

Hydrochloric acid is effective in the treatment of hypochlorhydria. Sodium bicarbonate acts as an antacid by neutralising hydrochloric acid of the stomach.

(9) Chelation :

Chelating agents like dimercaprol (B . A . L) combine with metals like arsenic and form water soluble complexes. This helps in the easy elimination of metal through urine.

II. MECHANISM OF ACTION DUE TO BIOLOGICAL PROPERTIES :

Drug – Receptor Interaction :

Receptor :

- It is the hypothetical component of the cell with which a drug interact.
- The receptor may be on the cell – membrane or inside the cell.
- The structural components of the cell with which drug combines are, the cell – membrane, nucleus, mitochondria, enzymes and endoplasmic reticulum.
- The receptors are usually proteinaceous in nature.
- The receptors are complementary in physical and chemical structure to the drug interacting with them.
- The receptors are the binding sites of high affinity and high specificity.
- The bond between drug and receptor are reversible in nature. Some drug may produce stable complex.

Silent Receptor :

The drug – receptor interaction, where the drug gets bound to protein or enzymes without initiating any action, is called silent receptor.

Agonist :

It is a drug which combines with the receptor and initiates a pharmacological action.

Antagonist :

It is a drug which combines with the receptor and blocks it without producing a pharmacological action.

Affinity :

It refers to liking or attraction of a drug to combine with the receptor.

Intrinsic Activity : (efficacy)

It refers to the capacity of a drug to produce pharmacological response after interacting with receptor.

- Agonist have both affinity and efficacy.
- Antagonist have only affinity but no efficacy.

Types of Antagonism :

It is of 4 types ----------

1. Pharmacological Antagonism.
2. Physiological Antagonism.
3. Chemical Antagonism.
4. Physical Antagonism.

1. Pharmacological Antagonism :

It is again of 2 types -------

(a) Competitive or Reversible Antagonism.

(b) Non – competitive o Irreversible Antagonism.

(a) Competitive or Reversible Antagonism :

If by increasing the concentration of agonist, the effect of antagonist is abolished, then such antagonism is called competitive or reversible antagonism.

- Here the agonist and the antagonist compete for the same receptor.
- Such type of antagonism is not permanent.

Ex : Acetylcholine and Atropine antagonism at muscarinic receptor.

Here, if the concentration of Ach at the receptor level is increased, the block produced by the atropine can be overcome.

(b) Non - Competitive or Irreversible Antagonism : -

If by increasing the concentration of agonist, the effect of antagonist is not changed, then such antagonism is called non - competitive or irreversible antagonism.

In this, the antagonist inactivates the receptor such a way that, the effective complex with the agonist cannot be formed.

Ex : Phenoxybenzamine & Epinephrine.

2. Physiological Antagonism :-

When a drug reduces the effect of other drug by producing opposite response due to its action on second type of receptors, then the antagonism is called physiological Antagonism.

Ex : Effect of histamine are antagonized by adrenalin.

3. Chemical Antagonism :-

When a drug causes change in the structure of other drug, the antagonism is called chemical antagonism.

Ex : Sodium. Calcium EDTA removes lead from the body.

4. Physical Antagonism :

Removal of free form of poisons by adsorbents like charcoal in gut.

IMPORTANCE OF DRUG ANTAGONISM : -

It helps in ---------

1. Correcting adverse effect of the drugs.
   Ex : Ephedrine and phenobarbitone.
2. Treating drug poisoning.
   Ex : Morphine with naloxone.
3. Producing drug combinations which would reduce drug efficacy.
   e.g. the penicillin and tetracycline combination is inferior to penicilline.

Types Of Drug Action :-

1. Stimulation :

Increase in the activity of specialized cells is called stimulation.

e.g. Adrenaline stimulates heart.
But excessive stimulation produces changes in the protoplasm of the cell, which may lead to depression.
e.g. high dose of picrotoxin, a CNS stimulant drug produces convulsion, followed by coma and respiratory depression.

2. **Depression :**
   Decrease in the activity of specialized cells are called depression.
   e.g. Barbiturates depress CNS.
3. **Irritation :**
   - The term indicates that a drug produces adverse effect or injurious effect on the growth, nutrition and morphology of living tissues.
   - Mild irritation may produces stimulation of the associated function.
     e.g. Bitters increases the salivary and gastric secretions.
4. **Replacement :**
   - When the endogenous substances is reduced, drugs may be used as replacement.
   - This refers to the use of natural metabolites hoemones in their deficiency state.
     e.g. - Insulin is used in Diabetes mellitus.
     - Iron is anaemia.
     - Levodopa in parkinsonism etc..
5. **Cytotoxic Action :**
   Drugs used for prevention, arrest, of infection act specifically on the causative organism.
   They produces selective cytotoxic action on cancer cells or in the invading parasites, affecting the host cells.
6. **Modification Of Immune Status :-**
   Vaccines, Sera act by altering the immune status of the body.

