Pharmacokinetics 3

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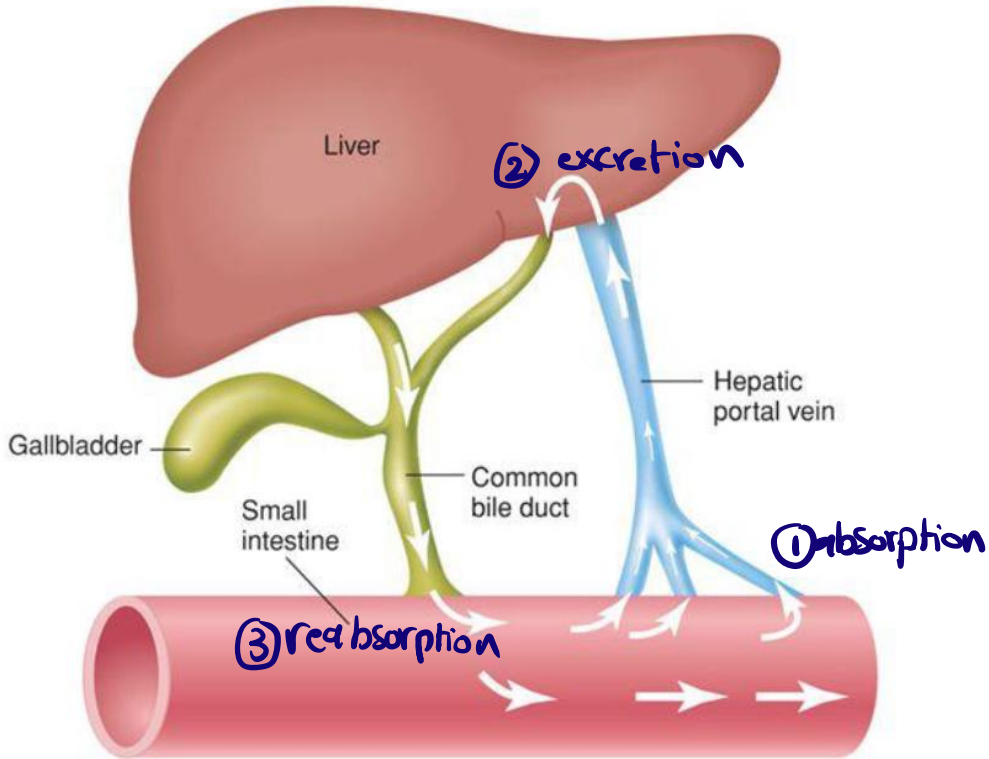
Enterohepatic Cycling of Drugs

In the case of enterohepatic cycling, the drug is reabsorbed by SI after being excreted in bile so it's basically a cycle (between SI and the liver)

- **After oral administration and absorption, a drug can be excreted in bile before reaching the systemic circulation, go back to gut lumen, and then reabsorbed again.**
- **This is called enterohepatic cycling of the drug.**
- **It reduces drug bioavailability and prolongs its half-life of elimination.**

Enterohepatic Circulation

- Is recirculation of compounds between liver and intestine
- Many compounds are released in bile, reabsorbed in SI, and returned to liver to be recycled
- Liver excretes drug metabolites into bile to pass out in feces



- As a result there's a portion of the dose is always present in the SI until complete absorption and elimination

⇐ That's why bioavailability would be reduced in case of enterohepatic cycling

Enterohepatic Cycling of Drugs

Application: In cases of drug overdose, we can use a binder that would trap the drug by preventing its reabsorption

- **This phenomenon can be taken advantage of in cases of drug overdose** using a certain binder
- **Activated charcoal** (The binder) **can adsorb may drugs and chemicals (except ionized ones) into its surface.**
- **If we give activated charcoal in cases of drug overdose, and the drug undergoes enterohepatic cycling, then the portion of the drug that is excreted into the gut through bile can be trapped and prevented from reabsorption back into the systemic circulation.**

Enterohepatic Cycling of Drugs

- **This will accelerate drug elimination from the body and reduces its half-life of elimination.**

- Activated Charcoal working mechanism: It's given orally and remains in the GI tract without being absorbed or metabolized due to its large surface area. So it binds to chemicals trapping them and carrying them out of the body without allowing them to to be absorbed into circulation.

except ionized drugs, they won't bind.

Volume of Distribution (V_D)

(a Relation between the dose and concentration of the drug in the plasma)

- It is the size of body fluid (Liters) that would be required if the drug molecules were to be homogeneously distributed through all parts of the body. ↳ actually it's not homogeneously distributed, some organs take more than the others, but we will assume it would be
- It reflects the apparent space available for the drug in the tissues of distribution.
- It does NOT represent a real volume.

