Pharmacokinetics

DISTRIBUTION

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- **Sources**
- **Lippincott Illustrated Reviews: Pharmacology 7th Edition**
- **Katzung ; Basic & Clinical Pharmacology 14th Edition**
- **Bennett & Brown ; Clinical pharmacology 11th edition**
- **Essentials of Medical Pharmacology; Lafi 09**

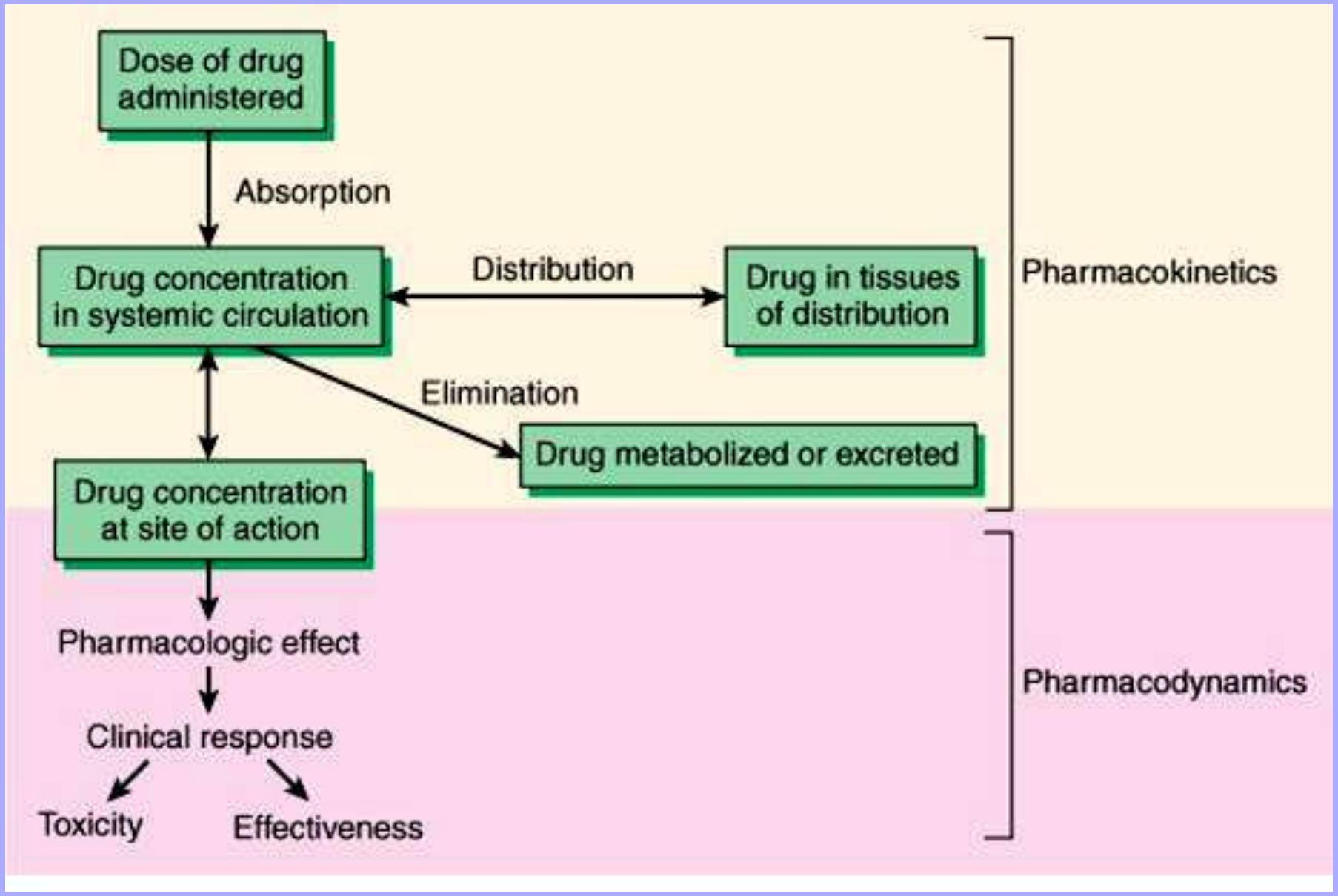
Pharmacokinetics

ABSORPTION

DISTRIBUTION

METABOLISM

Excretion


Dose of drug administered
Absorption
Drug concentration in systemic circulation
Distribution
Drug in tissues of distribution
Elimination
Drug metabolized or excreted
Drug concentration at site of action
Pharmacologic effect
Clinical response
Toxicity
Effectiveness
Pharmacokinetics
Pharmacodynamics

Pharmacokinetics vs. Pharmacodynamics

"Drug" "motion" "power"

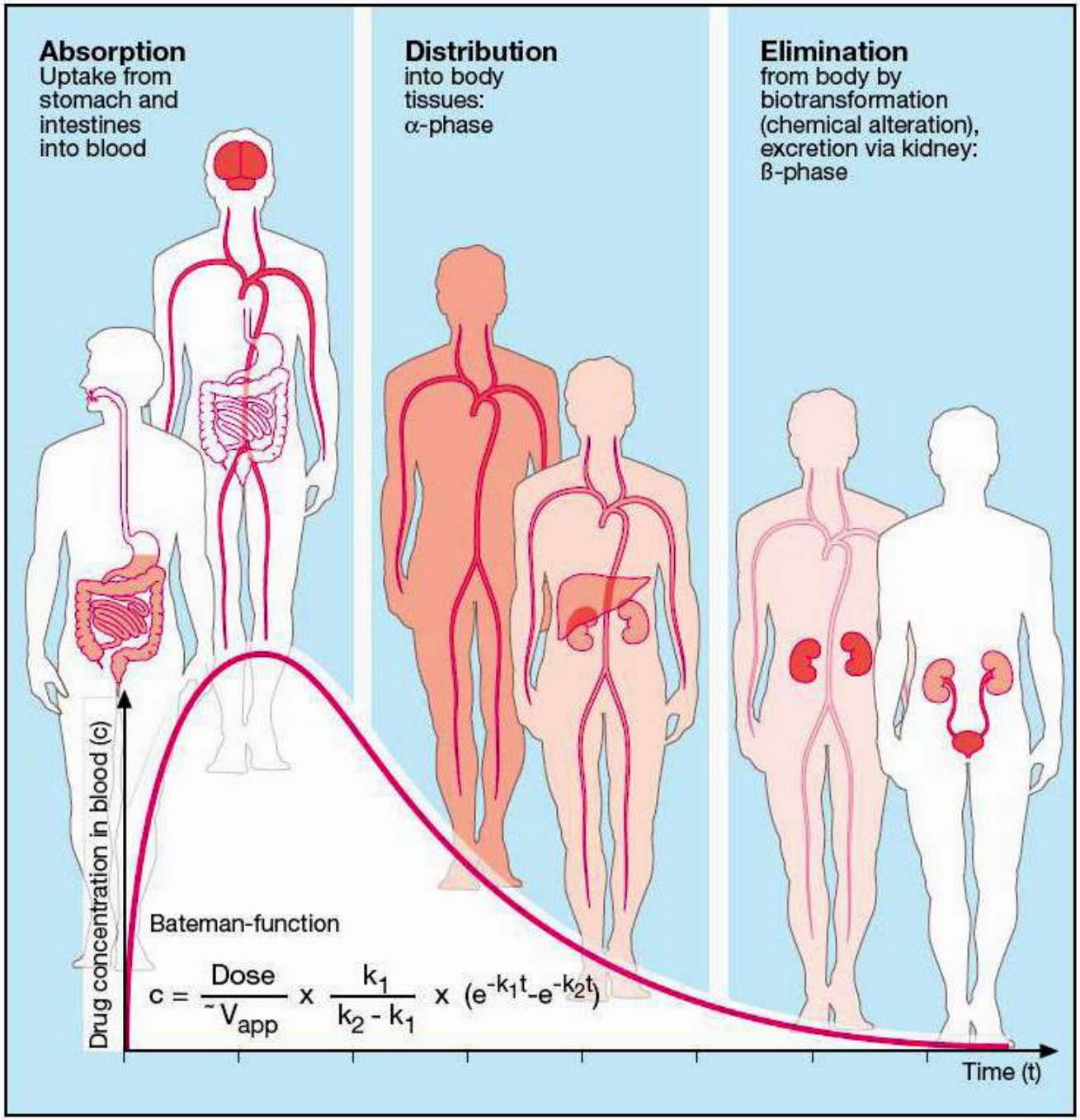
- PK: How does the drug concentration change as it moves through the different compartments of your body

