[redacted]

3.6 Distribution

Distribute- to share, separate and divided any things,

Distribution provides information on the extent/amount and time course of tissue accumulation and the elimination of drug and/or its metabolites. The disposition of drug into the organs and tissues via circulation depends upon the nature of the drug. The more lipophilic the drug is, the better will be the distribution into the organs and tissues.

After absorption of drugs enters or passes through the various body fluid compartments such as blood, plasma, tissue and fluid, which is called distribution. On the other way it is a reversible transfer of drugs between one compartment to anther compartment. Distribution carried out by the one compartment is blood or plasma and another compartment is extra vascular fluids and other body tissues.

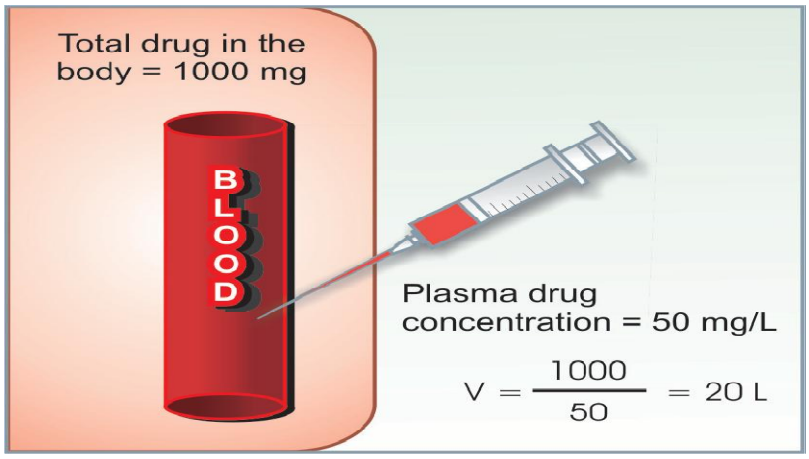

Fig. 4. Illustration of the concept of apparent volume of distribution (V). In this example, 1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L, apparent volume of distribution is 20 L

Volume of distribution:-

The volume of distribution *(Vd),* also known as apparent volume of distribution, is a pharmacological, theoretical volume that the total amount of administered drug would have to provide the same concentration as it is in blood plasma. If the amount of drug *(X)* and the resulting concentration *(C)* are known, then the volume of distribution *(Vd)* can be calculated using the simplified equations.

X =Vd/C,

Where X = amount of drug in body,
Vd = volume of distribution
C = plasma concentration

Volume of distribution = $\frac{\text{Total amount of drug administered}}{\text{Drug present in plasma concentration}}$

The interaction of drugs and protein complex formation is called protein binding of drug, it is two types.

a) **Intracellular/Primary receptor**
b) **Extracellular/Secondary/Silent receptor**

a) Intracellular/Primary receptor: - The drugs bound with cell protein, which may be drug receptor and such binding show a pharmacological response and such receptor, which bind/interact with drug called primary receptor.

b) Extracellular/Secondary/Silent receptor: - The drugs bind to extracellular protein, which is not show a pharmacological response that is called secondary or silent receptor. The most silent or secondary receptor of extracellular protein is plasma protein (particularly albumin).

A drug in the body can interact with several tissue components of which are generally the macromolecules, proteins, DNA and adipose.

Binding of drug are two types:-

A. Binding of drug to blood components
a) Plasma protein
b) Blood cells
B. Binding of drug to extra vascular tissues

A. Binding of drug to blood components:- The plasma protein and blood cells are a complex form of blood but these are separately bind with drugs and produces different pharmacological effects on these components.

a) Plasma protein drug binding:- It is a reversible process of drug interaction, where the interaction of drugs and plasma proteins (human albumin serum, α acid glycoprotein, lipoprotein and α_1-α_2 globulin) complex formation is called plasma protein drug binding. The plasma proteins bound drug nor metabolized nor excreted or nor pharmacologically active and these are not show a pharmacological response.

