

Pharmacokinetics: Distribution of Drugs (Part-1)

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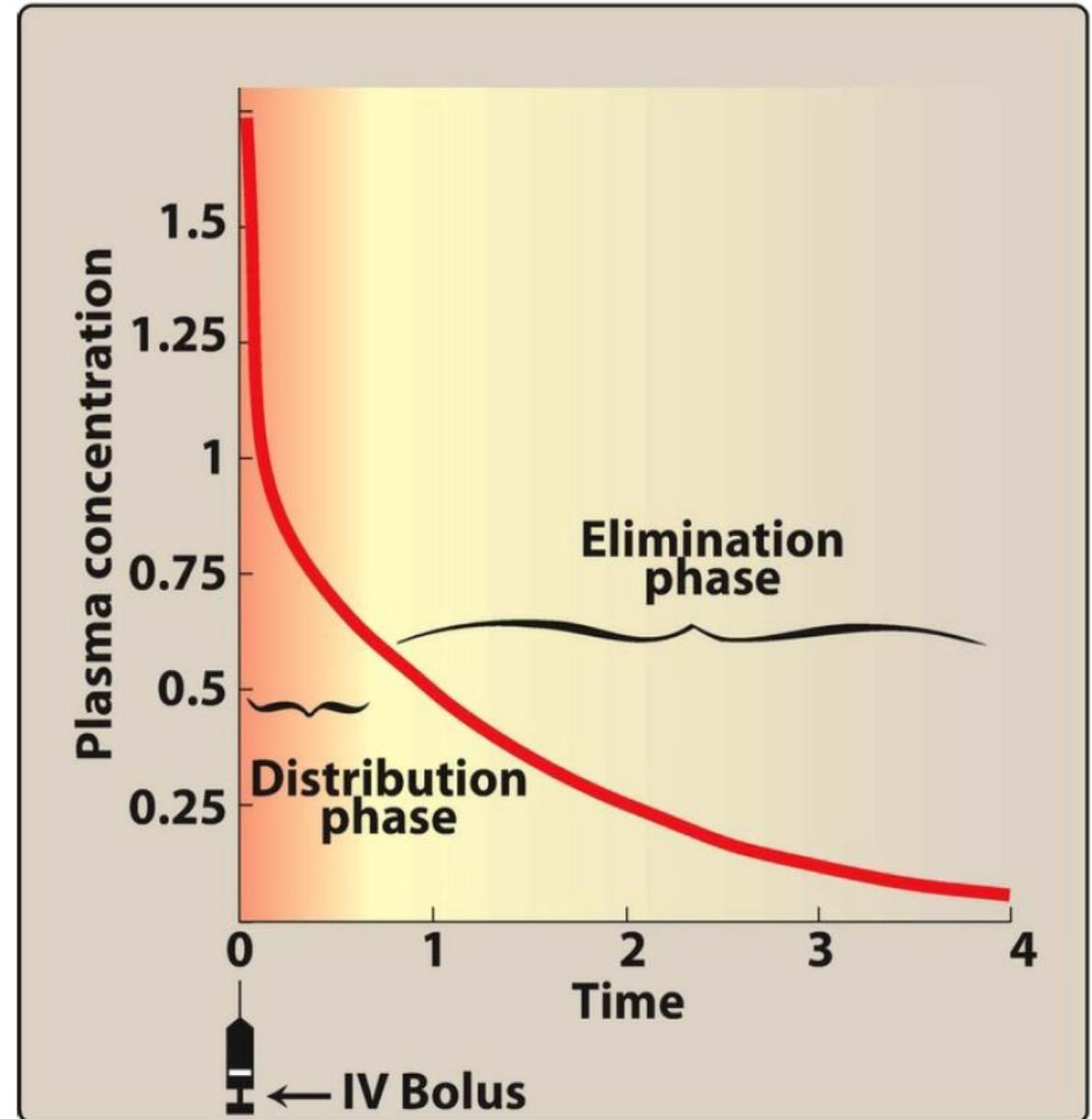
Drug Distribution

- It refers to reversible transfer of a drug between the blood and the extravascular fluids and tissues of the body (e.g. fat, muscle, brain tissue etc).
- Not all Tissues are equal: Distribution of a drug is not uniform throughout the body because of difference in perfusion rates.

✓ For drugs administered IV, absorption is not a factor.

✓ Distribution Phase:

The initial phase immediately following administration represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues.



Factors affecting Drug Distribution

✓ The distribution of a drug from the plasma to the interstitium depends on:-

(I) Cardiac output and local blood flow.