Volume of Distribution (V_D)

- **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
	Fat	= 14 - 25 L

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

we can say it's in the ECF

Small V_D

	Aspirin	= 11 L
	Ampicillin	= 20 L → TBW
	Phenobarbital	= 40 L

large V_D

	Digoxin (bound to muscles)	= 640 L
	Imipramine (bound to tissues)	= 1600 L
	Chloroquine (highly bound to tissues)	= 13000 L

Explanation: A large V_D indicates that the drug is distributed significantly into tissues

Drugs with large V_D have low Conc. in body

- small V_D - high Conc.

while a small V_D indicates that the drug is confined to the circulatory system (it's the real volume now)

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 (They cannot go to tissues because they are large)
2. when it is highly ionized at plasma pH. (So the drug can't cross the membrane)

- 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: $V_D = Ab/Cp$ (For memorization) (it's an apparent volume of Distribution)

Dose (only if the drug is absorbed 100%.)

- Note: If the bioavailability of the drug is so small, we replace Ab with the fraction of bioavailability of the dose

Drug Binding in Plasma (stored inactive drugs)

- **Albumin** is the most important drug- binding protein. (it binds both acidic and basic drugs)
  - maintain a concentration (There's a homeostasis of its concentration that doesn't increase or decrease in the case of inflammation for example)
- **α_1- Acid-glycoprotein** is also important for binding certain **basic** drugs. (Acidic drugs bind with albumin)
- **Binding to plasma proteins is mostly reversible.**
  - it's an acute phase reactant (in inflammation) so its conc. increases during an inflammatory response resulting in increasing the binding of basic drugs, reducing the free fraction of the drug (active form of the drug)

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

D + P ⟷ **DP**

Here we have equilibrium. for example if a drug is eliminated, the equilibrium shift to the left direction (Dissociation of the DP complex)

Drug Binding in Plasma

- **The free unbound drug fraction (D) is responsible for the pharmacological action (The active form) and is also available for elimination.**
- **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.**

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 – drug interactions and plasma protein binding of drugs

If (protein binding to drugs) was extensive, different drugs can displace each other from binding "They compete with each other" As a result the free fraction of the drug increases

→ More active forms of the drug → more action → more elimination

That's why the increased activity is only temporary at first (the elimination decreases conc.)

- plasma protein binding of drugs importance on explaining measurments.

for example, epilepsy drugs, their plasma concentration should be regulated every now and then (theraputic drug monitoring) to see if there's adequate conc or not. If the measurments indicate that there's decreasing in the plasma drug concentration, it doesn't necessarily mean that there's a decrease in the free form of drug. going back to protein drug binding and drug-drug interactions, the patient may be taking another drug and there's displacement caused by the other drug so binding decreases and the free fraction increases, metabolism increases so you don't have to increase the dose.

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.**

By elimination / distribution ← تصفية الدواء

Drug Clearance (CL)

(volume / time)

- 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 → to tissues of Distribution) the drug.
- Mathematically Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration:

CL = rate of elimination/Cp

(amount per time / amount pre volume ⇒ volume/time)

- Total clearance ⇒ Elimination + Distribution
- Hepatic oR Renal clearance ⇒ Elimination only

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

اكتبو ال units خاصل الحل عشانه ما تغلطو

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.**

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

  where Cu is concentration of drug in urine, V is urine flow rate, (Volume / time) and Cp is the plasma concentration of the drug.

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

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

Effect of First-Pass Effect on bioavailability

- The effect of first-pass hepatic elimination on bioavailability is expressed as the extraction ratio (ER):
- ER = Clearance$_{liver}$/ Blood flow to the liver (90 L/hour in a healthy 70 Kg man).

hepatic clearance

$$ER = Cl_{liver}/Q$$

- Bioavailability (F) can be predicted from the extent of absorption (f) and ER.

$$F = (f) . (1 - ER)$$

↳ fraction absorbed

if the drug is completely absorbed $f = 1 - ER$

Effect of First-Pass Effect on bioavailability

F = 1 − ER

- A drug like morphine is completely absorbed but its ER is 0.67, so its bioavailability is 33%. OR 0.33
- Drugs with high extraction ratio exhibit interindividual differences in bioavailability and drug concentration, because of differences among individuals in hepatic blood flow and hepatic drug metabolism.