- PD: How does the drug exert its effect on your body

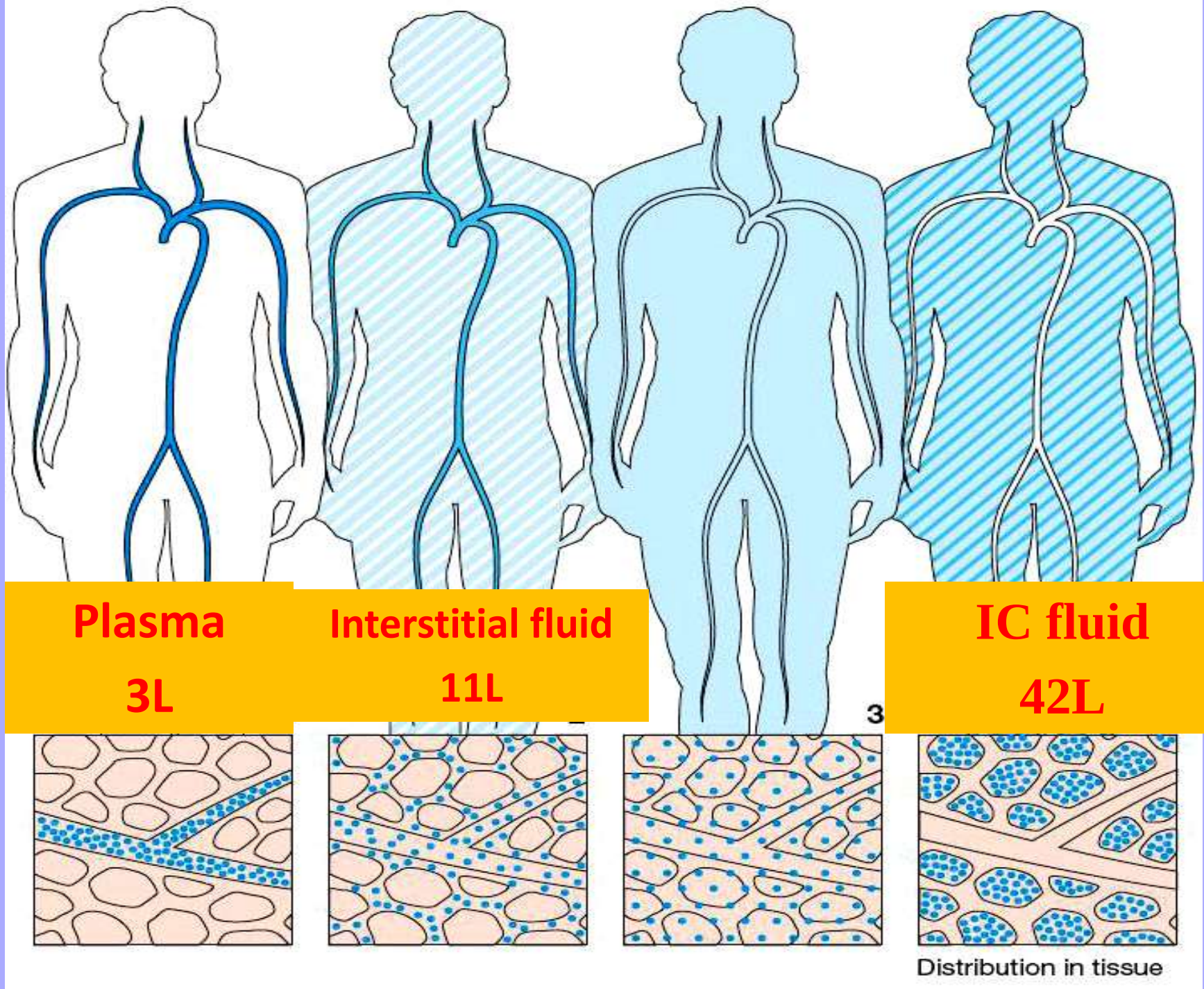
Potency, drug-receptor interactions

- Book Definition:
  - PK: What your body does to the drug
  - PD: What the drug does to your body

- PK:
  - The change in drug concentration as it moves through the different compartments of the body
- Absorption:
  - The process of a substance entering the systemic circulation
  - Depends on the route of administration