(II) Capillary permeability, tissue volume.

(III) Degree of binding of the drug to plasma and tissue proteins, and

(IV) Relative lipophilicity of the drug.

[I]. BLOOD FLOW

- The rate of blood flow to the tissue capillaries varies widely.
- For instance, blood flow to “vessel-rich organs” (brain, liver, and kidney) is greater than that to the skeletal muscles.
- Adipose tissue, skin, and viscera have still lower rates of blood flow.

Blood Flow

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- Not all Tissues are equal: Distribution of a drug is not uniform throughout the body because of difference in perfusion rates.

TABLE ■ DISTRIBUTION OF BLOOD FLOW IN 70-KG MALE AT REST

	KIDNEYS	HEART	LIVER	BRAIN	SKELETAL MUSCLE	FAT	REMAINDER	Σ
Blood Flow (mL/min)	1100	250	1700	800	900	250	500	5500
Mass (kg)	0.3	0.3	2.6	1.3	34	10	21.5	70
Flow/Mass (mL/min/kg)	3667	833	654	615	26	25	23	
% Cardiac Output	20	4.5	31	14.5	16.4	4.5	9.1	100

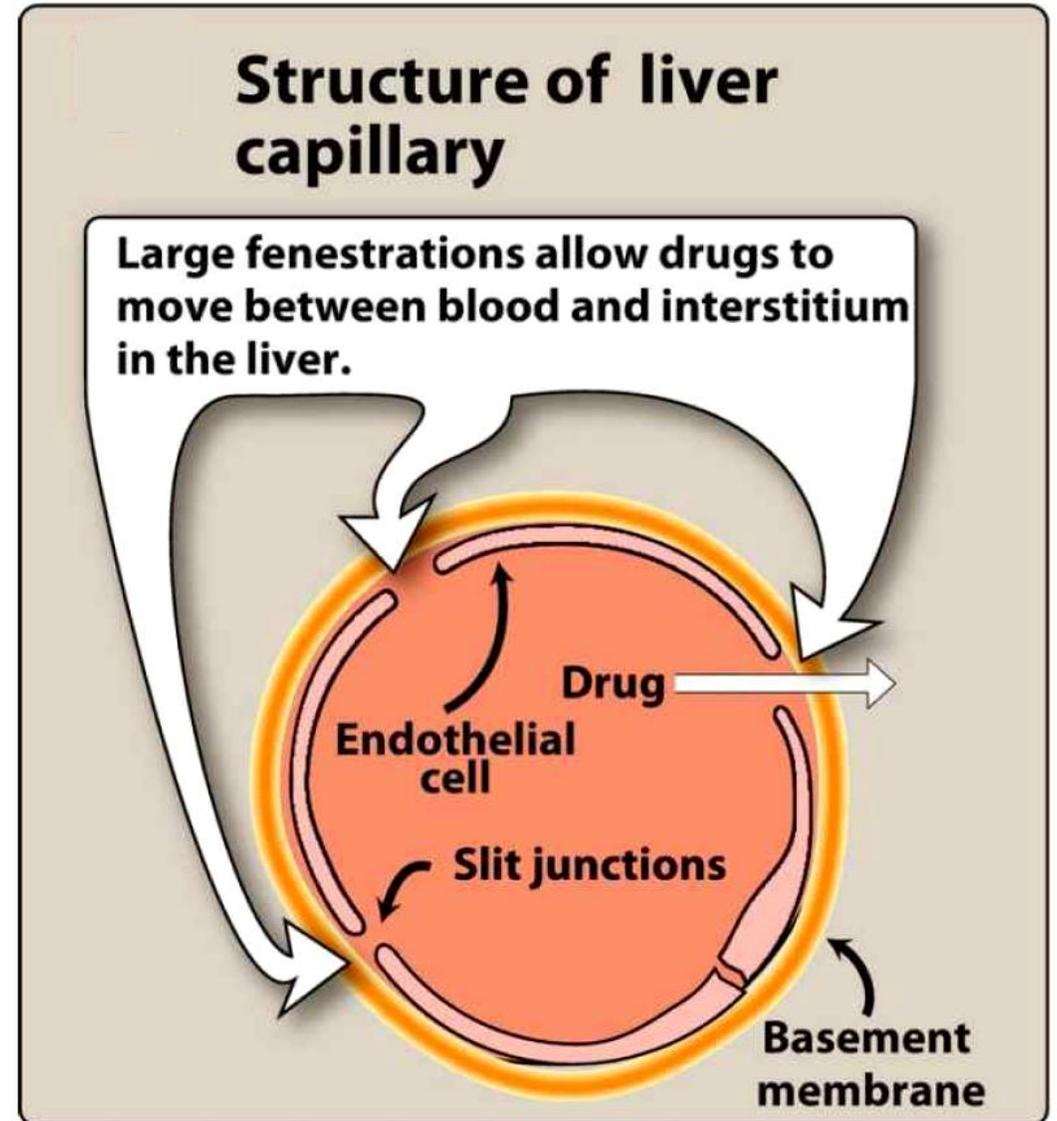
Blood Flow

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- Variation in blood flow partly explains the **short duration of hypnosis** produced by an IV bolus of **propofol**.
- High blood flow, together with high lipophilicity of propofol, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.

[II]. CAPILLARY PERMEABILITY

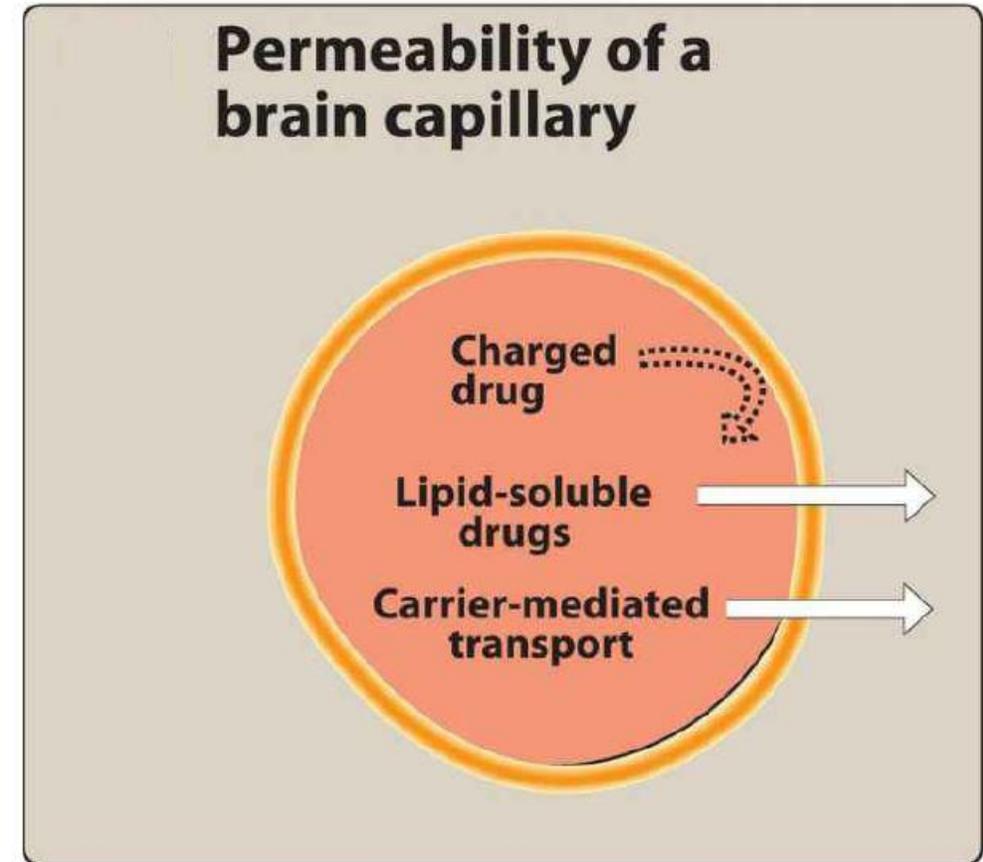
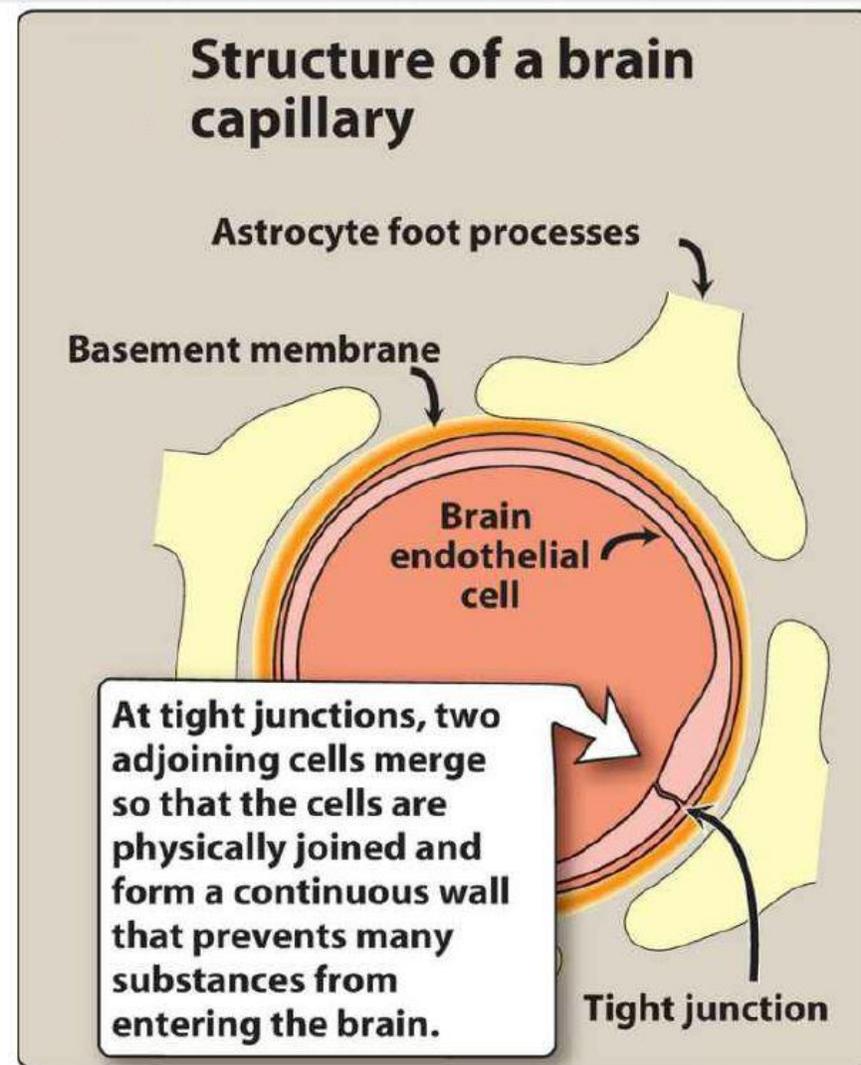
- Capillary structure varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells.
- In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass.