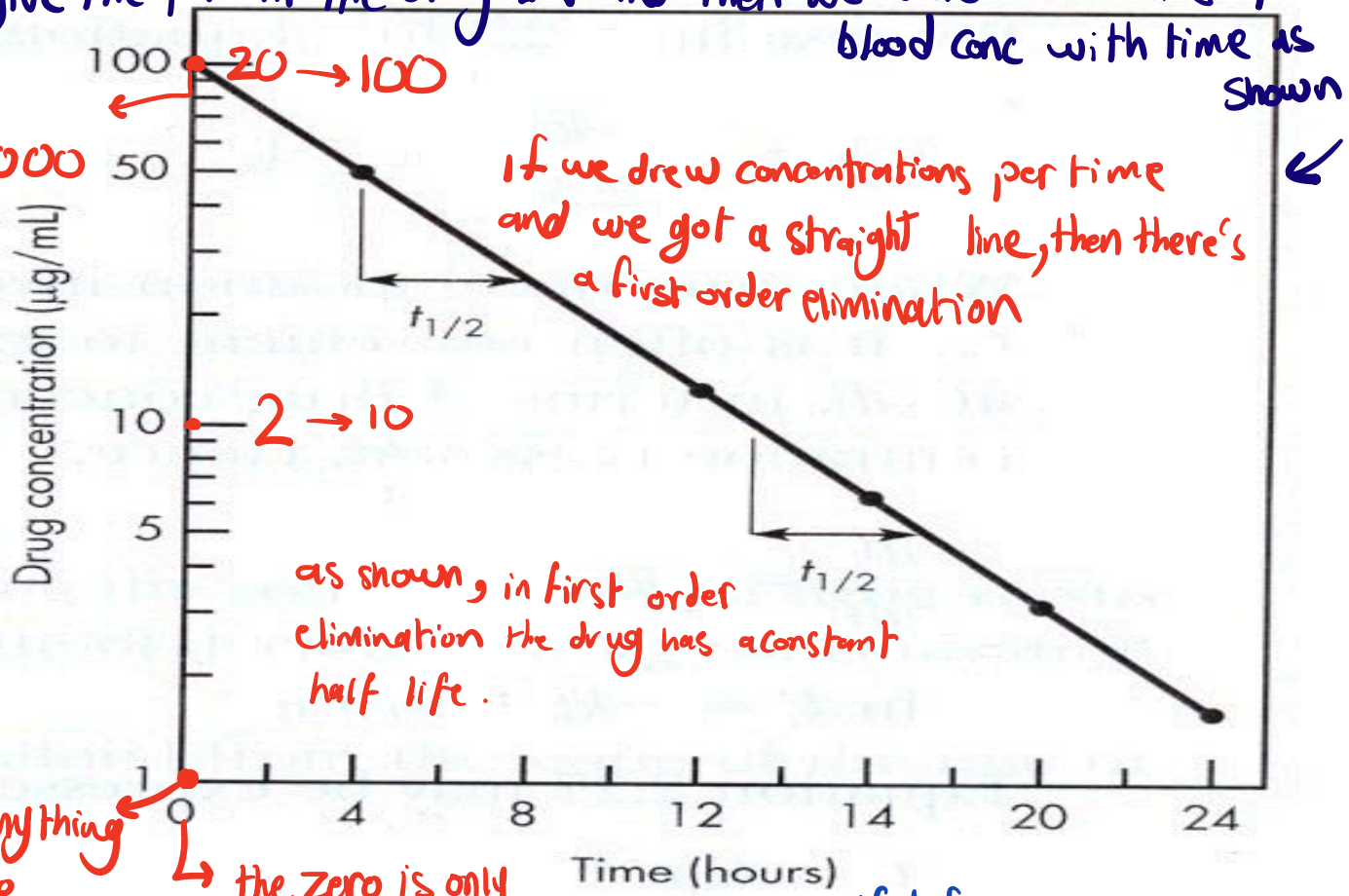
high ER ⇒ severe interindividual variations in drug metabolism.

First-Order Drug Elimination

- It occurs when the rate of drug elimination is directly proportional to the amount of drug in the body. ↑ drug conc. ↑ elimination rate
- Occurs with many drugs at therapeutic concentrations. which is good because sometimes drug accumulation is not significance
- A constant fraction of the drug is eliminated per unit time. (No saturation of the elimination process)
- The elimination rate constant is designated as k, and its units are reciprocal time (1/time) meaning fraction per unit time.

