Drug distribution

Objectives

1. Overview of drug distribution
2. Explain apparent volume of distribution with clinical implications
3Discuss drug binding to plasma proteins and tissues with clinical implications
4. Explain redistribution
5. Discuss blood brain barrier and Placental barrier

Drug Distribution ***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).

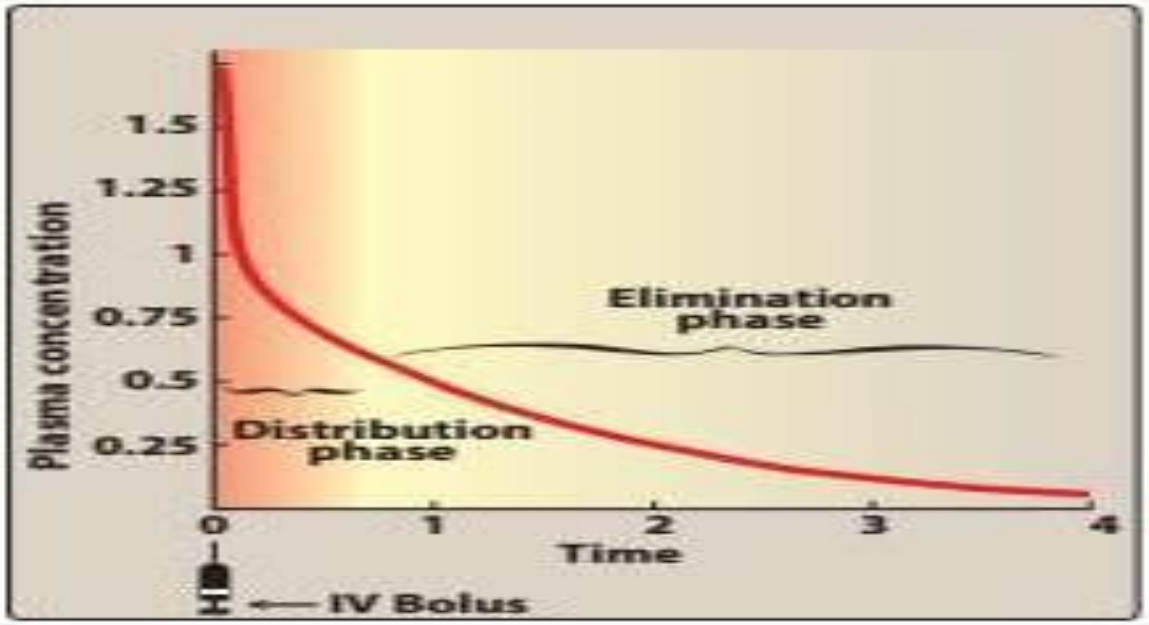
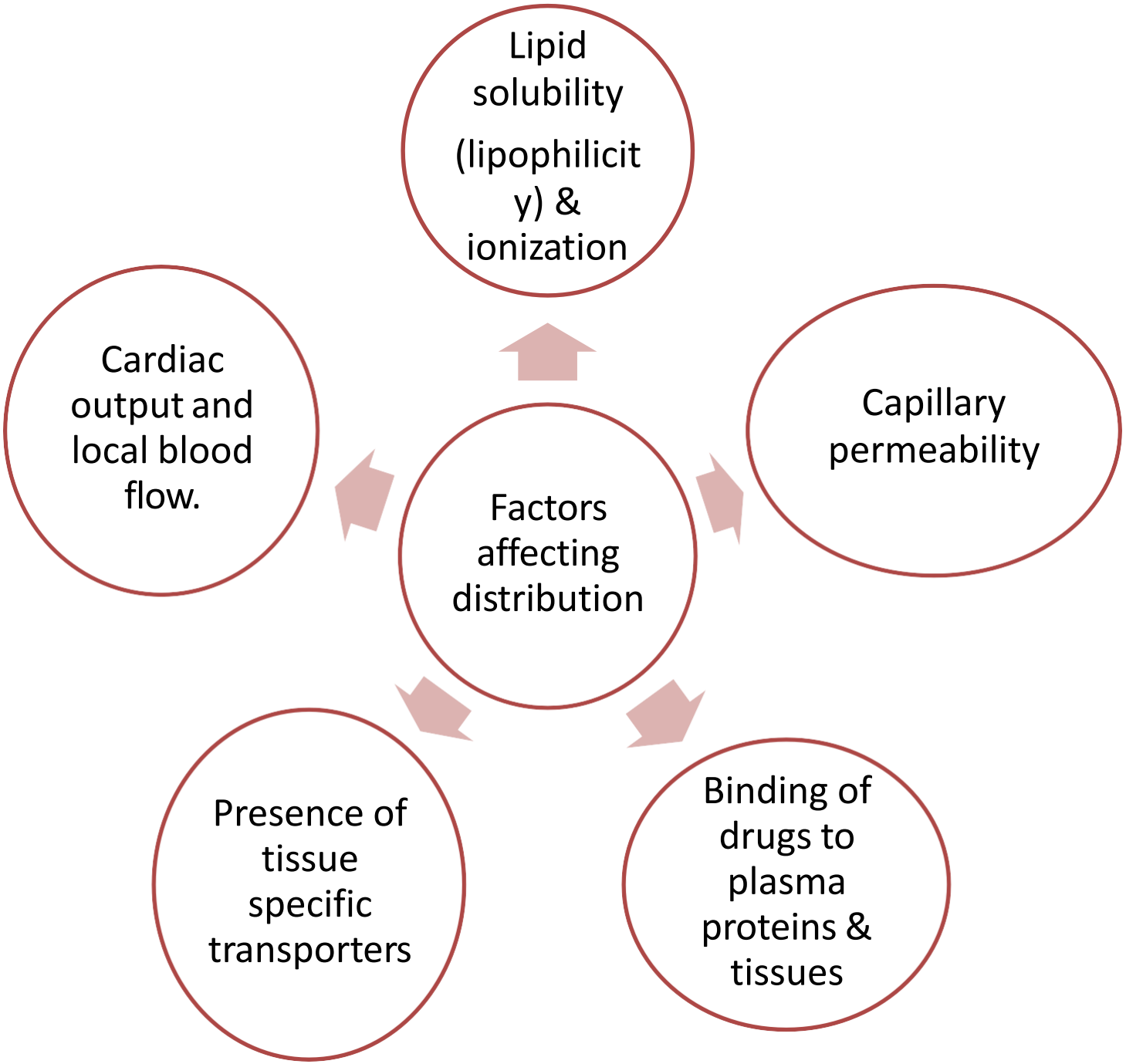


