DRUG – DISTRIBUTION

Once a drug has gained access to the blood stream, it gets distributed to other tissues that initially had no drug, concentration gradient being in the direction of plasma to tissues. The extent and pattern of distribution of a drug depends on its:

- lipid solubility
- ionization at physiological pH (a function of its pKa)
- extent of binding to plasma and tissue proteins
- presence of tissue-specific transporters
- differences in regional blood flow.

Movement of drug proceeds until an equilibrium is established between unbound drug in the plasma and the tissue fluids. Subsequently, there is a parallel decline in both due to elimination.

Apparent volume of distribution (V) Presuming that the body behaves as a single homogeneous compartment with volume *V* into which the drug gets immediately and uniformly distributed

$$V = \frac{\text{dose administered i.v.}}{\text{plasma concentration}} \quad ...(3)$$

Since in the example shown in Fig. 2.7, the drug does not actually distribute into 20 L of body water, with the exclusion of the rest of it, this is only an apparent volume of distribution which can be defined as "the volume that would accommodate all the drug in the body, if the concentration throughout was the same as in plasma". Thus, it describes the amount of drug present in the body as a multiple of that contained in a unit volume of plasma. Considered together with drug clearance, this is a very useful pharmacokinetic concept.

Lipid-insoluble drugs do not enter cells— *V* approximates extracellular fluid volume, e.g. streptomycin, gentamicin 0.25 L/kg.

Distribution is not only a matter of dilution, but also binding and sequestration. Drugs extensively bound to plasma proteins are largely restricted to the vascular compartment

and have low values, e.g. diclofenac and warfarin (99% bound) $V = 0.15$ L/kg.

A large value of V indicates that larger quantity of drug is present in extravascular tissue. Drugs sequestrated in other tissues may have, V much more than total body water or even body mass,

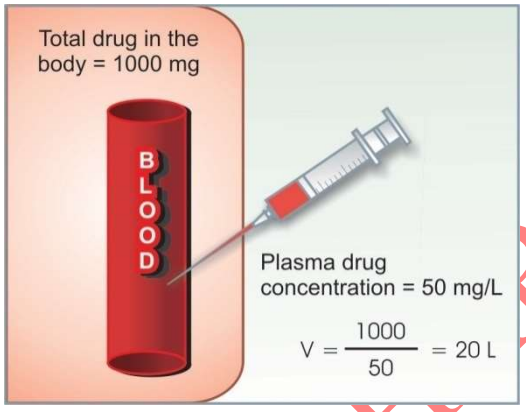

Fig. 2.7: Illustration of the concept of apparent volume of distribution (V).

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 e.g. digoxin 6 L/kg, propranolol 4 L/kg, morphine 3.5 L/kg, because most of the drug is present in other tissues, and plasma concentration is low. Therefore, in case of poisoning, drugs with large volumes of distribution are not easily removed by haemodialysis.

Pathological states, e.g. congestive heart failure, uraemia, cirrhosis of liver, etc. can alter the V of many drugs by altering distribution of body water, permeability of membranes, binding proteins or by accumulation of metabolites that displace the drug from binding sites.

More precise multiple compartment models for drug distribution have been worked out, but the single compartment model, described above, is simple and fairly accurate for many drugs.

Redistribution

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.

Factors governing volume of drug distribution

- Lipid: water partition coefficient of the drug
- *pKa* value of the drug
- Degree of plasma protein binding
- Affinity for different tissues
- Fat: lean body mass ratio, which can vary with age, sex, obesity, etc.
- Diseases like CHF, uremia, cirrhosis

Anaesthetic action of thiopentone sod. Injected is terminated in few minutes due to redistribution. A relatively short hypnotic action lasting 6–8 hours is exerted by oral diazepam or nitrazepam due to redistribution despite their elimination t ½ of > 30 hr. 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, an investment of neural tissue (Fig. 2.8B) covers the capillaries. Together they constitute the so called *blood-brain barrier (BBB).* A similar *blood-CSF barrier* is located in the choroid plexus: capillaries are lined by choroidal

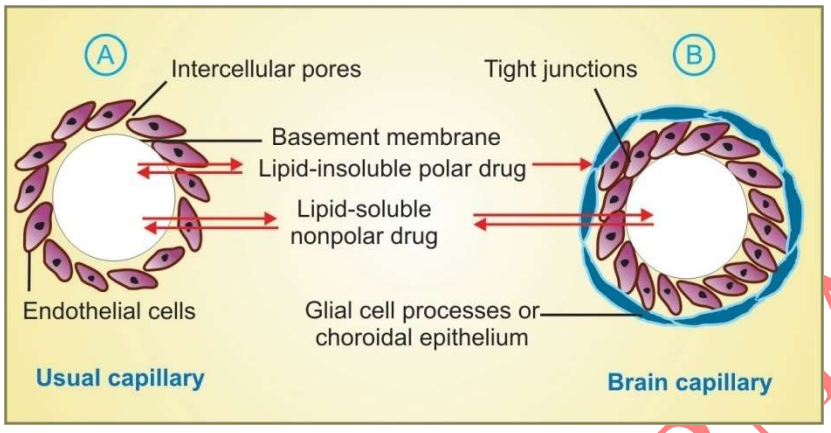

Fig. 2.8: Passage of drugs across capillaries

A. Usual capillary with large paracellular spaces through which even large lipid-insoluble molecules diffuse

B. Capillary constituting blood brain or blood-CSF barrier. Tight junctions between capillary endothelial cells and investment of glial processes or choroidal epithelium do not allow passage of non lipid-soluble molecules/ions epithelium having tight junctions. Both these barriers are lipoidal and limit the entry of nonlipid- soluble drugs, e.g. streptomycin, neostigmine, 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. Dopamine does not enter brain but its precursor levodopa does; as such, the latter is used in parkinsonism. Inflammation of meninges or brain increases permeability of these barriers. It has been proposed that some drugs accumulate in the brain by utilizing the transporters for endogenous substances.

