بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | Lecture #10

Pharmacokinetics pt.4

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Volume of Distribution (V_D)

- **It is the size of body fluid that would be required if the drug molecules were to be homogeneously distributed through all parts of the body.**
- **It reflects the apparent space available for the drug in the tissues of distribution.**
- **It does NOT represent a real volume.**

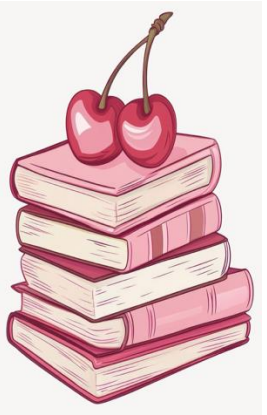
Will the distribution be actually homogeneous? Definitely not—because of differences in tissue affinity, blood flow between tissues and the physicochemical properties of the drug that influence its probability.

To simplify the concept, imagine placing a 100 mg substance into a container that holds a certain volume of fluid, then take a sample to measure its concentration. Suppose the concentration turns out to be 1 mg per liter. In that case, the fluid volume would be 100 liters.

Basically, the volume of distribution (Vd) describes the relationship between the amount of drug in the body and the plasma concentration of that drug.
Notice that we say “amount of drug in the body”—not “the dose”—because the actual amount available depends on bioavailability.

Now, why do we use plasma concentration(blood tissue) instead of concentrations in other tissues?
Because plasma (or blood) is much more accessible than other tissues.

So, VD expresses the relationship between the amount of drug in the body and the drug concentration in the blood.



Back to this example”imagine placing a 100 mg substance into a container that holds a certain volume of fluid. then take a sample to measure its concentration. Suppose the concentration turns out to be 1 mg per liter. In that case, the fluid volume would be 100 liters”.

This is a theoretical example. It shows how the drug would distribute if the system was homogeneous—meaning the 100 mg would spread evenly throughout the plasma. In reality, in the body, the drug doesn’t stay evenly in plasma; it moves into tissues, binds to proteins, and is eliminated. So, while the calculation is similar to finding Volume of Distribution (Vd), the number reflects distribution in the body, not just plasma volume.

So, unlike the fixed container, Vd reflects how the drug distributes throughout the body, not just the blood or extracellular fluid.

Volume of Distribution (V_D)

Real physiological volumes

- **In a normal 70 Kg man, the volume of:**

Plasma = 2.8 L

Blood = 5.6 L

Extracellular fluid

ECF = 14 L

Total body water

TBW = 42 L

Does the drug always goes to the 42 L?No

Fat = 14 - 25 L

- **But the volume of distribution for:**

ECF	**Aspirin**	**= 11 L**
ECF OR FAT	**Ampicillin**	**= 20 L**
TBW	**Phenobarbital**	**= 40 L**
	Digoxin	**= 640 L**
	Imipramine	**= 1600 L**
	Chloroquine	**= 13000 L**

It cannot be explained by physiological volumes that's why we call it apparent space it doesn't represent a real volume but it's extremely important because it give us an idea where is the drug in general

So, by dividing the amount of the drug by its concentration in the blood, we get a number. This number is called the volume of distribution (Vd), and it serves as an indicator of where the drug is located. It can sometimes be a very high value even hundreds of liters. This does not mean that our body actually contains that much fluid, but it has an important meaning regarding where the drug generally distributes. If the Vd is very low, it is close to the blood volume, meaning the drug mostly stays in the blood.

As the equation Vd = amount of drug in the body ÷ plasma concentration shows, if the Vd of a certain drug is very high, that means that the plasma concentration is extremely low. It does not mean that the amount of drug in the body is zero. Rather, it indicates that the drug does not remain in the plasma and instead gets distributed into the tissues.

If a drug has a volume of distribution equal to 5 liters, that means the drug would be in the blood. What are the properties of the drugs that are restricted and not distributed out of the blood?

1.Not able to pass through a membrane – They are ionized or charged. These drugs will remain in the circulation after being given IV.

2.Example: A very important group of antibiotics for gram-negative infections, the aminoglycosides, which have a very small distribution of about 5 liters.

3.Drugs that are highly bound to plasma proteins.

Digoxin is bound to tissues outside the blood and the extracellular fluids, with a higher affinity for muscles. This binding decreases the plasma concentration and consequently increases the Vd. Imipramine and chloroquine also distribute into tissues, so the amount present in the plasma is very small.