Figure 1.12
Drug concentrations in serum after a single injection of drug. Assume that the drug distributes and is subsequently eliminated.

DRUG ADMINISTRATION

May get distributed to…..

- Vascular compartment
- Total body water
- Interstitial fluid compartment
- Extracellular space
- Intracellular compartments
- Body fat
- Bones
- Placenta
- Brain
- Plasma proteins
- Liver
- Many more organs !!!


Lipid solubility (lipophilicity) & ionization
Capillary permeability
Binding of drugs to plasma proteins & tissues
Presence of tissue specific transporters
Cardiac output and local blood flow.
Factors affecting distribution

Volume of distribution

- Fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma.
- Calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Which means

- If 500 mg of drug reaches circulation…(total amount of drug)
- And if plasma concentration is 0.5 mg/ml
- Vd will be 500/0.5 = 1000 ml.
- Which means you require 1000 ml of fluid to accommodate total 500 mg of drug at concentration of 0.5 mg/ml.

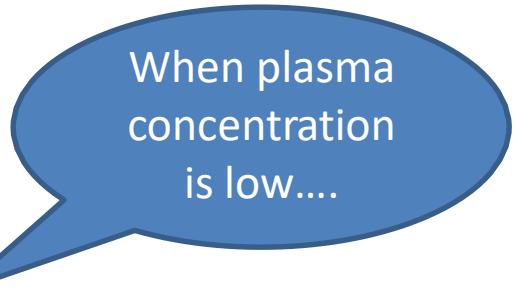
$$Vd(L) = \frac{\text{Total amount administered}}{\text{Plasma concentration}}$$

Vd is low….

When plasma concentration is high….

$$Vd(L) = \frac{\text{Total amount administered}}{\text{Plasma concentration}}$$

$$Vd(L) = \frac{\text{Total amount administered}}{\text{Plasma concentration}}$$



Apparent Volume of distribution

- A drug rarely associates exclusively with only one of the water compartments of the body.
- Vast majority of drugs distribute into several compartments, often avidly binding cellular components, such as lipids, proteins, and nucleic acids.
- Thus, the volume into which drugs distribute is called the apparent volume of distribution (Vd).

Plasma protein binding

- Most drugs posses physicochemical affinity for plasma proteins
  - Acidic drugs bind to plasma albumin, basic drugs bind to α- 1 acid glycoprotein.
  - Reversible manner
  - Extensive binding serves as a circulating drug reservoir
  - Other proteins to which drugs can bind: globulins, transferrin, cerulo-plasmin, tissue proteins & nucleoproteins.

