Drug Distribution

Distribution is defined as the reversible transfer of drugs between body fluid compartments. After absorption, a drug enters the systemic circulation and is distributed in the body fluids. Various body fluid compartments for a 70-kg person can be depicted as:

Apparent Volume of Distribution

The apparent volume of distribution (aVd) is defined as the hypothetical volume of body fluid into which a drug is uniformly distributed at a concentration equal to that in plasma, assuming the body to be a single compartment.

aVd = Total amount of drug in the body / Concentration of the drug in plasma

- Drugs with high molecular weight (e.g. heparin) or extensively bound to plasma protein (e.g. warfarin) are largely restricted to the vascular compartment; hence their aVd is low.
- If aVd of a drug is about 14–16 L, it indicates that the drug is distributed in the ECF, e.g. gentamicin, streptomycin, etc.
- Small water-soluble molecules like ethanol are distributed in total body water—aVd is approximately 42 L.
- Drugs that accumulate in tissues have a volume of distribution that exceeds total body water, e.g.
- chloroquine (13,000 L) and digoxin (500 L). Haemodialysis is not useful for the removal of drugs with large aVd in case of overdosage.
- In CCF, Vd of some drugs can increase due to an increase in ECF volume (e.g. alcohol) or decrease because of reduced perfusion of tissues.
- In uremia, the total body water can increase, which increases the Vd of small, water-soluble drugs. Toxins that accumulate can displace drugs from plasma-protein-binding sites resulting in an increased concentration of the free form of drug that can leave the vascular compartment leading to an increase in Vd.
- Fat: Lean body mass ratio—highly lipid-soluble drugs get distributed to the adipose tissue. If the ratio is high, the volume of distribution for such a drug will be higher and fat acts as a reservoir for such drugs.

Redistribution

The highly lipid-soluble drug, such as thiopentone, on intravenous administration, immediately gets distributed to areas of high blood flow such as the brain and causes general anaesthesia. Immediately within a few minutes, it diffuses across the blood-brain barrier (BBB) into the blood and then to the less-perfused tissues such as muscle and adipose tissue. This is called redistribution, which results in the termination of drug action. Thiopentone has a rapid onset of action and is used for induction of general anesthesia.

Drug Reservoirs or Tissue Storage

Some drugs are concentrated or accumulated in tissues or some organs of the body, which can lead to toxicity on chronic use. For example, tetracyclines—bones and teeth; thiopentone and DDT—adipose tissue; chloroquine—liver and retina; digoxin—heart, etc.

Blood-Brain Barrier

The capillary boundary that is present between the blood and brain is called the blood-brain barrier (BBB). In the brain capillaries, the endothelial cells are joined by tight junctions. Only the lipid-soluble and unionized forms of drugs can pass through BBB and reach the brain, e.g. barbiturates, diazepam, volatile anesthetics, amphetamine, etc. Lipid-insoluble and ionized particles do not cross the BBB, e.g. dopamine and aminoglycosides.

Pathological states like meningitis and encephalitis increase the permeability of the BBB and allow the normally impermeable substances to enter the brain. For example, penicillin G in normal conditions has poor penetration through BBB, but its penetrability increases during meningitis and encephalitis.

Placental Barrier

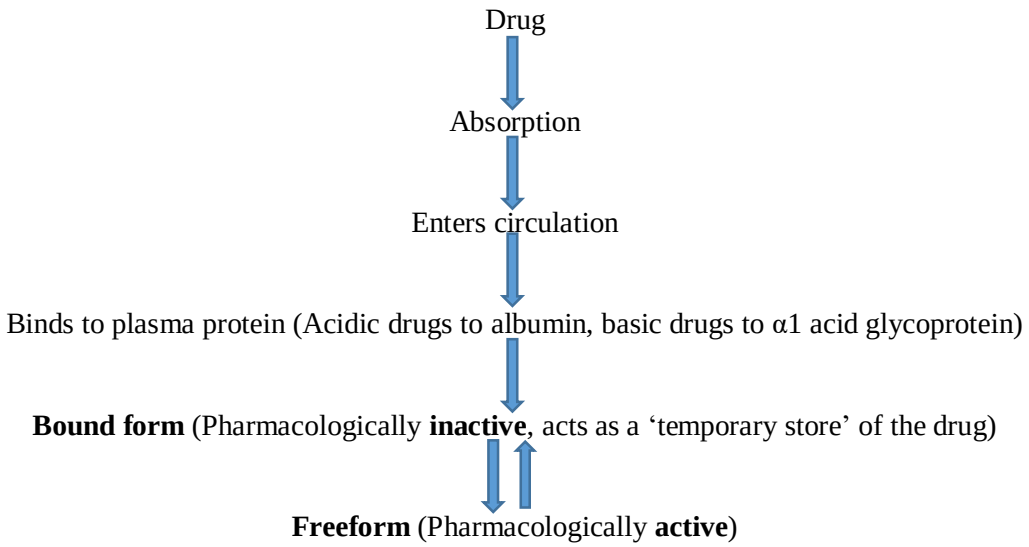
The lipid membrane between mother and fetus is called the placental barrier. Certain drugs administered to the pregnant woman can cross the placenta and affect the fetus/newborn, e.g. anesthetics, morphine, corticosteroids, etc. quarternary ammonium compounds, e.g. d-tubocurarine (d-TC), and substances with high molecular weight like insulin cannot cross the placental barrier.

Plasma Protein Binding

Many drugs bind to plasma proteins like albumin, _1 acid glycoprotein, etc.

Clinical Importance of Plasma Protein Binding

1.



2. Plasma protein binding favors drug **absorption**.

3. Drugs that are highly bound to plasma proteins have a low volume of **distribution**.

4. Plasma protein binding delays the **metabolism** of drugs.

5. Bound form is not available for filtration at the glomeruli; hence **excretion** of highly plasma protein-bound drugs are delayed.

6. Highly protein-bound drugs have a longer duration of action, e.g. sulphadiazine is less plasma protein bound and has a duration of action of 6 h, whereas sulphadoxine is highly plasma protein bound and has a duration of action of 1 week.

7. In case of poisoning, highly plasma-protein-bound drugs are difficult to be removed by hemodialysis.

8. In disease states like anemia, renal failure, chronic liver diseases, etc., plasma albumin levels are low. So there will be an increase in the free form of the drug, which can lead to drug toxicity.

9. Plasma protein binding can cause displacement interactions. More than one drug can bind to the same site on plasma protein. The drug with higher affinity will displace the one having lower affinity and may result in a sudden increase in the free concentration of the drug with lower affinity.