Digoxin = 640 L

Imipramine = 1600 L

Chloroquine = 13000 L

Volume of Distribution (V_D)

- **The apparent volume of distribution will be small if the drug is restricted to plasma:**

1. **due to binding to plasma proteins**
2. **when it is highly ionized at plasma pH.**

- **The apparent volume of distribution will be large when the drug distributes into tissues.**
- **It relates the amount of the drug in the body (Ab), with its plasma concentration (Cp), such that: $V_D = Ab/Cp$**

Calculations are required

Drug Binding in Plasma

- **Albumin is the most important drug- binding protein.**

  Always synthesised in the liver , for both acidic and basic drugs because it has different functional groups and different charges

- **α_1- Acid-glycoprotein is also important for binding certain basic drugs.**
- **Binding to plasma proteins is mostly reversible.**

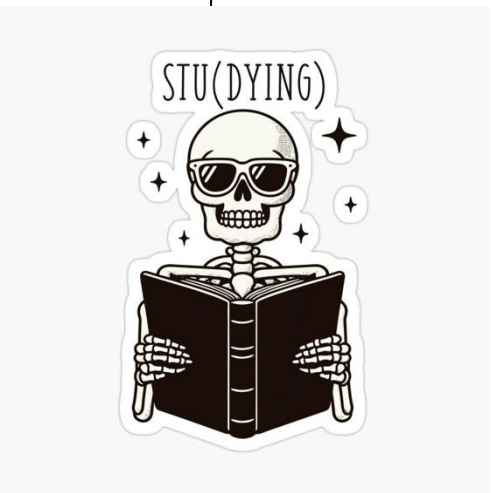
Drug + Protein ⟷ **Drug-Protein complex**

Covelent Binding damages the protein

D + P ⟷ **DP**

Alpha-1 Acid Glycoprotein (AAG) is a minor plasma protein in terms of quantity, but it plays an important role as an acute-phase reactant. Its level increases in certain diseases, such as inflammation or infection. When this happens, drugs that are basic and normally bind to AAG will show increased binding during the disease. After recovery, AAG levels return to normal, leading to less binding and therefore more free (active) drug in the plasma. This increase in free drug enhances its pharmacological action, elimination, and distribution.

So, during acute-phase conditions, when giving drugs that bind to Alpha-1 Acid Glycoprotein, precautions must be taken, because changes in binding can significantly affect the drug's activity and safety.



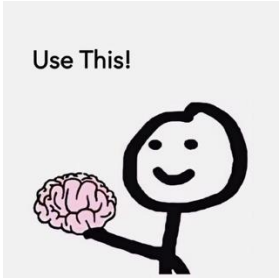
Drug Binding in Plasma

- **The free unbound drug fraction (D) is responsible for the pharmacological action and is also available for elimination.** And distribution.
- **The bound drug fraction (DP) is not so available, and it represents a reservoir for the drug.**
- **One clinical importance of plasma protein binding of drugs is to help interpretation of measured plasma drug concentration of such drugs.** that are highly pound to plasma proteins

Phenytoin is about 95% bound to plasma proteins. It is used in the treatment of the chronic neurological disorder epilepsy.
If the patient had a problem in albumin and as in liver diseases
Albumin is not formed very well so the free fraction will be more than 5% there will be more action, more distribution and more elimination. then dissociation will occur between the drug and albumin this will keep the free fraction normal, but there will be a decrease in the overall drug concentration
In patients with low albumin (like in liver disease), if you measure phenytoin levels, the total plasma concentration will appear lower than normal.

Important: Do not automatically increase the dose based on this total concentration. Even though total levels are low, the free (active) fraction may already be normal or even slightly elevated. Increasing the dose could lead to toxicity or adverse effects.

- ↓ Albumin → ↑ Free Phenytoin → ↑ Effect, Distribution, and Elimination
- After equilibrium → Free level normalizes, but total concentration decreases



Drug Binding in Plasma

- When plasma protein concentrations are lower than normal, then the total drug concentration will be lower than expected, but the free concentration may not be affected (why?).
- Plasma protein binding is also a site for drug-drug interactions.
- If a drug is displaced from plasma proteins it would increase the unbound drug concentration and increase the drug effect and, perhaps, produce toxicity.