Drugs highly bound to plasma proteins

- To albumin
- Barbiturates
- Benzodiazepines
- NSAIDs
- Valproic acid
- Phenytoin
- Penicillins
- Sulfonamides
- Tetracyclines
- Warfarin

- To α1 acid glycoprotein
- β-blockers
- Bupivacaine
- Lidocaine
- Disopyramide
- Imipramine
- Methadone
- Prazosin
- Quinidine
- Verapamil

Clinical implications of plasma protein

1. Highly plasma protein bound drugs does not cross membranes so largely restricted to vascular compartments.
2. Temporary storage of the drug which is not available for any action.
3. High degree of protein binding generally makes the drug long acting.
4. Plasma concentrations of the drug refer to bound as well as free drug.

Clinical implications of plasma protein

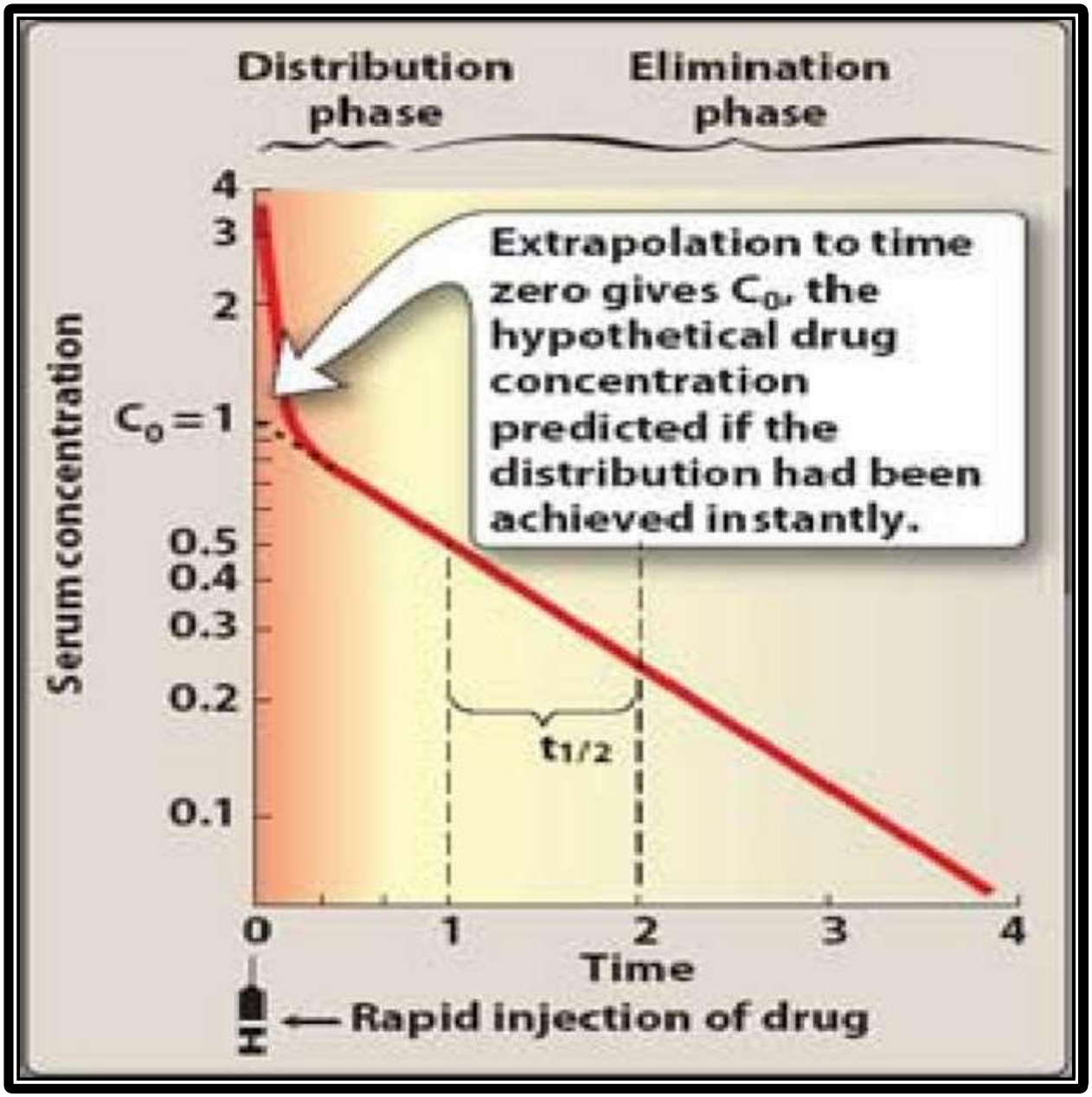
5. One drug can bind to many sites on the albumin molecule. Conversely, more than one drug can bind to the same site.
6. Displacement reactions- (Drug interactions)
   - **Salicylates displace sulfonylureas & methotrexate.**
   - **Indomethacin, phenytoin displace warfarin.**
   - **Sulfonamides and vit K displace bilirubin(kernicterus in neonates) .**
7. In hypoalbuminemia, reduced binding leads to high concentrations of free drug e.g. phenytoin and furosemide.
8. Other diseases: e.g. phenytoin and pethidine binding is reduced in uraemia;