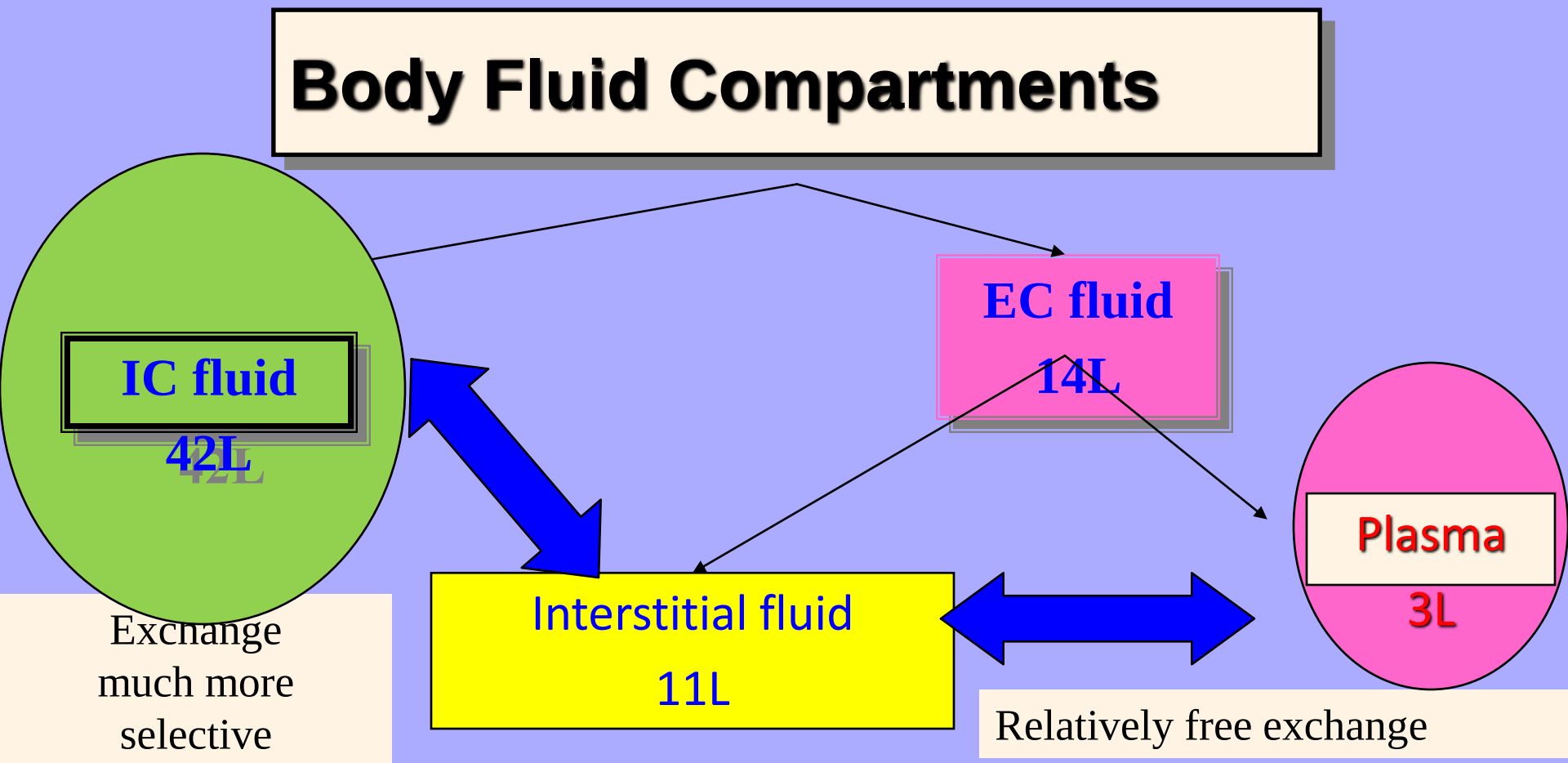


Time course of drug concentration

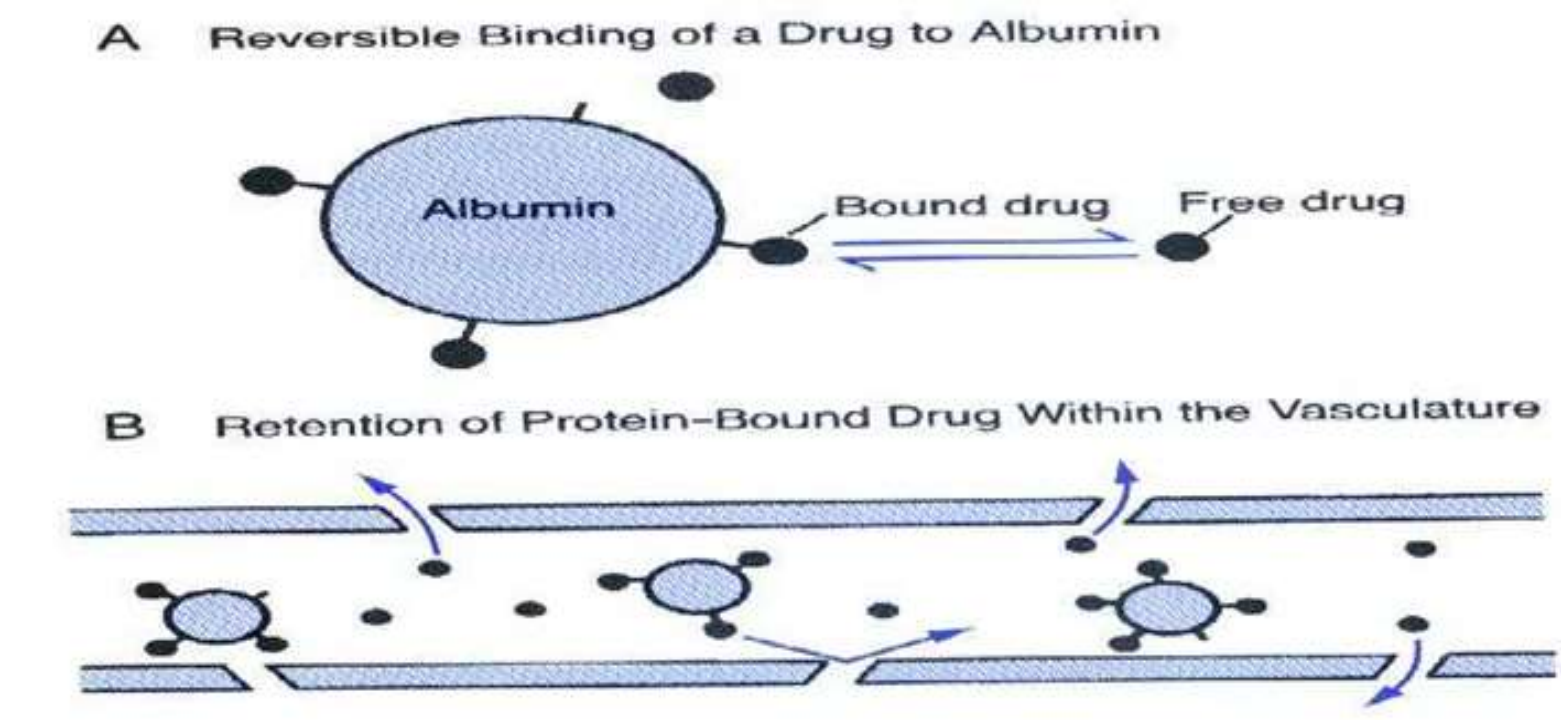

Plasma
3L
Interstitial fluid
11L
IC fluid
42L
Distribution in tissue

DISTRIBUTION

The movement of a drug from the systemic circulation to organs and tissue.



- Many drugs bind to plasma proteins, including albumin, with an equilibrium between bound and free molecules



Drug + Protein (Active, free) ⇌ Drug-Protein Complex (Inactive, bound)

(only unbound drugs cross biomembranes)

-Competition between drugs for plasma protein-binding sites may increase the "free fraction, possibly enhancing the effects of the drug displaced.

- Example: sulfonamides and bilirubin in a neonate with physiological jaundice

Special Barriers to Distribution

- **Placental—most**

small molecular weight drugs cross the placental barrier or lipid-soluble drugs

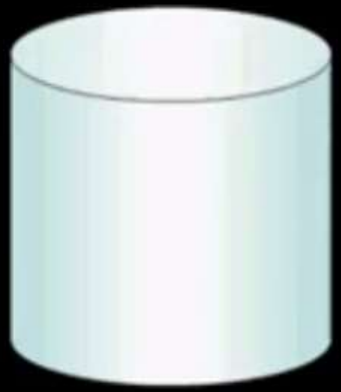
- **Blood-brain**

permeable only to lipid-soluble drugs or those of very low molecular weight.

Volume of Distribution

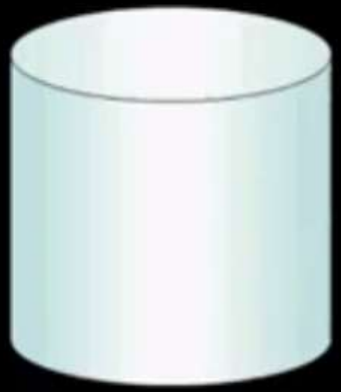
Volume of Distribution

- Volume of distribution tells us how extensively drug is distributed to the rest of the body compared to the plasma.



Here is any volume of water, measured in liters.

Drug



Let’s add any amount of drug, (dose) measured in mass units.

