◉Sheet ○Slides

number : 4

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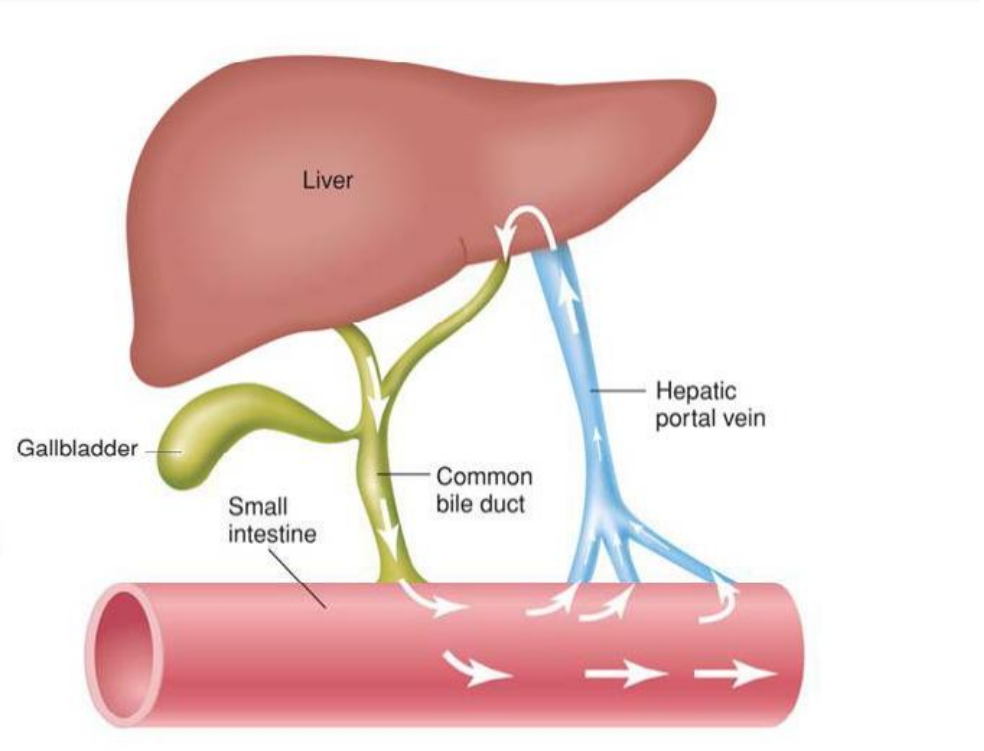
1. Enterohepatic Cycling of Drugs (EHC)

Refers to the circulation of the drug after oral administration and before reaching the systemic circulation, where it's absorbed in the small intestines, then goes through the portal circulation to the liver, followed by biliary excretion, then back into the intestines for reabsorption.

Note:

Portal circulation: Circulation of blood to the liver from the small intestines, the colon and the spleen



- **Importance of EHC:**
  - A- Prolongation of the drug half life of elimination.
  - B- Reduction of the drug bioavailability (less dose reaches the systemic circulation).
  - C- **Clinical implication→** Interrupting the EHC in case of overdose through what's called **"gastrointestinal dialysis"**;

If we give the patient activated charcoal in cases of drug overdose, and the drug undergoes EHC, then the portion of the drug that is excreted into the gut through the bile can be trapped and prevented from reabsorption back into the systemic circulation. This will accelerate drug elimination from the body and reduces its half life of elimination.

How?

Activated charcoal is charcoal that has been treated to increase its adsorptive power, so it can adsorb many drugs and chemicals (except ionized ones) into its surface and it travels along with feces. Thus, prevention of reabsorption which logically leads to acceleration of drug elimination.

2. Drug Distribution:

The process by which the drug leaves the systemic circulation and enters the interstitium (extracellular fluid) and the tissues.

You should keep in mind that distribution of the drug is not always homogenous since it may be affected by both its affinity toward different tissues as well as the blood flow to the tissues.