Drugs concentrated in body tissues

- Digoxin, emetine: Skeletal muscles, heart, liver, kidney
- Chloroquine: retina and liver
- Iodine: Thyroid
- Chlorpromazine: eye
- Atropine: iris
- Tetracyclines: Bone and teeth
- Thiopentone , DDT: Adipose tissue

Redistribution

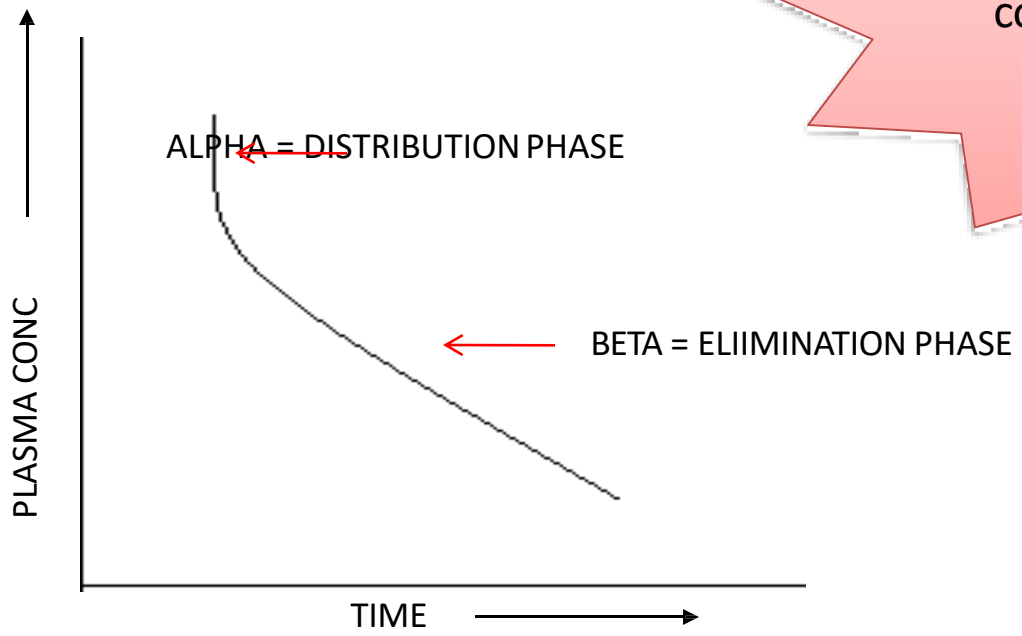
- Highly lipid-soluble drugs get initially distributed to organs with high blood flow (brain, heart, kidney) & later into bulky less vascular tissues (muscle, fat).
- So plasma concentration falls and the drug is withdrawn from these sites
- If the site of action of drug is one of highly perfused organs, redistribution may result in termination of drug action.
- Greater the lipid solubility faster is the redistribution of drug.
- Anaesthetic action of thiopentone sod. injected i.v. is terminated in few minutes due to redistribution.
- To overcome , give continous infusion


Distribution phase
Elimination phase
Serum concentration
4
3
2
$C_0 = 1$
0.5
0.4
0.3
0.2
0.1
Extrapolation to time zero gives C_0, the hypothetical drug concentration predicted if the distribution had been achieved instantly.
$t_{1/2}$
0
1
2
3
4
Time
Rapid injection of drug

PLASMA HALF LIFE

- It is the time taken for the plasma concentration or amount of the drug present in the body to reduce to 50% of previous level.

Clinically t ½ that is calculated from BETA ELIMINATION PHASE is considered as t ½ of drug.