Let's add any amount of drug, (dose) measured in mass units.

We now have a *concentration* of drug in solution, measured in

dose / volume

Here is any volume of water, measured in liters, we can call it a “compartment”.

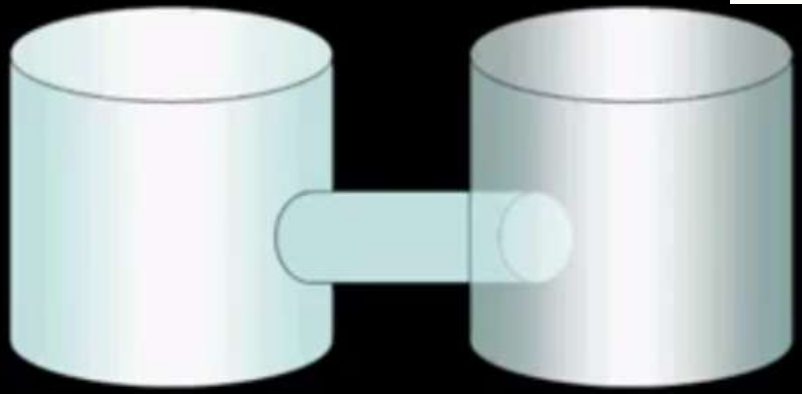
So when we put drug into a single compartment

we can easily surmise amount of drug in "total body".

dose / volume

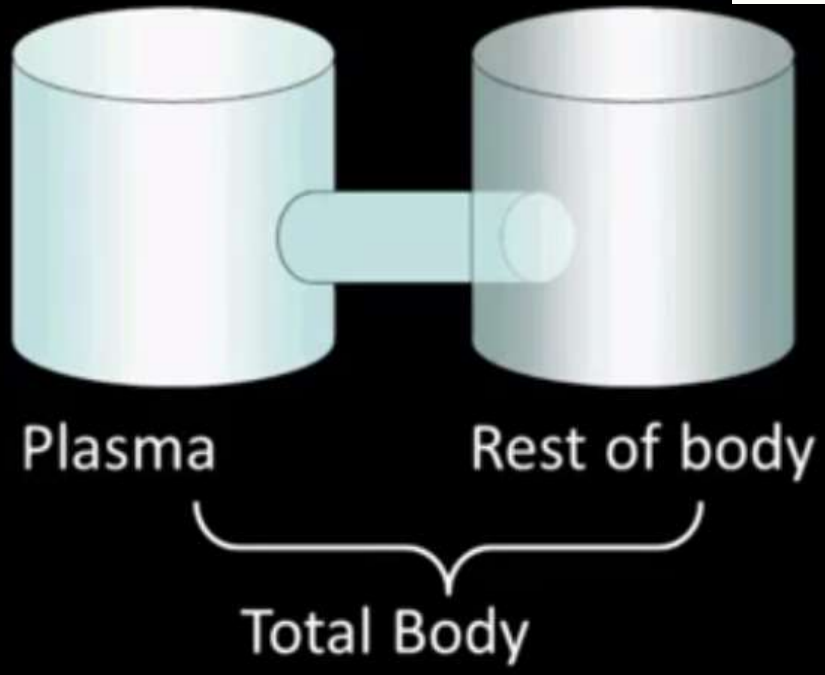
we can easily surmise amount of drug in "total body".

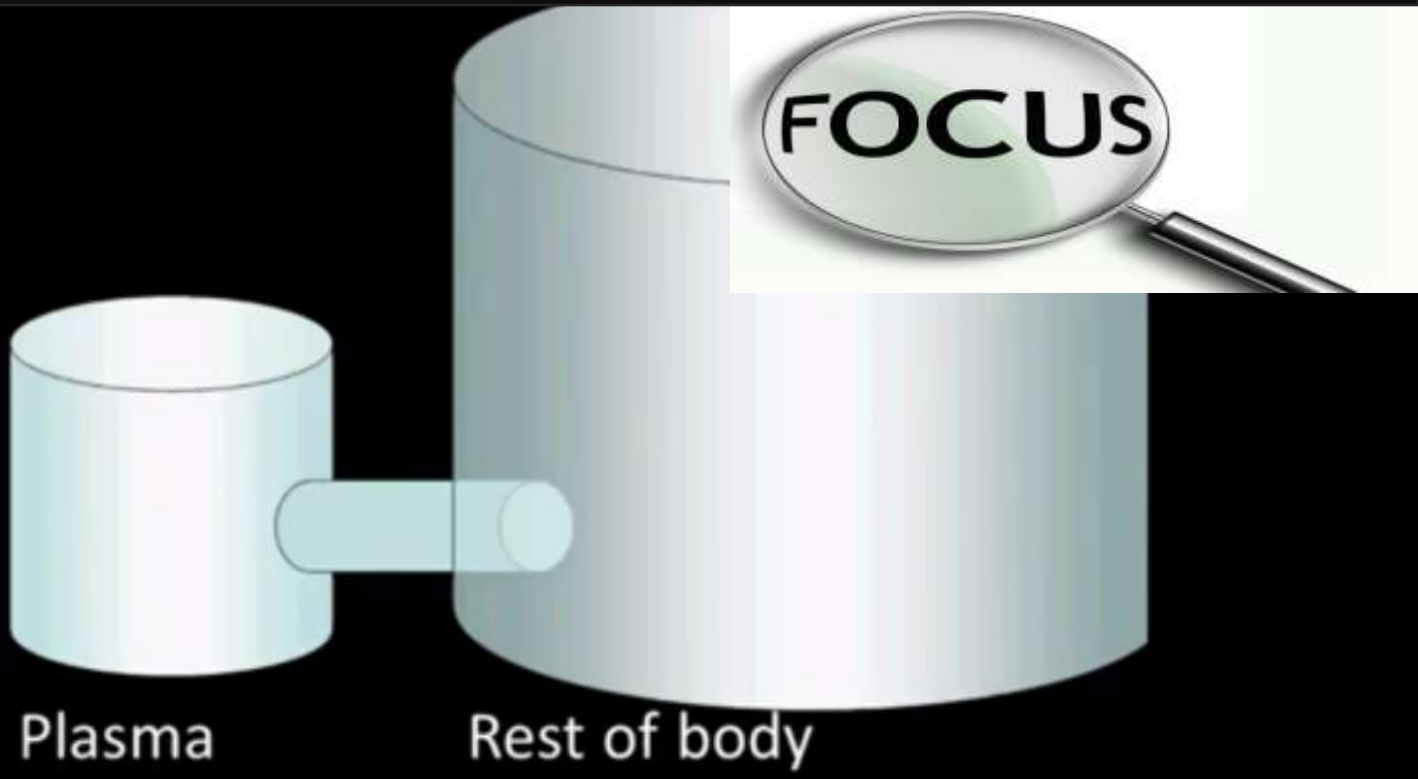
dose / volume



Let's divide the "total body" compartment into 2 compartments.

