

DRUG DISTRIBUTION

❖ **Drug distribution**

- It refers to the reversible transfer of a drug between the blood and the extra vascular fluids and tissues of the body (for example, fat, muscle, and brain tissue).

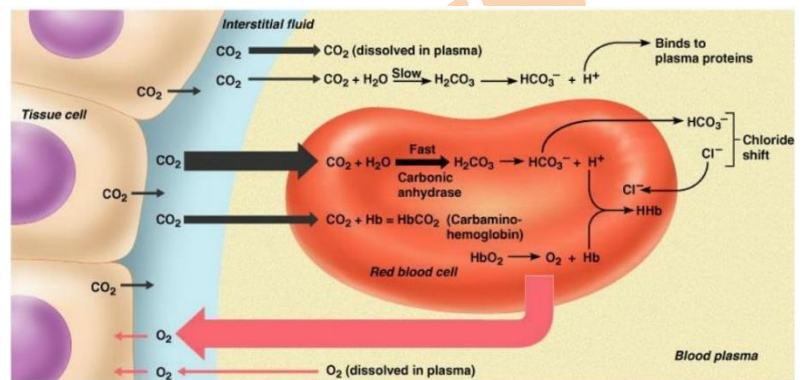
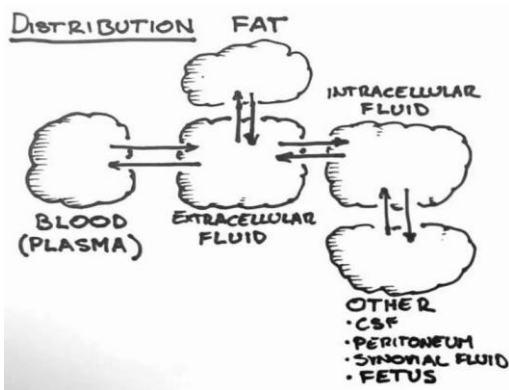
Drugs come into the circulation after absorption



From plasma, drugs have to cross the capillary membrane to come to interstitial space



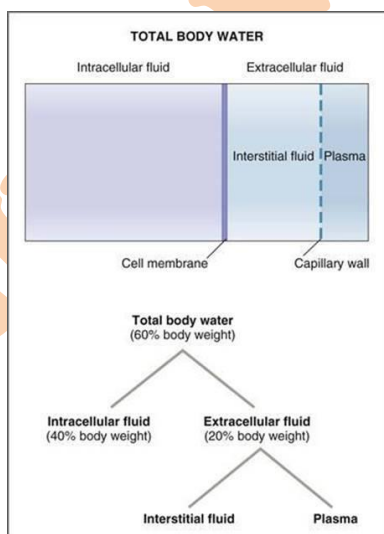
And then need cross the cell-membrane to enter into the intracellular fluid.



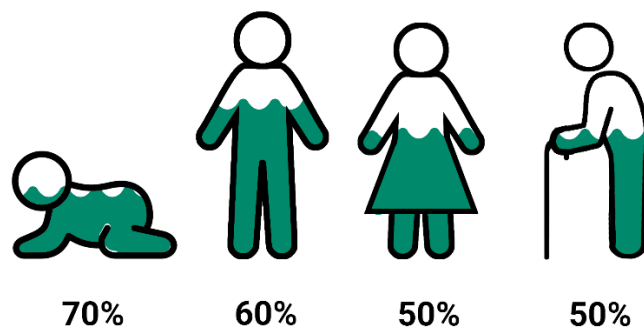
❖ **Volume of distribution (V_d) of drug:**

- V_d means the amount of fluid in which the administered drug is distributed.
- The Volume of distribution (VD), also known as Apparent volume of distribution, is used to quantify the distribution of a drug between plasma and the rest of the body after oral or parenteral dosing.
- It is called as Apparent Volume because all parts of the body equilibrated with the drug do not have equal concentration.

$$V_d = \frac{\text{amount of drug in the body}}{\text{concentration of drugs in the plasma}}$$