- Volume of Distribution

The **apparent** volume of distribution (Vd), is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation (D) by the plasma concentration at time zero (C_0), which's why it's a **theoretical** volume.

Minute: 00:00-10:00

$V_d = Ab / C_p$ ⟹ - Relating the dose given (amount of the drug in the body Ab) with the blood /plasma concentration of the drug. ($V_d = Ab / Cp$)

[Ab= dose * bioavailability]

To explain: if a given dose was 100 mg and the bioavailability was 0.9 according to the equation Ab = 100 * 0.9 = 90 mg , this amount represents the actual amount of the drug in the body.

⟹ - Used as a pharmacokinetic parameter to measure the theraputic dose

- It reflects the apparent space available for the drug in the tissues of distribution.

Examples:

Although V_d has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

You should know the physiological body fluids in a normal 70 Kg person:

Plasma: 2.8 L Total Body Water (TBW): 42 L

Blood = 5.6 L Extra Cellular Fluid (ECF)= 14L

Fat = 14 - 25 L

Accordingly, by having the volume of distribution for different drugs, we can tell where the drug has been distributed to;

1- Aspirin, V_d = 11 L → Distributed to ECF

2- Ampicillin, V_d = 20 L

3- Phenobarbital, V_d = 40 L → Distributed to TBW

4- Digoxin, V_d = 640 L

5- Imipramine, V_d = 1600 L

6- Chloroquine, V_d = 13000 L

Drugs 4,5,6 are distributed to body tissues and organs (V_d above 40)

In order to determine how much should I give (the dose) I have to know the therapeutic concentration TC of the blood though I am concerned about the TC at the site of action but the concentration in the blood is proportional to the concentration at the site of action thus it acts as an indicator

Calculated by → dose = Vd * TC

Further illustration,

- High V_d indicates a drug with large tissue distribution:

  Remember that C_0 and V_d are inversely related, so if drug A has a V_d of 1600 (high) it indicates that this drug binds weakly to plasma proteins (extensively to tissue proteins), so there'll be a large amount of drug molecules leaving the plasma to bind with tissues, thus, a low C_0 of drug in plasma. In addition, the high value V_d indicates a low molecular weight.

- Low V_d indicates a drug primarily found in the blood:

  - If drug B has a V_d of 2.8 (low) it indicates that this drug binds extensively to plasma proteins, so there'll be a small amount of drug molecules leaving the plasma to bind with tissues, thus, a high C_0 of drug in plasma. In addition, the low V_d value indicates a high molecular weight.
  - If the drug is highly ionized at plasma pH, it'll be restricted to plasma, so V_d value will be small.

Minute: 10:00-20:00

I recommend you to read this topic from the book, since there are further details that weren't mentioned in the record, that are important for our knowledge

3. Binding of drugs to plasma proteins

- Binding to plasma proteins is a **reversible** process that reaches equilibrium.
- Follows the law of mass action.
- **Albumin** is the major drug-binding protein (for **both** acidic and basic drugs) and may act as a drug reservoir (as the concentration of free drug decreases due to elimination, the bound drug dissociates from the protein).
- **α1 Acid-glycoprotin**, an acute phase reactant, is also important for binding certain **basic** drugs.
- Maintains the free drug concentration as a constant fraction of the total drug in the plasma.

e.g. If the percentage of bound drug was 90%, then 10% is free (constant). So, if there's 50 mg of a drug, then 45 mg is bound and 5 mg is free, and if that amount was reduced to 25 mg of the total drug, then 22.5 mg is bound and 2.5 mg is free → *constant fraction of free drug, *chemical equilibrium exists between bound and unbound states

Drug + Protein ⟷ Drug-Protein complex
(Active, Free) (Inactive, Bound)

- The free unbound drug fraction (D) is responsible for the pharmacological action. It is also the fraction that may be metabolized and / or excreted.
- The bound drug fraction (DP) it is not so available, and it represents a reservoir for the drug.

When does the fraction of free drug increase?