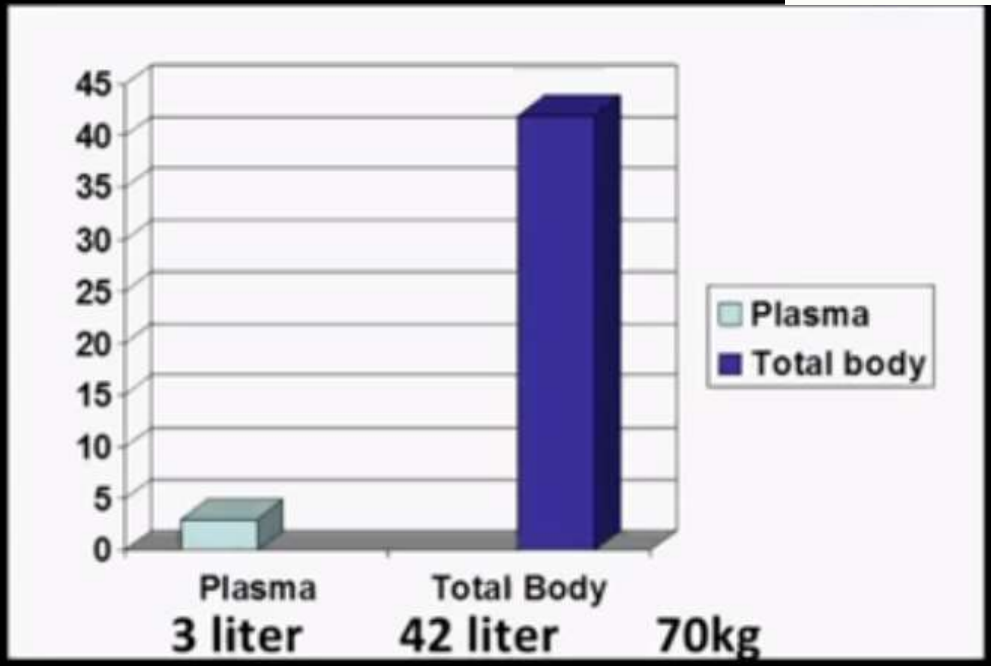

FOCUS

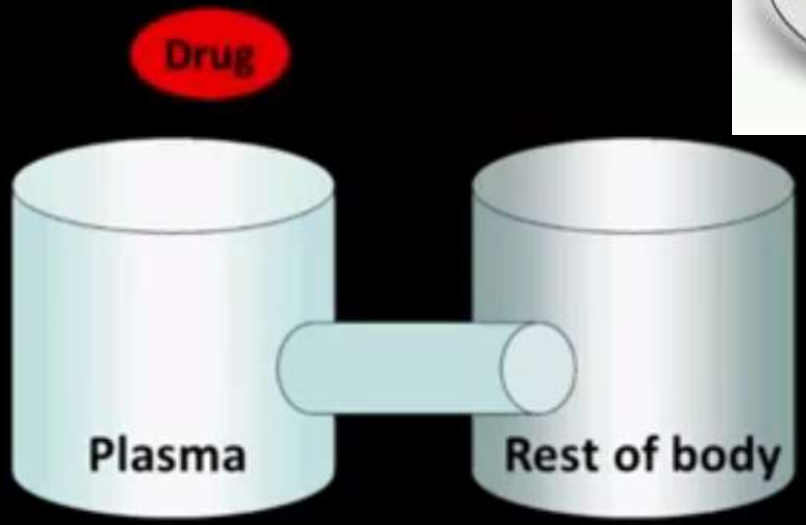

Plasma
Rest of body
Total Body



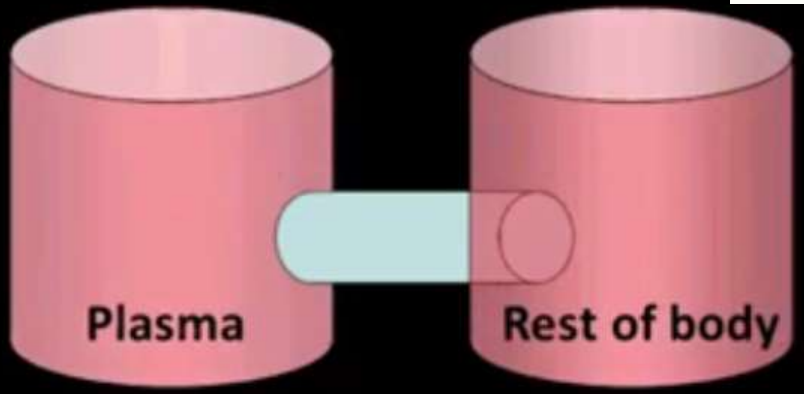
(not the same size)

Volume of Water Compartments

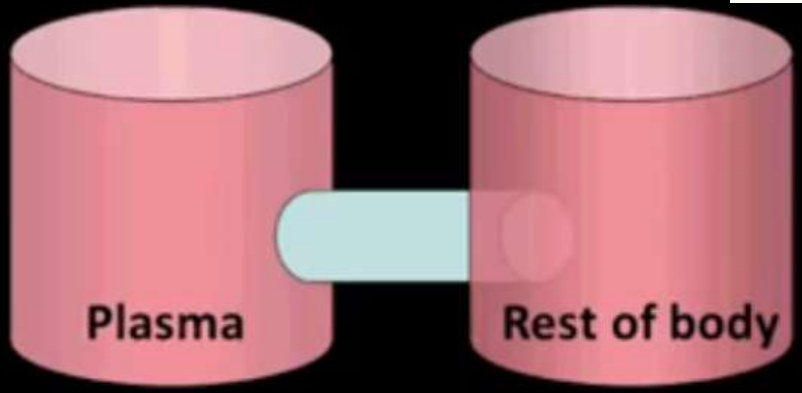




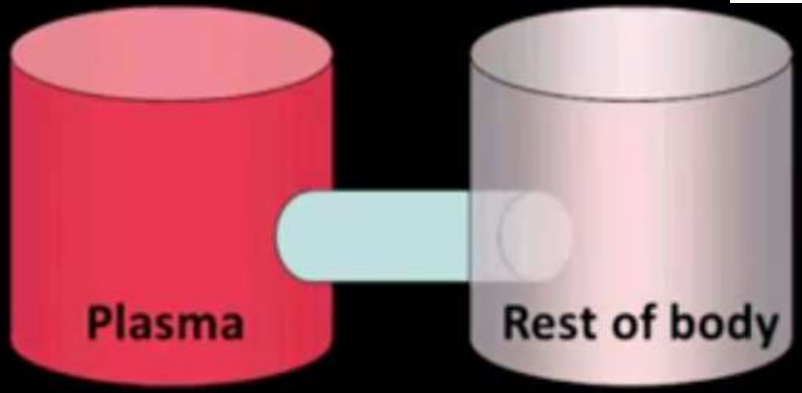
It would be simple if the drug was distributed evenly, as if a single compartment.



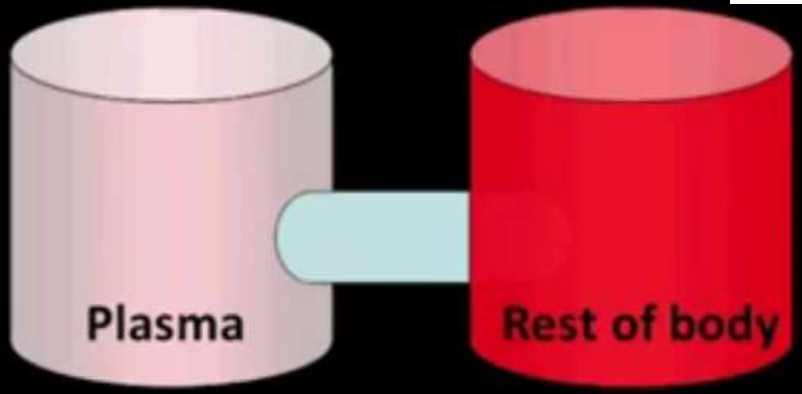
It would be simple if the drug was distributed evenly, as if a single compartment.