A) Human albumin serum
B) α acid glycoprotein
C) Lipoprotein
D) α_1-α_2 globulin
E) β_1 - β_2 & γ globulin

b) Blood cells binding:- The RBC is a major cell component of drug binding it is bind with drugs and shows a pharmacological response. It has been shown that the rate and extent/amount of entry into RBC is more for lipophilic/lipid soluble drugs, e.g. phenytoin. Hydrophilic/water soluble drugs like ampicillin do not enter RBC.

A) Hemoglobin
B) Carbonic anhydrase
C) Cell membrane

A) Hemoglobin:-

It has a molecular weight of 64,500 (almost equal to that of HSA) but is 7 to 8 times the concentration of albumin in blood. Drugs like phenytoin, pentobarbital and phenothiazines bind to haemoglobin.

B) Carbonic anhydrase:-

Drugs known to bind to it are acetazolamide and chlorthalodone (i.e cabonic anhydrase inhibitors).

C) Cell membrane:-

Imipramine and chlorpromazine are reported to bind with the RBC membrane.

B. Binding of drug to extra vascular tissues:-

A drug can bind to one or more of the several tissue components. The drugs bind to extra vascular tissue are Liver>kidney>lungs>muscle>intestine other are skin, eye, hair, bone, fat. Several example of extravascular tissue drug binding are:

Liver:- As stated earlier, epoxides of a number of halogenated hydrocarbons and paracetamol bind irreversibly to liver tissues resulting in hepatotoxicity.

Lungs:- Basic drugs like Imipramine, chlorpromazine and antihistamines accumulate in lungs.

Kidney:- Metallothionin, a protein present in kidney, binds to heavy metals such as lead, mercury and cadmium and results in their renal accumulation and toxicity.

Skin:- Chloroquine and phenothiazines accumulate in skin by interacting with melanin.

Eyes:- The retinal pigments of the eye also contain melanin. Binding of chloroquine and phenothiazines to it is responsible for retinopathy.

Hairs:- Arsenicals, chloroquine and phenothiazines are reported to deposit in hair shafts.

Bones:- Tetracycline is a well known example of a drug that binds to bones and teeth. Administration of this antibiotic to infants or children during odontogenesis results in permanent brown yellow discoloration of teeth. Lead is known to replace calcium from bones and cause their brittleness.

Fats:- Lipophilic drugs such as thiopental and the pesticide DDT accumulate in adipose tissue by partitioning into it. Receptors have stated that adipose localization of drugs is a result of binding competition between adipose and non adipose tissue (lean tissues like muscles, skin and viscera) and not partitioning.

Nucleic acids:- Molecular components of cells such as DNA interact strongly with drugs like chloroquine and quinacrine resulting in distortion of its double helical structure.

3.7 Redistribution

When highly lipid soluble drugs given in intravenous and inhalational, its distributed to organs with high blood flow (i. e. brain, heart, kidney etc) later less vascular but more bulky tissues (muscle, fat) take up the drug plasma concentration falls and the drug is not involve these site. Greater the lipid solubility of the drug, faster is its redistribution.

Kinetics of protein drug binding:- If P represents proteins and D the drug, then applying low of mass action to reversible protein drug binding: we can write;

$$P + D \leftrightarrow PD$$

At equilibrium

$$K_a = \frac{[PD]}{[P][D]}$$

$$[PD] = K_a [P][D]$$

Where, [P] = concentration of free protein
[D] = concentration of free drug
[PD] = concentration of protein drug complex
K_a = association rate constant

Factor affecting drugs distribution are:-

1. Physiochemical properties of drug

a) Particle size
b) Aqueous/lipid solubility
c) pKa value of drug
d) Diffusion of drug
e) Ph
f) Mass

2. Pharmaceutical factor

a) Lipid : water partition
b) Drug interaction
c) Coefficient of the drug
d) Binding of drug to blood components

3. Biological factors

a) Organ/tissue size
b) Age
c) Diet
d) Obesity
e) Pregnancy
f) Degree of plasma protein binding
g) Fat lean body mass ratio
h) Disease state