There is also an enzymatic BBB: Monoamine oxidase (MAO), cholinesterase and some other enzymes are present in the capillary walls or in the cells lining them. They do not allow catecholamines, 5-HT, acetylcholine, etc. to enter brain in the active form.

The BBB is deficient at the CTZ in the medulla oblongata (even lipid-insoluble drugs are emetic) and at certain periventricular sites—(anterior hypothalamus). Exit of drugs from the CSF and brain, however, is not dependent on lipid-solubility and is rather unrestricted. Bulk flow of CSF (alongwith the drug dissolved in it) occurs through the

arachnoid villi. Further, nonspecific organic anion and cation transport processes (similar to those in renal tubule) operate at the choroid plexus.

Passage across placenta

Placental membra- nes are lipoidal and allow free passage of lipo- philic 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 newborn (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 alpha acid glycoprotein. Binding to albumin is quantitatively more important. Extent of binding depends on the individual compound; no generalization for a pharmacological or chemical class can be made (even small chemical change can markedly alter protein binding), for example the binding percentage of some benzo- diazepines is: Flurazepam 10% Alprazolam 70% Lorazepam 90% Diazepam 99%

Increasing concentrations of the drug can pro- gressively saturate the binding sites: fractional binding may be lower when large amounts of the drug are given. The generally expressed percen- tage binding refers to the usual therapeutic plasma concentrations of a drug. 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 (except through large paracellular spaces, such as in capillaries). They tend to have smaller volumes of distribution.

Drugs highly bound to plasma protein

To albumin	*To alpha 1-acid glycoprotein*
Barbiturates	beta-blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lidocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Tolbutamide	Verapamil
Warfarin	

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. Plasma protein binding thus tantamounts to temporary storage of the drug.

iii). 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 tubules. Glomerular filtration does not reduce the concentration of the free form in the efferent vessels, because water is also filtered. Active tubular secretion, however, removes the drug without the attendant solvent □ concentration of free drug falls □ bound drug dissociates and is eliminated resulting in a higher renal clearance value of the drug than the total renal blood flow (*see* Fig. 3.3). The same is true of active transport of highly extracted drugs in liver. Plasma protein binding in this situation acts as a carrier mechanism and hastens drug elimination, e.g. excretion of penicillin (elimination t½ is 30 min); metabolism of lidocaine. Highly protein bound drugs are not removed by haemodialysis and need special techniques for treatment of poisoning.

(i) The generally expressed plasma concentra- tions of the drug refer to bound as well as free drug. Degree of protein binding should be taken into account while relating these

to concentrations of the drug that are active *in vitro,* e.g. MIC of an antimicrobial.

(ii) 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. If just 1% of a drug that is 99% bound is displaced, the concentration of free form will be doubled. This, however, is often transient because the displaced drug will diffuse into the tissues as well as get metabolized or excreted: the new steady- state free drug concentration is only marginally higher unless the displacement extends to tissue binding or there is concurrent inhibition of metabolism and/or excretion. The overall impact of many displacement interactions is minimal; clinical significance being attained only in case of highly bound drugs with limited volume of distribution (many acidic drugs bound to albumin) and where interaction is more complex. Moreover, two highly bound drugs do not necessarily displace each other—their binding sites may not overlap, e.g. probenecid and indomethacin are highly bound to albumin but do not displace each other. Similarly, acidic drugs do not generally displace basic drugs and *vice versa*. Some clinically important displacement interactions are:

- Aspirin displaces sulfonylureas.
- Indomethacin, phenytoin displace warfarin.
- Sulfonamides and vit K displace bilirubin (kernicterus in neonates).
- Aspirin displaces methotrexate.

(iii) In hypoalbuminemia, binding may be redu- ced and high concentrations of free drug may be attained, e.g. phenytoin and furosemide. Other diseases may also alter drug binding, e.g. phenytoin and pethidine binding is reduced in uraemia; propranolol binding is increased in pregnant women and in patients with inflammatory disease (acute phase reactant $\square_1$ acid-glycoprotein increases).

Skeletal muscle, heart	— digoxin, emetine (bound to muscle proteins).
Liver	— chloroquine, tetracyclines, emetine, digoxin.
Kidney	— digoxin, chloroquine, emetine.
Thyroid	— iodine.
Brain	— chlorpromazine, acetazolamide, isoniazid.
Retina	— chloroquine (bound to nucleoproteins).
Iris	— ephedrine, atropine (bound to melanin).
Bone and teeth	— tetracyclines, heavy metals (bound to mucopolysaccharides of connective tissue), bisphosphonates (bound to hydroxyapatite)
Adipose tissue	— thiopentone, ether, minocycline, phenoxybenzamine, DDT dissolve in neutral fat due to high lipid-solubility; remain stored due to poor blood supply of fat.

Drugs concentrated in tissues

Tissue storage

Drugs may also accumulate in specific organs by active transport or get bound to specific tissue constituents (*see* box).

Drugs sequestrated in various tissues are unequally distributed, tend to have larger volume of distribution and longer duration of action. Some 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.