But rarely is a drug distributed evenly.



Some drugs remain mostly in plasma.



Some drugs are extensively distributed to other parts of the body.

Volume of Distribution

Volume of distribution tells us how extensively drug is distributed to the rest of the body compared to the plasma.

Volume of Distribution

Volume of distribution is defined by the ratio of the amount of drug in total body to the concentration of drug in plasma.

Volume of Distribution

$$\text{Volume of distribution} = \frac{\text{Amount of drug in body}}{\text{Plasma concentration}}$$

Volume of Distribution

$$V = \frac{A}{C}$$

Volume of Distribution

So if a dose of 50 mg of Drug A results in a plasma concentration of 0.1 mg per liter

Volume of Distribution

$$V = \frac{50\ mg}{0.1 mg/liter}$$

Volume of Distribution

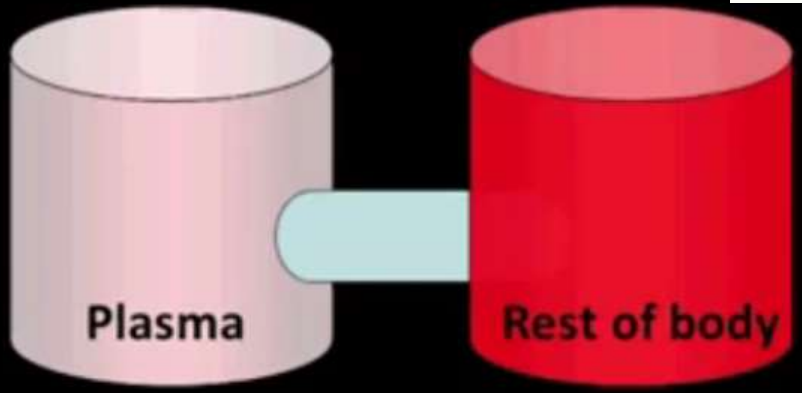
If a 50 mg dose of Drug A results in a plasma concentration of 0.1 mg per liter.

The Volume of distribution for Drug A is 500 liters

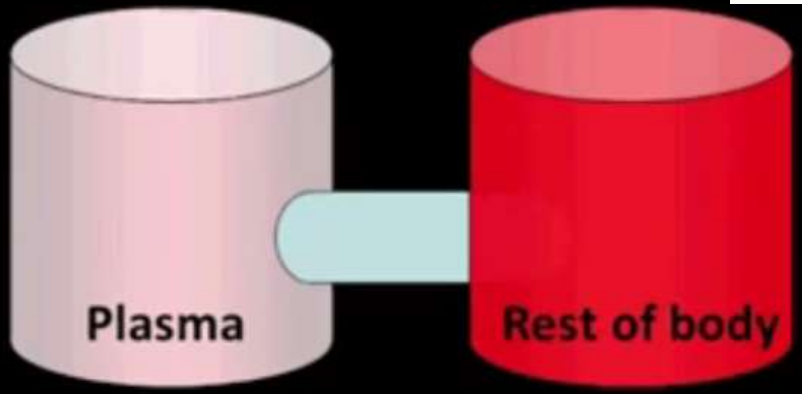
Volume of Distribution

If the Volume of distribution of Drug A is 500 liters

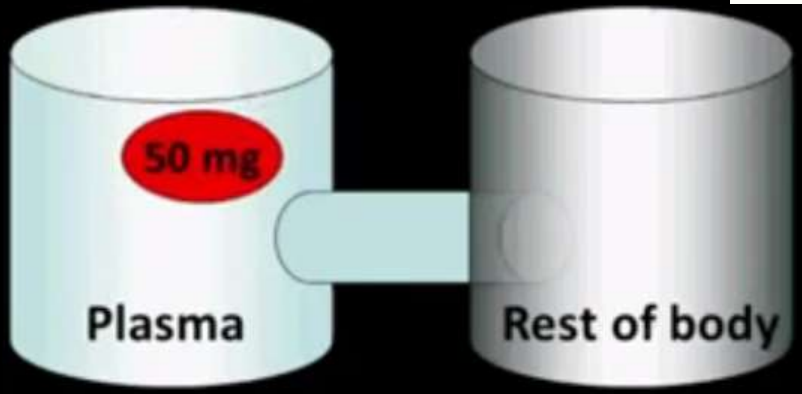
How is it that the volume of distribution of Drug A is far greater than any actual compartment volume?



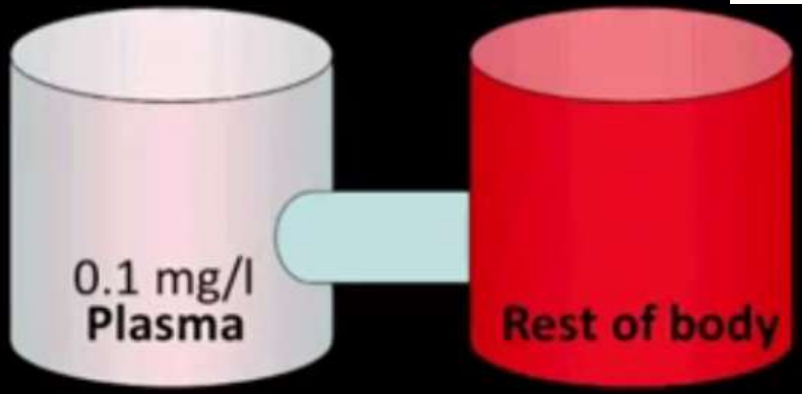
Drug A is extensively distributed to other parts of the body.