- When two drugs are administered together, competition between drugs for plasma protein- binding sites occurs, leading to displacement of one of the competing drugs (or both on varying levels, depending on the affinity of the drug towards the binding site). Which causes an increase in the free active fraction of the drug, and as a result an increase in the effect (or in some cases toxicity) of the displaced drug.

The clinical importance of plasma protein binding of drugs

Interpretation of measured plasma drug concentration. When plasma protein concentrations of drug are lower than normal, then the total drug concentration will be lower than expected, but notice that the free drug concentration may not be affected.

Why??

A- Competition between drugs for plasma protein- binding:
Drug A and Drug B are competing to bind with albumin, drug A has a higher affinity for binding with this plasma protein, this will lead to displacement of drug B (becomes unbound from albumin), resulting in an increased fraction of free drug B molecules (that are active), which distribute throughout the volume of distribution leading to an increased elimination rate and a decreased concentration of drug B in the plasma.

So, if drug B has a narrow therapeutic range, this increase in concentration may lead to reaching toxic concentrations. However, in wide therapeutic ranges, this increase in concentration may increase the effect without reaching toxic concentrations.

❖ This is a common mistake practiced by some doctors, when they immediately order to increase the dose once they see the low concentration of drug in plasma, without noticing the active free fraction of the drug, this unneeded increase in dose might lead to toxicity.

B- Other factors, such as low level of albumin due to liver diseases, which will lead to a low capacity of protein-binding in comparison with drug concentration. Therefore, higher fraction of free active drug. **Minute:** 20:00-30:00

4. Drug Clearance (CL)

It is the volume of **blood or plasma** that is completely cleared of drug per unit time.

- Used to determine the rate of elimination (the amount of the drug that's being eliminated per unit time) :

Rate of Elimination (mass/time) = CL (volume of blood/time) *Plasma Drug Concentration (mass/volume)

Notice that,

There's a difference between elimination and clearance:

- Elimination: The process of removing drugs from the **body**, clearance refers to movement of the drug outside the **blood** (could be excreted, distributed, stored, eliminated… etc as long as it's not in the blood).
- Elimination could be through multiple methods: metabolism (oxidation, hydrolysis, conjugation...), or through excretion (renal excretion, bile excretion, exhalation, sweat excretion…) and the rate of elimination is the sum of all these methods.

Clearance of the drugs from the blood occurs via a number of routes such as renal clearance, hepatic clearance and pulmonary clearance. The most important method of clearance is through the kidney.

a- Renal clearance (CL_R)

The rate at which drug is cleared from the blood by the kidney

(CL_R) = Cu.V/Cp , where Cu.V is the rate of elimination

Cu: Concentration of drug in urine V: Urine flow rate

Cp: The plasma concentration of the drug.

If the (CL_R) = 50 ml/hour → indicates that the kidney clears 50 ml of blood from drug per one hour

b- Hepatic clearance (CL_H)

- The rate at which drug is cleared from the blood by the liver

✓ Drug Extraction Ratio (ER) =

$$\frac{\text{Drug concentration entering the liver (Cin) - Drug concentration leaving the liver (Cout)}}{\text{Drug concentration entering the liver (Cin, plasma concentration of the drug)}}$$

- Drug concentration entering the liver could be through portal vein (Oral administration) or through the hepatic vein (Intravenous administration)

ER = Clearance $_{(H)liver}$/ Blood flow to the liver (90 L/hour in a healthy 70 Kg man).

- ER = $Cl_{(H)liver}$/Q

✓ (CL_H)= Q*ER, Q is the liver blood flow **Minute:** 30:00-40:00

* If 0.33 fraction of the blood is cleared of the drug by the liver and the liver blood flow rate is 1.5 L/Min, find the hepatic clearance (CL_H)?

(CL_H)= Q*ER → 1.5 * 0.33 = 0.5 L/Min which means that the liver is able to clear 0.5 L of the blood from the drug per one minute

*(Renal and hepatic clearance occur through different stages. So, there're detailed and indirect methods to estimate the renal and hepatic clearance)

5- First Order Elimination Rate

A constant **fraction** of the drug is eliminated per unit time. It occurs with many drugs at therapeutic concentrations. Most drugs follow first–order elimination.