Percentage of Body Made up of Water



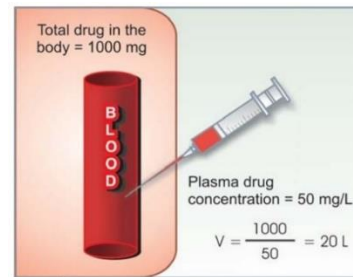
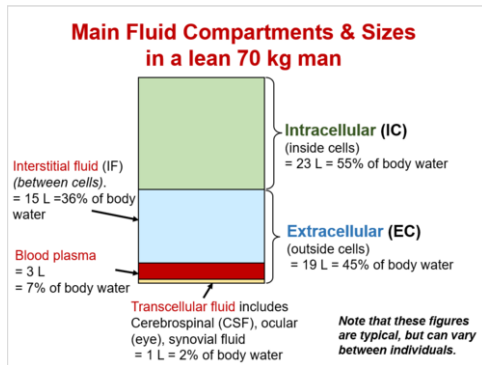


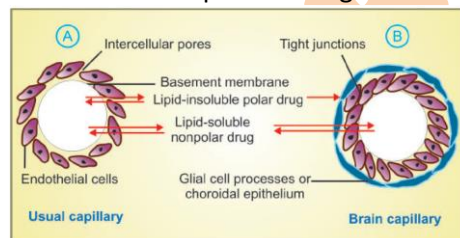
Figure: Illustration of the concept of apparent volume of distribution (V). In this example, 1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L, apparent volume of distribution is 20 L.

❖ Redistribution of drugs

- Highly lipid-soluble drugs get initially 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 withdrawn from the highly perfused sites.
- If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of drug action.
- Greater the lipid solubility of the drug, faster is its redistribution.
- Anaesthetic action of thiopentone sod. injected i.v. is terminated in few minutes due to redistribution. However, when the same drug is given repeatedly or continuously over long periods, the low perfusion high capacity sites get progressively filled up and the drug becomes longer acting.

❖ Penetration into brain and CSF

- The capillary endothelial cells in brain have tight junctions and lack large paracellular spaces. Further, a layer of neural tissue covers the capillaries. Together they form *blood-brain barrier (BBB)*.



- A similar *blood- CSF barrier* is located in the choroid plexus: capillaries are lined by choroidal epithelium having tight junctions.
- Both these barriers are lipoidal and limit the entry of nonlipid-soluble drugs, e.g. streptomycin, eostigmine, etc.
- Only lipid-soluble drugs, therefore, are able to penetrate and have action on the central nervous system.
- In addition, efflux transporters like P-gp and anion transporter (OATP) present in brain and choroidal vessels extrude many drugs that enter brain by other processes and serve to augment the protective barrier against potentially harmful xenobiotics

❖ Passage across placenta

- Placental membranes are lipoidal and allow free passage of lipophilic drugs, while restricting hydrophilic drugs.
- The placental efflux P-gp and other transporters like BCRP, MRP3 also serve to limit foetal exposure to maternally administered drugs.
- Placenta is a site for drug metabolism as well, which may lower/modify exposure of the foetus to the administered drug.
- However, restricted amounts of nonlipid-soluble drugs, when present in high concentration or for long periods in maternal circulation, gain access to the foetus.
- Some influx transporters also operate at the placenta. Thus, it is an incomplete barrier and almost any drug taken by the mother can affect the foetus or the new born (drug taken just before delivery, e.g. morphine).

❖ Plasma protein binding

- Most drugs possess physicochemical affinity for plasma proteins and get reversibly bound to these.
- Acidic drugs generally bind to plasma albumin and basic drugs to α_1 acid glycoprotein.
- Extent of binding depends on the individual compound;
- **The clinically significant implications of plasma protein binding are:**
 - i) Highly plasma protein bound drugs are largely restricted to the vascular compartment because protein bound drug does not cross membranes. They tend to have smaller volumes of distribution (V_d).
 - ii) The bound fraction is not available for action. However, it is in equilibrium with the free drug in plasma and dissociates when the concentration of the latter is reduced due to elimination.
 - iii) Plasma protein binding thus behave as temporary storage of the drug.
 - iv) High degree of protein binding generally makes the drug long acting, because bound fraction is not available for metabolism or excretion, unless it is actively extracted by liver or by kidney.
 - v) The generally expressed plasma concentrations of the drug refer to bound as well as free drug.
 - vi) One drug can bind to many sites on the albumin molecule. Conversely, more than one drug can bind to the same site. This can give rise to displacement interactions among drugs bound to the same site(s). The drug bound with higher affinity will displace that bound with lower affinity and tend to increase the concentration of its free form.
 - vii) In hypoalbuminemia, binding may be reduced and high concentrations of free drug is attained. Some disease may also alter drug binding, e.g. phenytoin and pethidine binding is reduced in uraemia

❖ Tissue storage

- Drugs may also accumulate in specific organs by active transport or get bound to specific tissue constituents.
- Drugs sequestered in various tissues are unequally distributed, and have larger volume of distribution and longer duration of action.
- Some drugs may exert local toxicity due to high concentration, e.g. tetracyclines on bone and teeth, chloroquine on retina, streptomycin on vestibular apparatus, emetine on heart and skeletal muscle.
- Drugs may also selectively bind to specific intracellular organelle, e.g. tetracycline to mitochondria, chloroquine to nuclei.