At peak → blood concentration will be 100 %

After 1 half life → blood concentration will be 50 %

After 2 half lives → blood concentration will be 25 %

After 3 half lives → blood concentration will be 12.5 %

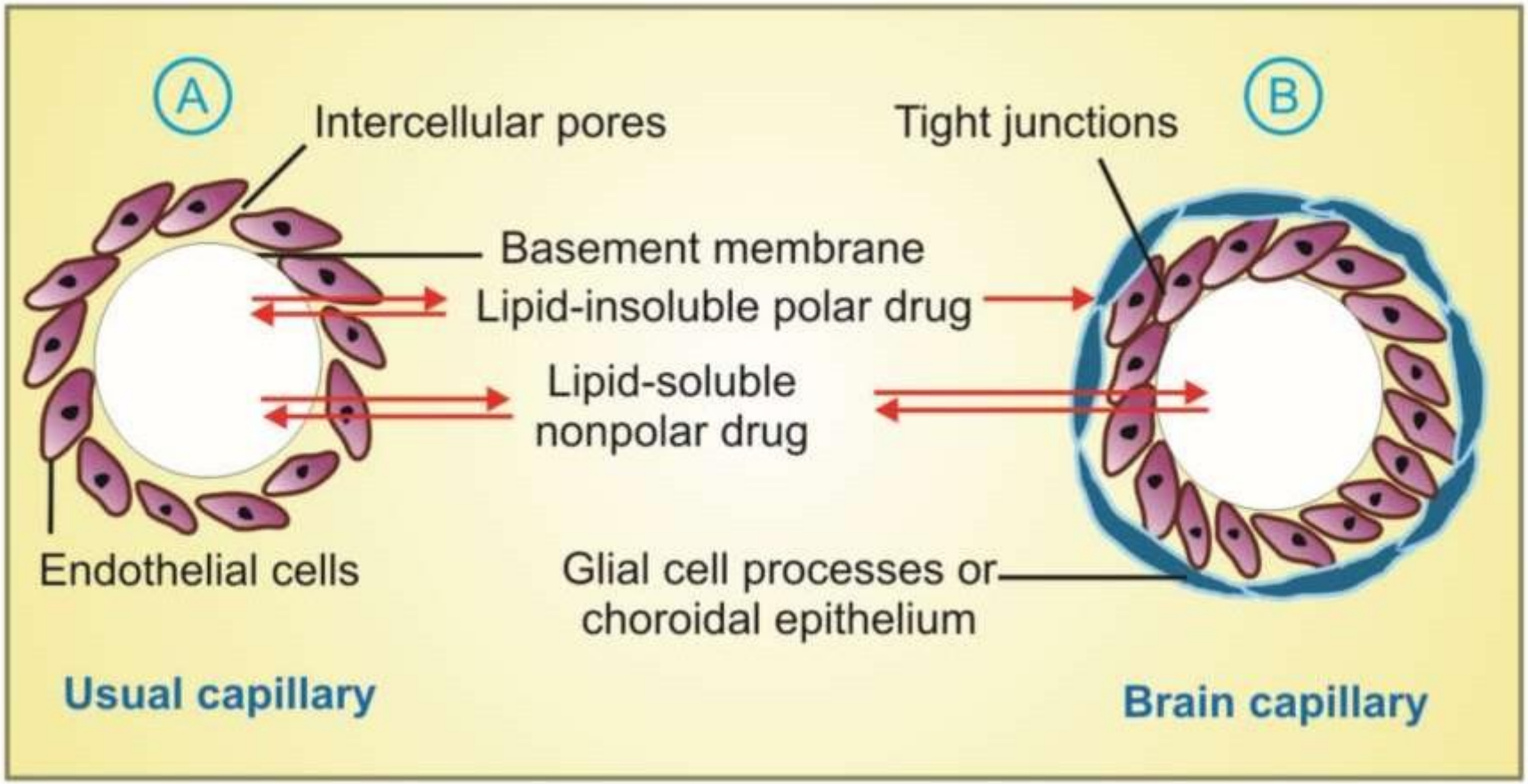
After 4 half lives → blood concentration will be 6.25 %

After 5 half lives → blood concentration will be 3.125 %

So after 4-5 half lives drug will be almost completely eliminated from the body

If you administer a drug before that there will be accumulation of the drug in the body.

Blood brain barrier



Functions and Properties of the BBB

- Protects the brain from "foreign substances" in the blood that may injure the brain.
- Protects the brain from hormones and neurotransmitters in the rest of the body.
- Maintains a constant environment for the brain.

Properties of drugs that can cross BBB

- low molecular weight
- High degree of lipid solubility
- Non ionized
- Tertiary structure and
- Free drug

Placental Barrier

- Lipoidal and allows free passage of lipophilic drugs
- Glycoprotein limits exposure to maternally administered drugs
- Also placenta is site of metabolism- lowers exposure to drugs
- Incomplete barrier
- Congenital anomalies

thanks