For example, if 100 mg of a drug is administered and its elimination half – life = 1 hour, the time course of elimination, is:

100 mg $\xrightarrow{1h}$ 50 mg $\xrightarrow{1h}$ 25 mg $\xrightarrow{1h}$ 12.5 mg

So, as shown in Fig 2:

- The rate of drug elimination is directly proportional to the amount of drug in the body (The higher the amount, the more rapid the elimination per unit time). In the previous example; starting with 100 mg, the elimination rate of the first hour was 50mg/h, while in the second hour (starting with 50 mg) the elimination rate was 25 mg/h. This is important in case of exposure to toxic dose; rapid elimination rate (gradually decreases with decreasing amount of drug in plasma) until reaching the therapeutic dose (continued elimination at a lower rate)
- The half life is constant (can be calculated from the plot)
- The elimination rate constant is designated as k, and its units are reciprocal time (1/time) meaning fraction per unit of time
- The plot is a semi logarithmic plot used to get a straight line, which allows easy prediction of pharmacological relations.
- If a semi logarithmic plot was created to show the relation between time and Concentration of drug X in plasma (by taking serial blood samples and recording the concentration over measured times), and the plot was a similar linear

plot→indication that drug X follows a first – order drug elimination rate (remember that the rate of elimination is directly proportional to the amount of drug in plasma in first – order elimination).

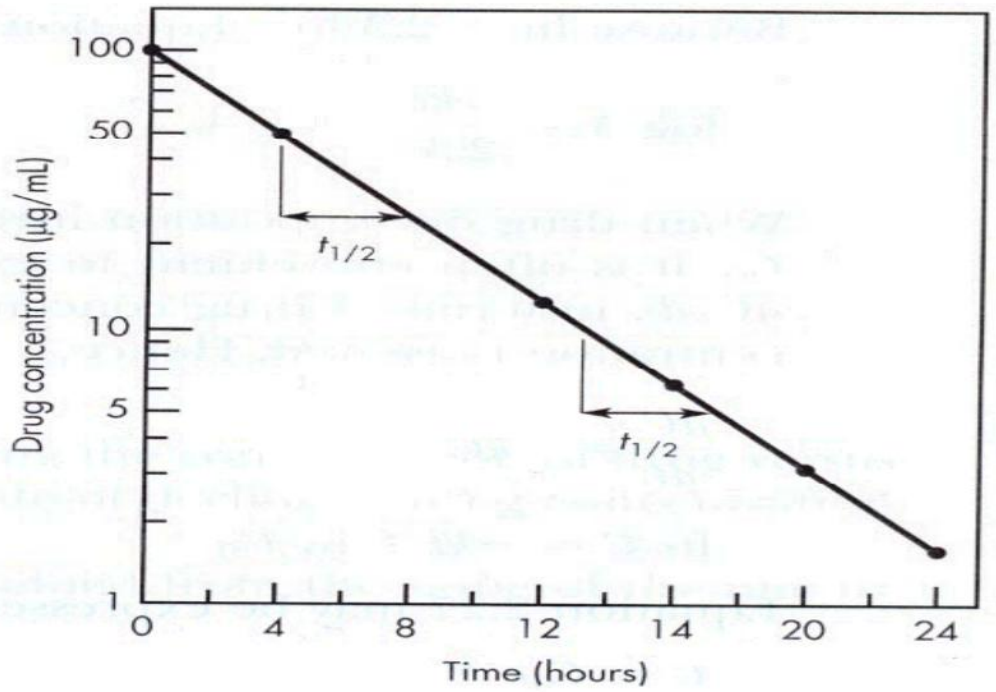


Fig2. Rate of drug elimination per unit time. **Minute:** 40:00-50:00

Please, refer to the questions in the book for further practice on the equations and a better understanding.