❖ Factors affecting drug distribution

1. Tissue Permeability of Drugs
 - a. Physicochemical Properties of drug like: Molecular size, pKa, o/w Partition Coefficient
 - b. Physiological barriers to diffusion of drugs
2. Organ/tissue size and perfusion rate
3. Binding of drugs to tissue components.
 - a. Binding of drug to blood components
 - b. binding of drug to extra cellular components
4. Miscellaneous
 - a. Age
 - b. Pregnancy
 - c. Obesity
 - d. Diet
 - e. Disease states
 - f. Drug interactions

1. TISSUE PERMEABILITY OF DRUGS

- The tissue permeability of a drug depends upon the physicochemical properties of the drug as well as the physiologic barriers that restrict diffusion of drug into tissues.
- a) **Physicochemical Properties of drugs of the drug-** Important physicochemical properties that influence its distribution are molecular size, degree of ionization, partition coefficient
 - i) Molecular size-
 - Almost all drugs having molecular weight less than 500 to 600 Daltons easily cross the capillary membrane to diffuse into the extracellular interstitial fluids
 - penetration of drugs from the extracellular fluid into the cells is a function of molecular size, ionization constant(K_a) and lipophilicity of the drug. Only small, water-soluble molecules and ions of size below 50 Daltons enter the cell through aqueous filled channels whereas those of larger size are restricted unless a specialized transport system exists for them.
 - ii) Degree of ionisation(pK_a) –
 - Most drugs are either weak acids or weak bases and their degree of ionization at plasma or ECF pH depends upon their pK_a . All drugs that ionise at plasma pH (i.e. polar, hydrophilic drugs), cannot penetrate the lipoidal cell membrane and tissue permeability is the rate-limiting step in the distribution of such drugs. Only unionized drugs which are generally lipophilicity, rapidly cross the cell membrane.
 - iii) $K_{o/w}$ Partition Co-efficient-
 - In drug discovery and development, lipophilicity is usually expressed by the partition between water and octan-1-ol.
 - A sample of the drug is shaken with a mixture of octan-1-ol and water and its concentration in each layer is determined.
 - The partition coefficient is the measure of the lipophilicity of a drug and an indication of its ability to cross the cell membrane. Higher the partition coefficient, the higher the permeability of the membrane to that particular substance.
- b) **Physiological barriers to Distribution of Drugs**
 - i) Simple Capillary Endothelial Barrier
 - All drugs, ionised or unionised, with a molecular size less than 600 Daltons, diffuse through the capillary endothelium and into the interstitial fluid.
 - Only drugs that bound to that blood components can't pass through this barrier Because of larger size of complex.
 - ii) Simple Cell Membrane Barrier
 - Simple cell Membrane is similar to the lipoidal barrier (absorption) Non polar & hydrophilic drugs will pass through it (passively).
 - Lipophilic drugs with 50-600 Dalton molecular size & Hydrophilic, Polar drugs with < 50 dalton will pass this membrane
 - iii) Blood Brain Barrier
 - A solute may cross to brain via only one of the two pathway:
 - 1) Passive diffusion through the lipoidal barrier: Which restricted to smaller molecules (with a molecular weight less than 700 Daltons) having high o/w partition coefficient.
 - 2) Active transport of essential nutrients such as sugars and amino acid. Thus structurally similar foreign molecules can also penetrate the BBB by the same mechanism.
 - Approaches of BBB Three different approaches have been utilized successfully to promote crossing the BBB by drugs:
 - 1) Use of permeation enhancer: Dimethyl sulphoxide (DMSO)
 - 2) Osmotic disruption of the BBB by infusing internal carotid artery (main blood vessels that **carry blood and oxygen to the brain**)with mannitol.
 - 3) Use of dihydropyridine redox system as drug carriers to the brain.