How to know that the drug is undergoing first order elimination ?

we give the patient the drug IV and then we write down series of blood conc with time as shown



going up
200 → 1000
and so on

20 → 100

2 → 10

if we drew concentrations per time and we got a straight line, then there's a first order elimination

as shown, in first order elimination the drug has a constant half life.

Could be anything but zero (0.1, 0.0000007....)

the zero is only for the linear scale

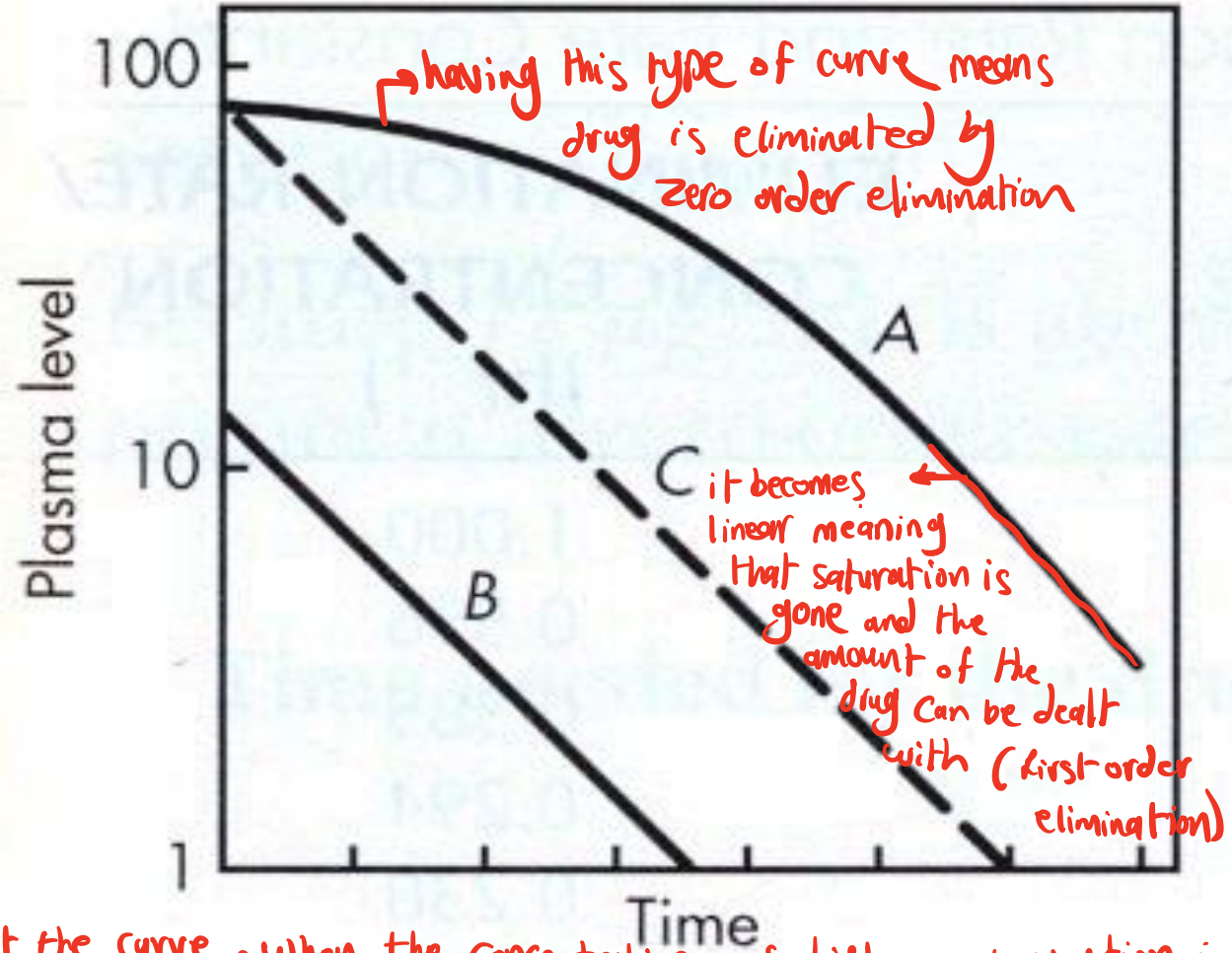
- half life is the time required for concentration to drop to the half and here it's 4 hours

Zero-Order Drug Elimination

Certain amount is lost per unit time

- 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.**

- increasing the dose increases accumulation of the drug, half life will be prolonged (That's why it's called saturable)



- looking at the curve, when the concentration was high ⇒ elimination is slow
- As the drug drops, the elimination becomes faster until the curve becomes linear