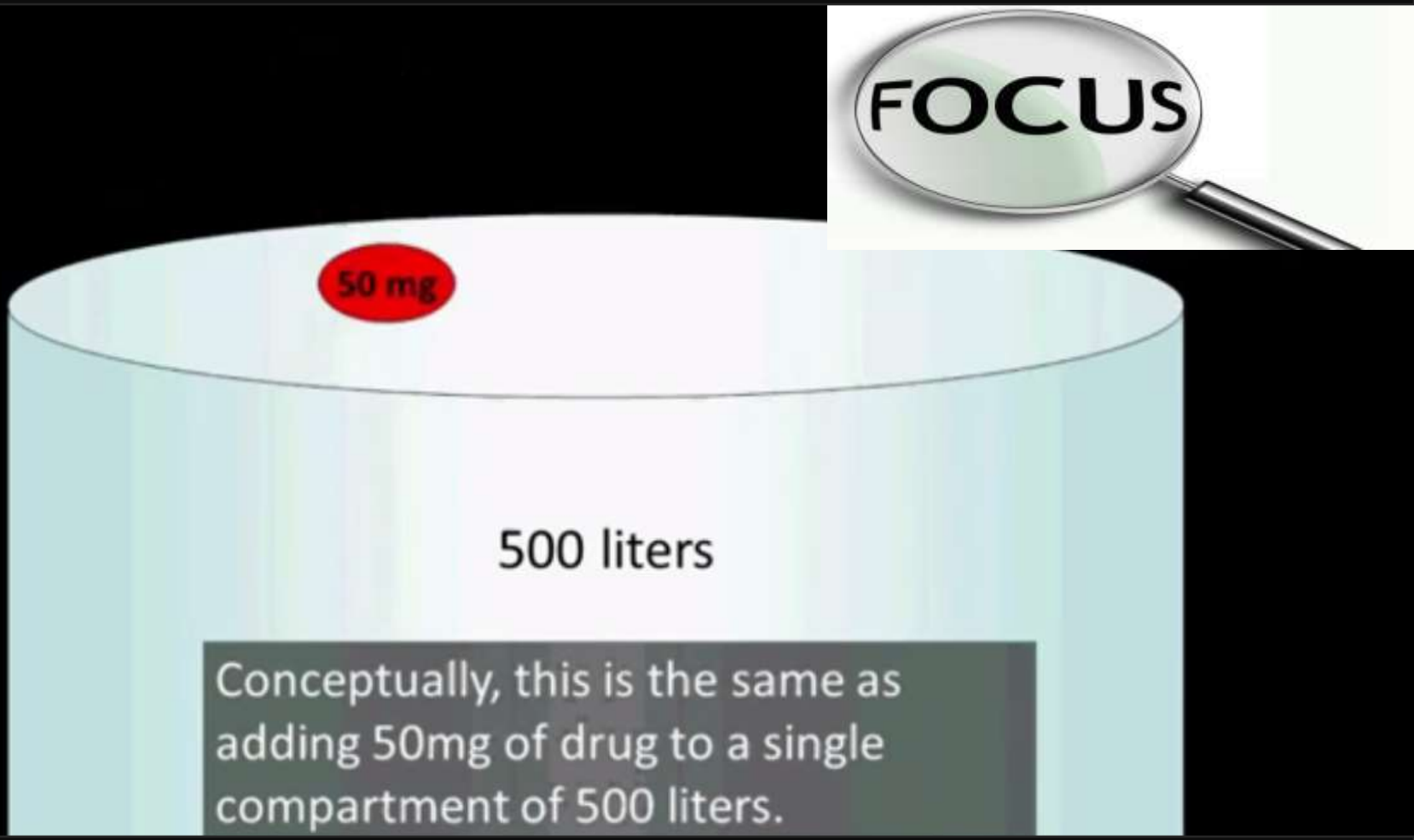
In this situation it is due to extensive tissue binding of Drug A in the rest of the body .



If we add 50mg of Drug A, resulting in a plasma concentration of 0.1 mg/liter.



If we add 50mg of Drug A, resulting in a plasma concentration of 0.1 mg/liter.


FOCUS
50 mg
500 liters
Conceptually, this is the same as adding 50mg of drug to a single compartment of 500 liters.

Volume of Distribution

- Volume of distribution tells us how extensively drug is distributed to the rest of the body compared to the plasma.

Volume of Distribution

- Volume of distribution *abstractly* describes this in terms of the plasma as a single lone compartment.
- It is NOT an actual volume, so it may be much higher than any real body volume.

Volume of Distribution

- Because it is based on easily measured parameters, volume of distribution is an essential component of many pharmacotherapeutic equations.

Volume of Distribution

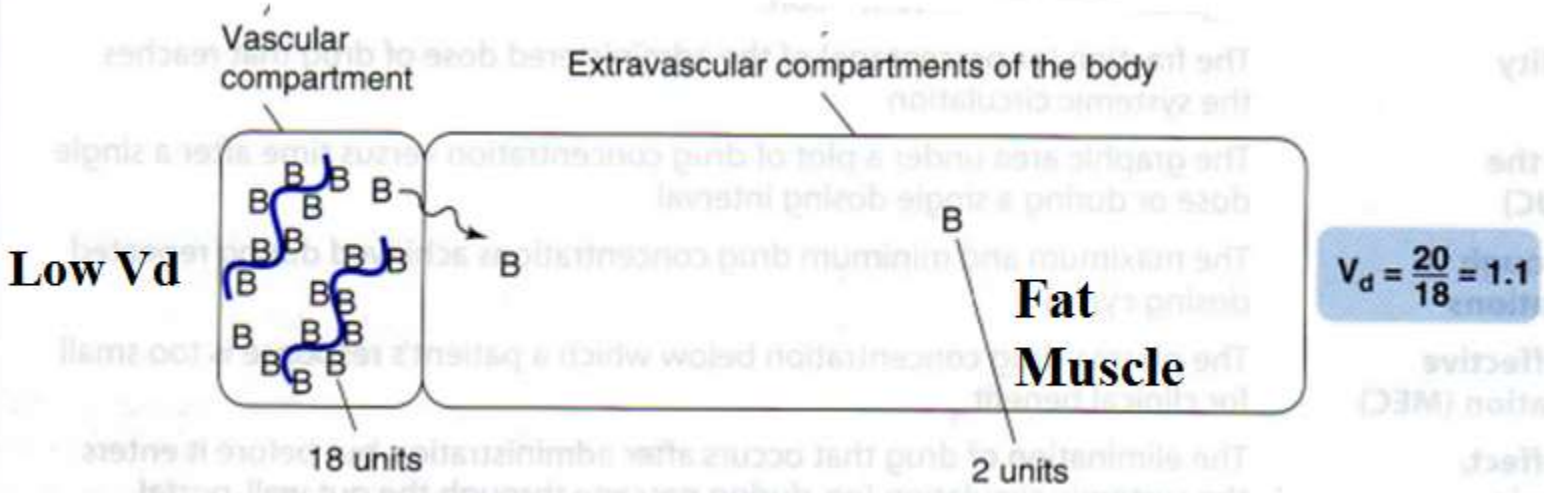
$$\text{Volume of distribution} = \frac{\text{Amount of drug in body}}{\text{Plasma concentration}}$$

$$V = \frac{A}{C}$$

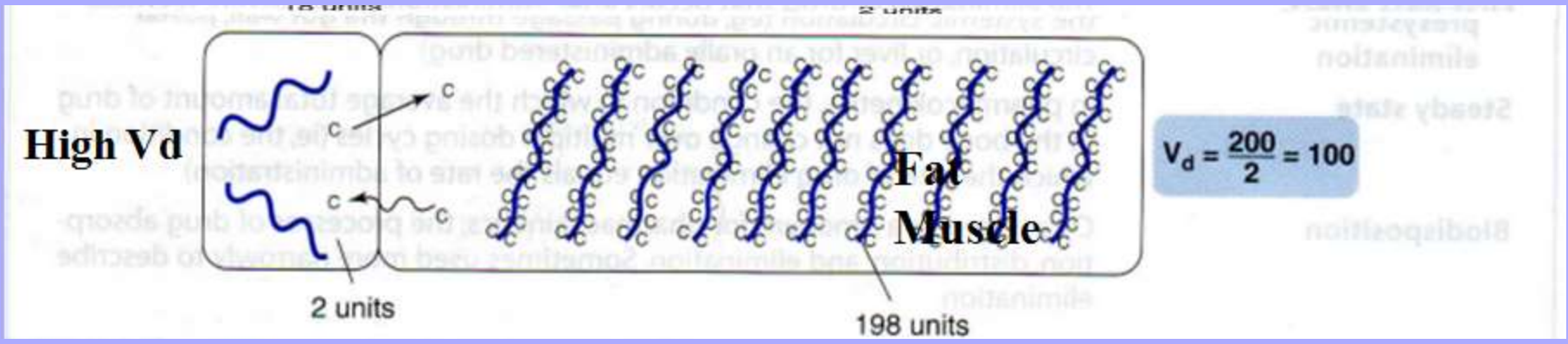
Apparent volume of distribution (V_d)

This is a theoretical volume of fluid, which would be required to contain the total body content of a drug at a concentration equal to the plasma concentration.