- iv) Blood – CSF Barrier-
 - Blood- CSF barrier which has permeability characteristics similar to that of the BBB.
 - But For any given drug, its concentration in the brain will always be higher than in the CSF.
- v) Blood Placental Barrier
 - Many drugs having molecular weight less than 1000 daltons and moderate to high lipid solubility e.g. ethanol, sulfonamides, barbiturates, gaseous anaesthetics, steroids, narcotic analgesics, anticonvulsants and some antibiotics, cross the barrier by simple diffusion quite rapidly
 - An agent that causes toxic effect on foetus is called as teratogen. Teratogenicity is defined as foetal abnormalities caused by administration of drug during pregnancy
- vi) Blood Testis Barrier
 - This barrier is located at Sertoli Sertoli cell junction.
 - It is the tight junctions between the neighbouring Sertoli cells that act as the blood-testis barrier. This barrier restricts the passage of drugs to spermatocytes and spermatids.

2. ORGAN/TISSUE PERFUSION RATE

- Under perfusion-rate diffusion of the highly lipophilic drug from the systemic circulation to a specific tissue/organ is primarily dependent on the blood flow within an organ or tissue.
- Organs like the liver and the heart are highly perfused with blood. By contrast, the bone and the adipose tissues experience less blood perfusion. Therefore, drugs are likely to distribute more rapidly to tissues/organs that are more richly perfused with blood.

3. BINDING OF DRUGS TO TISSUE COMPONENTS

a) Binding of drugs to blood components

i) Plasma proteins

- Human serum albumin:-all types drug
- α 1- acid glycoprotein :-basic drugs(impr)
- Lipoproteins :-basic, lipophilic drugs(chlorpromazin)
- α 1-Globuline :-steroids like corticosterone ,vit-B12
- α 2-Globuline :-vit-A,D,E,K, cupric ions.
- Haemoglobin :-Phenytoin, phenothiazines
- The binding of drug to plasma protein is reversible –The extent or order of binding of drugs to various plasma proteins is:

Albumin > α 1-Acid Glycoprotein > Lipoproteins > Globulins > Human Serum Albumin (HSA)

ii) Blood cells

- RBC : 40% of blood comprise of blood cells out of that 95% cells are RBC (RBC comprise of haemoglobin), drugs like, phenytoin, phenobarbitone binds with Hb imipramine, chlorpromazine binds with RBC Cell wall
- The RBC comprises of 3 components each of which can bind to drugs:
 - a) Haemoglobin
 - b) Carbonic Anhydrase
 - c) Cell Membrane

b) Binding of drugs to extra vascular tissues

- Tissue-drug binding result in localization of drug at specific site in body and serve as reservoir
- As binding increases it also increase bio-logical half life.
- Irreversible binding leads to drug toxicity
- Liver > kidney > lungs > muscle > skin > eye > bone > Hair, nail

4. Miscellaneous Factors

Difference in distribution pattern of a drug in different age groups are mainly due to differences in:

- i) Age:
 - a) Total body water-(both Intracellular & Extracellular) greater in infants lower in older
 - b) Fat content - It is also higher in infants & in elderly
 - c) Skeletal muscles- It is also higher in infants & in elderly
 - d) Organ composition- BBB is poorly developed in infants & myelin content is low & cerebral blood flow is high, hence greater penetration of drug in brain
 - e) Plasma protein content- low albumin content in both infants & in elderly
- ii) Pregnancy
 - During Pregnancy, due to growth of UTERUS, PLECENTA and FETUS increases the volume available for distribution drug.
 - The plasma & ECF Volume also increase but albumin content is low
- iii) Obesity –
 - In obese persons, high adipose (fatty acid) tissue so high distribution of lipophilic drugs.
- iv) Diet
 - A diet high in fats will increases free fatty acid levels in circulation thereby affecting binding of acidic drugs
- v) Disease states- disease state change the following conditions
 - Altered albumin & other drug-binding protein concentration.
 - Alteration or reduced perfusion to organ or tissue
 - Altered tissue pH.
 - Alteration of permeability of physiological barrier (BBB) EX- BBB (in meningitis & encephalitis)
- vi) Drug interaction:-
 - Drug interaction that affect distribution are mainly due to difference in plasma protein or tissue binding of drugs.
 - Ex:- Warfarin (Displaced Drug) & Phenylbutazone (Displacer)HSA