Drug Binding in Plasma

- **Drug displaced from plasma protein will of course distribute throughout the volume of distribution, and its rate of elimination will also increase, thus, its plasma concentration will NOT increase dramatically.**

تصفية الدم

Drug Clearance (CL)

•Elimination = amount of drug removed per time (mg/hour)
•Clearance = volume of plasma cleared of drug per time (L/hour)

Dialysis is an artificial clearance of the drug, but the drug doesn't go to the pile or urine; it goes to the artificial machine.

- It is the volume of blood or plasma that is completely cleared of drug per unit time.
- It is a measure of the ability of the body to eliminate (and distribute) the drug.
- Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration:

$$CL = \text{rate of elimination}/Cp$$

Plasma concentration of the drug

Drug Clearance (CL)

- **Assume that the rate of elimination of a drug is 10 mg/hour, and the plasma concentration is 1 mg/L. What is drug clearance?**
- **CL = [10 mg/hour] / [1 mg/L]**
  = 10 L/hour

Drug Clearance (CL)

- **There may be more than one method of elimination, and thus the rate of elimination will be the sum of all these methods.**

  (Creatinine clearance)

- **Renal clearance (CL_R) = Cu.V/Cp ,**

  where Cu is concentration of drug in urine, V is urine flow rate, and Cp is the plasma concentration of the drug.

  Notice that, in the renal equation, Cu.V represents the elimination rate from the urine (it is just the same as the original equation.

Drug Clearance (CL)

- **Hepatic clearance (CL_H) =**
  [(blood flow. C_i)- (blood flow. C_o)]/ C_i
  CL_H = blood flow (C_i- C_o)/ C_i
  CL_H = Q.ER

C_i is drug concentration in blood going to the liver, C_o is drug concentration in blood leaving the liver, Q is blood flow, ER is the extraction ratio of the drug.

The renal clearance and hepatic clearance: elimination (the drug is not distributed)
Total body clearance: distribution and elimination
Elimination can be renal, hepatic, or sweat clearance

- Types of Elimination: A drug can undrego:
  1) First-order elimination
  2) Zero-order elimination
  3) Flow-dependent elimination

First-Order Drug Elimination

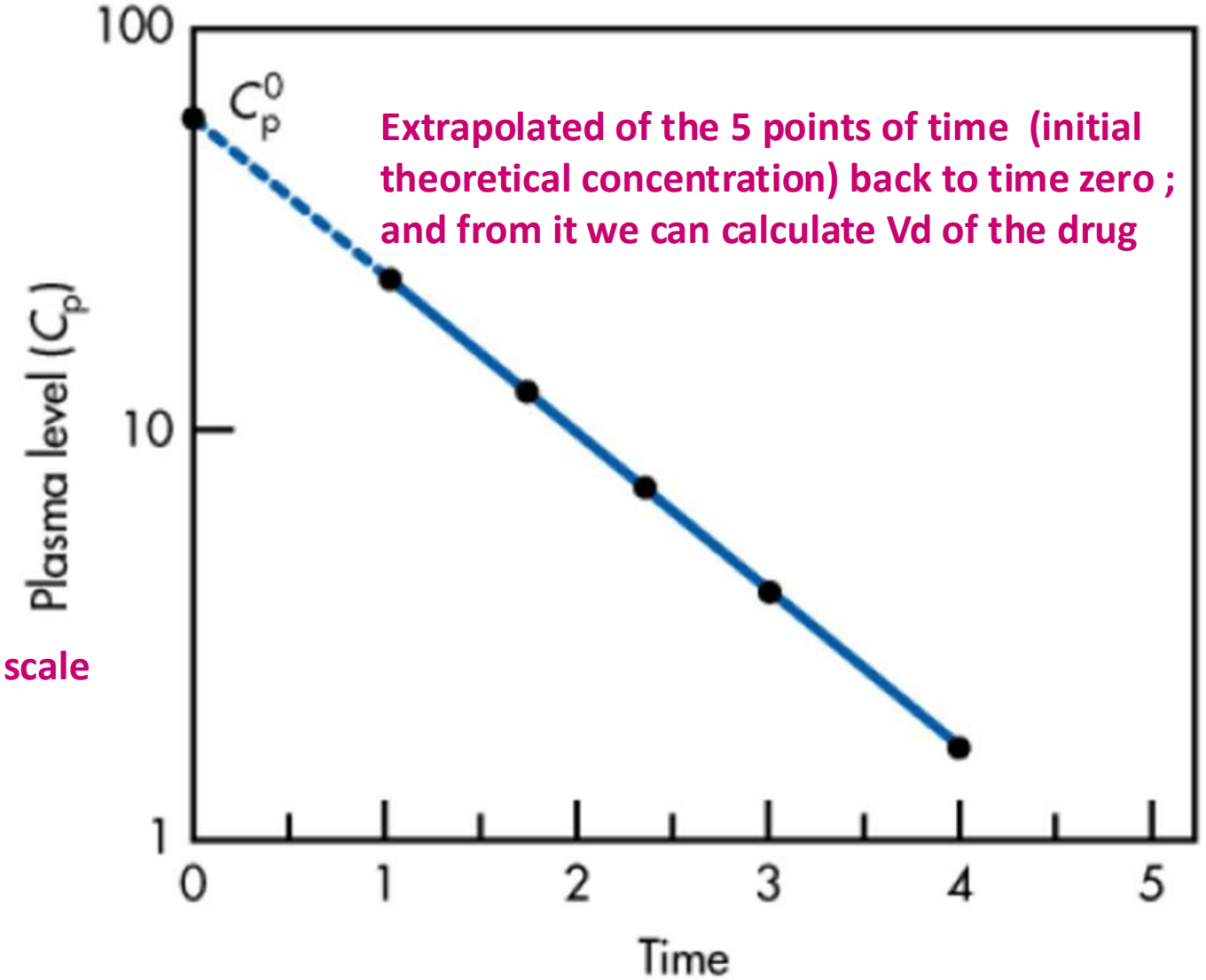
- It occurs when the rate of drug elimination is directly proportional to the amount of drug in the body.
- Occurs with many drugs at therapeutic concentrations.
- A constant fraction of the drug is eliminated per unit time.
- The elimination rate constant is designated as k, and its units are reciprocal time (1/time)
  meaning fraction per unit time.