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

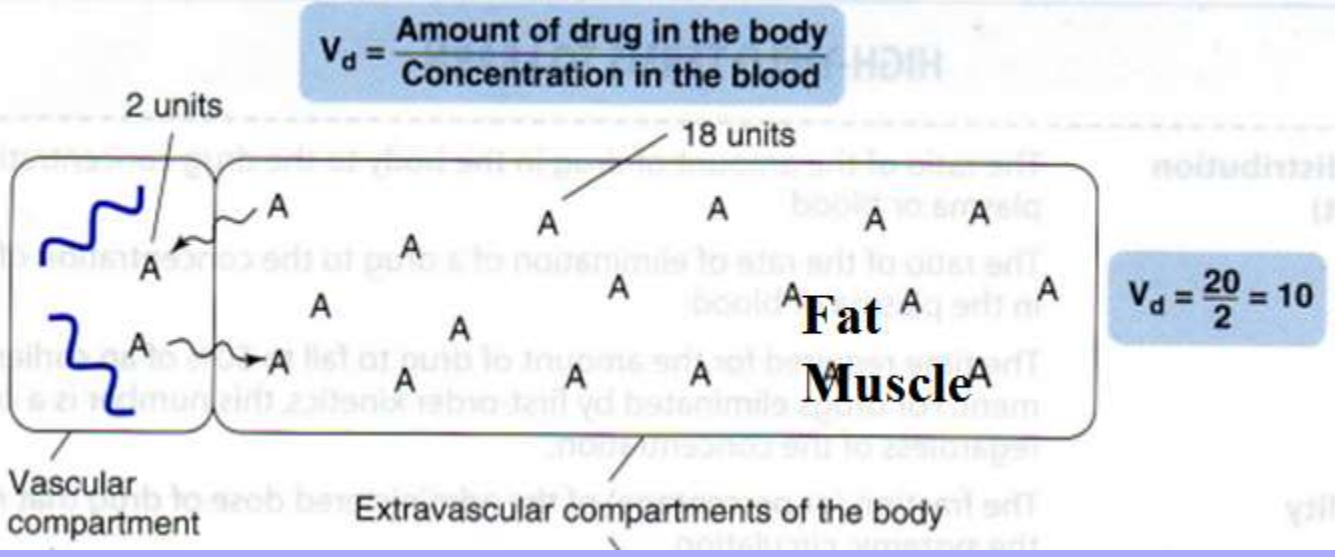


- Vd is low when a high percentage of a drug is bound to plasma proteins .



- *Vd is high when a high percentage of a drug is being sequestered in tissues.*

Med Vd


$V_d = \frac{\text{Amount of drug in the body}}{\text{Concentration in the blood}}$
2 units
18 units
A
Fat
Muscle
$V_d = \frac{20}{2} = 10$
Vascular compartment
Extravascular compartments of the body

Important Point:

- Why do we care about plasma drug concentration?

- Because we assume that the plasma drug concentration is proportional to the target tissue concentration exceptions: inhaler, topical lotion, eyedrop.

Clinical applications of Vd

- **It is useful to calculate the amount of drug needed to achieve a desired plasma concentration:** (loading dose)
- Ex Digoxin
- Vd 500 L

- the value of V_d of a drug can influence the **rate of elimination**

- **Assuming a drug with a large V_d, most of this drug is in the extraplasmic space and is unavailable to the excretory organs.**

- **Therefore, a drug with a large V_d would be expected to have a**
  - **long t½ and**
  - **extended duration of action** and
  - difficulty or slow excretion in cases of overdose

Clinically, the knowledge of V_d of a drug may be useful

when over dosage occurs.

Removing a drug by **haemodialysis** is likely to be of benefit if a major proportion of the total amount of the drug is in the plasma.

Example:

- For **salicylate**, which has a small Vd, (11L) haemodialysis is appropriate treatment;

- while for **pethidine**, which has a large Vd, (28L) is not appropriate one.

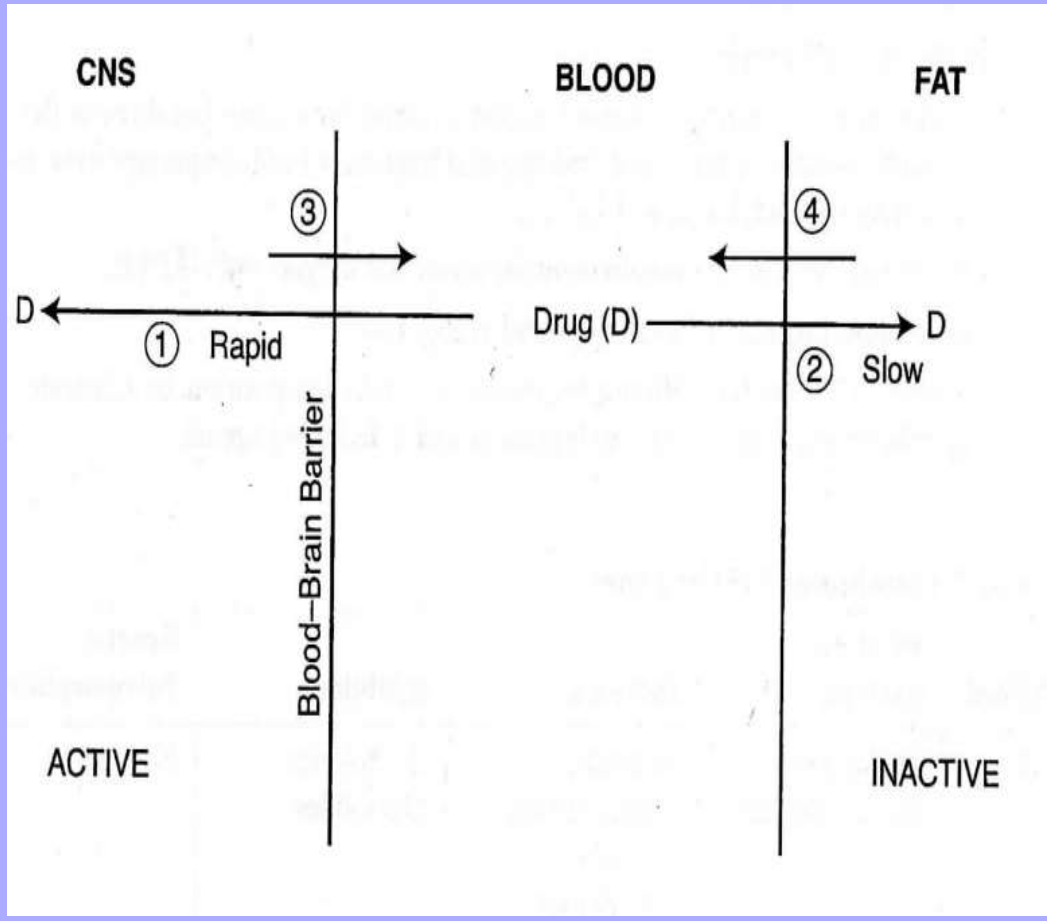
- **????? Digoxion** Fab

Redistribution
of lipid-soluble drugs

In addition to crossing the blood-brain barrier (BBB),

lipid-soluble drugs redistribute

into fat tissues prior to elimination



Redistribution

of lipid-soluble drugs

In the case of CNS drugs , the duration of action of an initial dose may depend more on the redistribution rate than on the half-life.

With a second dose , the blood/fat ratio is less; therefore, the rate of redistribution is less and the second dose has a longer duration of action .

Ex thiopental in general anaesthesia


Thank you