Capillary Permeability

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- In the brain, the capillary structure is continuous, and there are no slit junctions.



Capillary Permeability

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- ✓ To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or undergo active transport.
- ✓ For example, a specific transporter carries levodopa into the brain.
- ✓ Lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane.
- ✓ By contrast, ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions. These closely juxtaposed cells form tight junctions that constitute the blood-brain barrier.

[III]. BINDING OF DRUGS TO PLASMA PROTEINS AND TISSUES

1. Binding to plasma proteins

- ✓ Reversible binding to plasma proteins **sequesters drugs** in a non-diffusible form and slows transfer out of the vascular compartment.
- ✓ **Albumin is the major drug-binding protein**, and it may act as a drug reservoir.
- ✓ As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

Clinically significant implications of Plasma protein binding:-

- ✓ High plasma protein bound drugs are largely restricted to the vascular compartment and tend to have lower volumes of distribution.
- ✓ The **bound fraction** is not available for action. (Bound form - **Temporary storage** of drug).
- ✓ High degree of plasma protein binding generally makes the drug **long acting**, because the bound fraction is not available for metabolism or excretion. (NB: Highly protein bound drugs are not removed even by haemodialysis).
- ✓ **Competition between drugs for protein binding** can lead, rarely, to clinically important drug interactions.

Accumulation and storage of drugs in the body:-

- ✓ Drugs may accumulate in specific organs by binding to specific tissue structures (sequestration).

The examples are -

Digitoxin and emetine	-	Skeletal muscles
Iodine	-	Thyroid
Chloroquine	-	Retina
Tetracyclines & heavy metals	-	Bone and teeth
Thiopentone, DDT, ether etc.	-	Adipose tissue
Chlorpromazine	-	Brain
Calcium	-	Collagen
Griseofulvin	-	Skin, nails & hair roots

Binding of Drugs to Plasma Proteins & Tissues

2. Binding to tissue proteins

- ✓ Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood.
- ✓ Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues.
- ✓ **Tissue reservoirs** may serve as a major source of the drug and **prolong its actions** or cause local drug toxicity. (For example, acrolein, the metabolite of cyclophosphamide, can cause hemorrhagic cystitis because it accumulates in the bladder).

[IV]. LIPOPHILICITY

- The chemical nature of a drug strongly influences its ability to cross cell membranes.
- Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface.
- The major factor influencing the distribution of lipophilic drugs is blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

Thank You

