Volume of Distribution

Dr. Husnain Qadir,
M.Phil. Scholar Pharmacology,
PGMED, KGMC.

Drug Distribution

- Drug distribution is the process by which a drug reversibly leaves the blood stream and enters the interstitium or cells of the tissues.

Volume of distribution

- It is the hypothetical volume, into which a drug is supposed to be dispersed.
- Volume of distribution is calculated by measuring plasma concentration during distribution phase, before elimination has occurred.

- Equation for calculation of volume of distribution is :

- $$Vd = \frac{\text{Total amount of drug in the body}}{\text{Plasma drug concentration}}$$

- For example:

- If 100 molecules of a drug are injected into blood vessels, 94 molecules are distributed into interstitial spaces and cells of body while 6 molecules remain in plasma.

As physiological plasma volume is about 3 liters, so plasma concentration of drug is 6/3= 2 molecules/liters.

- As Vd = $\frac{\text{Total amount of drug in the body}}{\text{Plasma drug concentration}}$
- The total amount of drug in body is 100 molecules & plasma concentration of drug is 2

- Vd = $\frac{100}{2}$
- So 50 is the volume of distribution of the said drug.

- Drugs with high volume of distribution means, the drug has been largely distributed out of vascular compartment.
- Drugs with low volume of distribution mean most of drug is restricted to plasma.

Drugs with small volume of distribution

- Tolbutamide -7 liters
- Furosemide – 8 liters
- Warfarin – 10 liters

Drugs with large volume of distribution

- Digoxin – 500 liters
- Imipramine – 1600 liters
- Chloroquine – 13000 liters

- As vol of distribution is hypothetical value, that is why it exceeds the physiological body fluids volume (42 liters).

- It simply means that these drugs have the potential to be distributed in large volumes of fluids.

Clinical significance of Vd:

- Drugs highly bound to plasma protein e.g. warfarin or very large molecular weight e.g. heparin also have small Vd being confined only to vascular compartment.

- Abnormal accumulation of fluid e.g. edema, ascities, pleural effusion etc. can markedly increase Vd of drugs.

Clinical significance of Vd cont.

- In case of poisoning/ toxicity, drugs with low Vd can be easily removed by hemodialysis and hemoperfusion, as large amount of drug will be in vascular compartment.
- Vd is also used for deravation of some pharmacological parameters like, Half life, loading dose etc.

Factors effecting distribution of drugs

- Plasma protein binding
- Size of organ
- Tissue blood flow
- Solubility
- Selective distribution
- Redistribution
- Physiological barriers to drug distribution.

Plasma protein binding

- Drugs occurs in two forms
- Free form
  - Freely movable
  - Pharmacologically active
  - Subject to metabolism
- Bound to plasma protein
  - Pharmacologically inactive
  - Acts as reservoir
  - Not subjected to metabolism

Plasma proteins for binding drugs

- Albumin
  - It is the major plasma protein, binding drugs
  - It binds both acidic & basic drugs
- Lipoproteins
- Globulin.

Factors effecting distribution of drugs cont…

- Size of organ
  - Larger the organ greater its ability to take up the drug & vice versa.
- Tissue blood flow
  - Well perfuse tissue faster will be the rate of uptake of drug.

Factors effecting distribution of drugs cont.

- Solubility
  - High lipid solubility higher will be the distribution of drug including CNS.
  - Low lipid solubility lower will be the distribution of drug.

- Selective distribution
  - Some drugs have high affinity for a particular tissue e.g. iodine in thyroid glands and thiopental in CNS.(this is known as selective distribution)

Factors effecting distribution of drugs cont.

- Physiological barriers to drug distribution:
  - Simple barriers
  - Binding barriers
  - Retention barriers
  - Specialized barriers

- Simple barriers:
  - These barriers include all types of cell-membrane.
- Binding barriers:
  - These barriers are capable to bind drug molecules thus bound molecules are not available for distribution.

  For examples:
  - Plasma proteins
  - Tissue proteins

- Retention barriers (Trans-cellular reservoirs)
  - Certain drugs accumulate in these trans-cellular spaces.
    For example:
  - Aqueous humor, synovial fluid, CSF, Endolymph.

Specialized Barriers:

- Blood brain barrier (BBB).
- Blood CSF Barrier.
- Placental barrier.
- Placental barriers.
- Blood-testicular barrier.

- Blood brain barrier (BBB):
  - It separates blood from CSF.
- It is formed due to:
  - Tight –junctions between endothelial cells, those prevent passage of drugs.
  - Capillaries are covered by glial cells, which retard easy transport of drugs.

Blood brain barrier cont.

- Lipid soluble and non-ionized drugs can cross the BBB easily.
- Sometime a transporter can transport a drug across BBB e.g. levodopa is transported by transporter for amino acids.
- Thiopental highly lipid soluble crosses BBB readily, hence used for rapid induction of general anesthesia.
- Neostigmine is highly ionized so can’t cross BBB.
- In meningitis, BBB is disturbed, so drugs are easily distributed to CNS

- Blood CSF Barrier:
  - It is present where BBB is not present i.e. choroid plexus.
- Placental barriers:
  - Non-ionized lipid-soluble drugs can cross this barrier and may harm fetus.
  - This barrier is composed of chorionic villi.
  - Drugs with molecular weight 600 or less can cross placental barrier.

- Blood-testicular barrier:
- It is formed between Sertoli cells of the seminiferous tubule and isolates the further developmental stages of germ cells from the blood.
- Due to this barrier cytotoxic cancer drugs cannot harm active proliferation of germ cells.

Thanks