FACTORS MODIFYING DRUG ACTION :-

The response to a drug varies from one individual to the other, due to the following factors ---------

1. **Age :**
   Children are hyper reactive to certain drugs. The reasons are immaturity of renal functions or poor development of enzymes needed for inactivation. So, a lesser dose must be given for children than for adults.
2. **Body Weight :**
   The average dose is specified in terms of total single dose in mg. for adult weighing 50 – 100 kgs. But such dose may be ineffective in excessive obese individual, as some portion of dose will be accumulated in the body fat. So, increase in dose is necessary.
3. **Sex :**
   Women are more susceptible to the effects of certain drugs.
   e.g. morphine produces more excitation in women than in men.
4. **Route of administration :**

The rate of absorption of a drug differs with the route of administration. The dose also varies with the route of administration.
e.g. intravenous dose of a drug is less than subcutaneous dose.

5. **Time of administration :-**

Drugs which produce nausea and vomiting (due to gastric irritation) should be taken after food. But anthemintics should be taken in empty stomach.

6. **Genetic Factors :**

The effects of a drug may vary due to genetic factors like inherited enzyme deficiencies e.g. primaquine produces hemolysis in individuals with a deficiency of Glucose – 6 – phosphate dehydrohenase.

7. **Physiological Factors :**

Body temperature and acid – base status are some factors which modify drug effects.
e.g. Salicytes lower body temperature only in fever but not in normal individuals.

8. **Psychological Factors :**

Sometimes it is necessary to please the patient by psychological means.
Placebo which is a dummy medication having the same colour, smell, etc. as the actual medication is used for the purpose.

9. **Presence Of Disease :**

Any pathological condition specially of liver, kidney and GIT is very important.

- Liver is the main site for detoxification of drugs. So, in disease state of liver, the action of phenobarbitone is prolonged.
- When there is dysfunction of kidney, the main organ of excretion, reaction of drugs are prolonged because of slow excretion of drugs.
- Inflammation of intestine results in decreased absorption of drugs administered orally.

10. **Cumulation :**

Accumulation of drug following its repeated administration is termed as cumulation.
It happens when the drug is excreted slowly and rapidly absorbed or due to sudden arrest of excretion. Cumulation results in increase in concentration of drug in the body, which may prove toxic.

11. **Additive Effect :**

- The total pharmacological response produced by two drugs is equal to the sum of the individual effects.
- Here two or more drugs having similar action is given together.
- This combination also reduces the development of tolerance.
  e.g. Ephedrine & aminophyllin in bronchial asthma.

12. **Synergism :-**

When the total effect produced by two drugs are greater than the sum of individual effects, the phenomenon is called synergism.

e.g.

- Codeine and aspirin as analgesic.

- Combination of sulphamethoxazole and trimethoprim produces more antibacterial action.

13. **Antagonism :**

The opposite actions of two drugs on the same physiological system is called antagonism.

It is of following types -----

(i) Pharmacological Antagonism.
(ii) Physiological Antagonism.
(iii) Chemical Antagonism.
(iv) Physical Antagonism.

14. Tolerance :

The unusual resistance to normal therapeutic dose of a drug is called tolerance. So a large dose is required to produce an effect.

- This is generally occurs due to repeated administration of some drug.
- Drug tolerance can be classified into following types -------

(i) True tolerance.
(ii) Pseudotolerance.
(iii) Tachyphylaxis.

(i) True tolerance

It is produced on both oral and parenteral administration of drugs.

It is of 2 types ----

- Natural tolerance.
- Acquired tolerance.

- When the tolerance occurs by nature, it is called natural tolerance. e.g. tolerance for atropine in rabbits.
- Repeated administration of certain drugs produces a tendency to tolerate that particular drug. This is known as acquired tolerance. e.g. Morphine produces tolerance to it's euphoriant effect but the pupil & g.i.t never become tolerant.

(ii) Pseudotolerance :

It is observed only with oral administration. When a small dose of poison is taken orally, repeatedly then tolerance is developed by g.i.t and due to local changes in the g.i.t, the poison cannot get absorbed to systemic circulation.

But if any other rout of administration is chosen, then poisoning will occur.

(iii) Tachyphylaxis :

It is an acute type of tolerance. When certain drugs administered repeatedly at short interval of time, the pharmacological response that drug decreases. This is known as tachyphylaxis.

e.g. Repeated administration of ephedrine in the treatment of asthma may produce diminishing response to it.

15. Drug Dependence :-

Repeated administration of certain drugs produces habit and tolerance. If the habit forming agent is not made available to the habitué, the person may develop withdrawal symptoms like psychological upset, headache, convulsions and even vasomotor collapse. These symptoms disappear on readministration of drug.

Drug dependence is of 2 types ----

(i) Physical dependence.

(ii) Psychological dependence.

e.g. 1. Tea and coffee develops dependence but is not harmful.

2. Tobacco causes physical harm to the user.