If elimination rate constant was 0.1, and the amount of drug in the body is 500 mg , then the drug eliminates 50 mg per unit time

Slope = drug elimination rate constant (k) and from it we can indicate the drug's half life

Cp0 Can be used to calculate the volume distribution of the drug (amount of drug/cp0

A Log scale



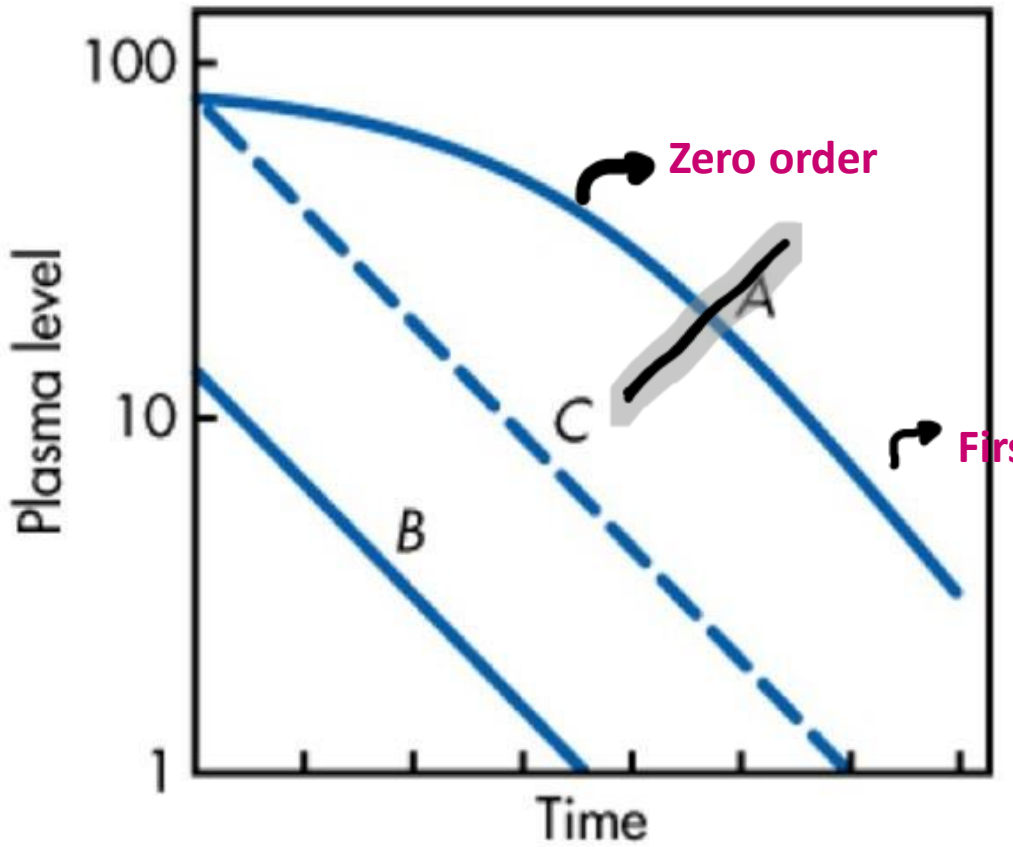
Extrapolated of the 5 points of time (initial theoretical concentration) back to time zero ; and from it we can calculate Vd of the drug

Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Zero-Order Drug Elimination

(Capacity limited elimination)

- Also called Saturable elimination.
- Occurs with few drugs (aspirin, phenytoin, ethanol, ..).
- Elimination rate is NOT proportional to the amount of drug in the body, but a constant amount is removed per unit time, because of saturation of the elimination process.



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

A: zero order elimination . And at low concentration- below saturation process it becomes first order elimination

C : first order elimination (if the drug followed first order elimination third is how will the curve look like)

B: first order elimination

B , C are not that important

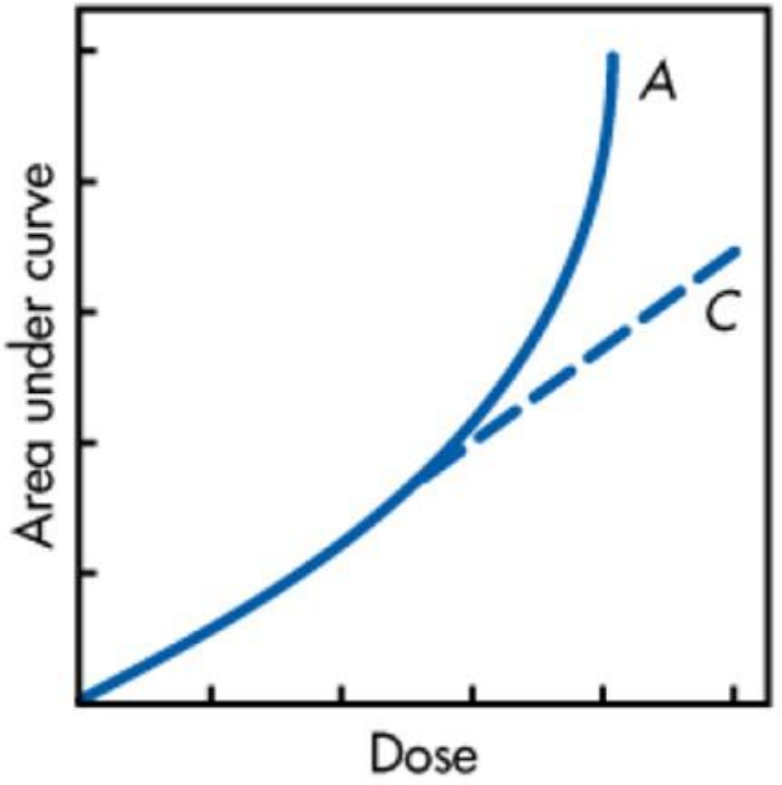
Zero-Order Drug Elimination

- **Rate of elimination = V_{max}. C / K_m + C**

Where V_{max} is the maximal elimination capacity, and K_m is the drug concentration at which rate of elimination is 50% of V_{max}.

Enzymatic kinetics are saturable in the body

AUC increase out of proportion



Linear -> (dose and concentration are directly proportional) dose is more restricted if drug follows it

Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Curve C represent first-order kinetics

The doctor said it's called : الطايح رايح

Flow-Dependent Drugstore Elimination

- Some drugs are cleared very rapidly by the organ of elimination (liver), so that at clinical concentrations of the drug, most of the drug perfusing the liver is eliminated on first pass through it.

The liver enzymes may differ inter individually
Kidney doesn't have enzymes (only have filtration)

- Rate of elimination is determined by the rate of hepatic blood flow.

Drug Concentration and Vd will stop having an effect

- Drugs that have this property are called "high extration ratio" drugs.
- Include morphine, lidocaine, propranolol, verapamil, and others.

Names not included (for now)

رسالة من الفريق العلمي:

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			