Pharmacology

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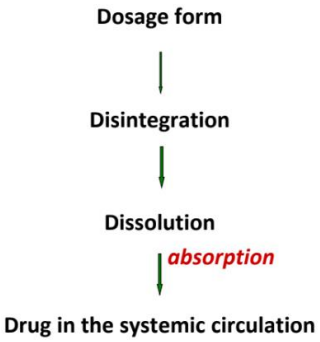
ARKAN ACADEMY

First-Pass Effect

- It is the *incomplete delivery* of the dose given to the systemic circulation.
  - It is also called *First-pass metabolism* or *Pre-systemic elimination*
  - It occurs because the drug could be metabolized in the ***gut***, ***portal vein*** and ***liver*** before reaching the systemic circulation or eliminated by the ***liver into the bile***
  - Therapeutic blood concentration may still be reached by using larger dose
    - ✓ If the patient is having *liver cirrhosis* and there is shunting of blood by-passing the portal circulation, giving a larger dose orally will lead to substantial increases in concentration of the drug and *drug toxicity*
  - That's why the oral drugs usually have higher doses than intravenous
    - ✓ The concentration of drug metabolites after oral administration will be higher than after intravenous administration

Bioavailability

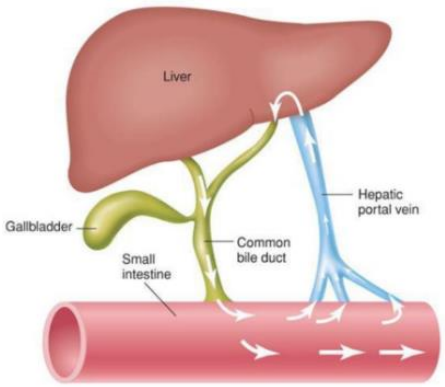
- It is the fraction of the unchanged active drug *reaching the systemic circulation*, following drug administration; irrespective of the route
  - It is equal to *1 or 100%* following intravenous drug administration
  - After *oral* administration, bioavailability may be *less than 1*, because of:
    - ✓ *First-pass effect* and *Enterohepatic cycling*
    - ✓ *Incomplete absorption*
    - ✓ *Incomplete disintegration and dissolution*.
    - ✓ *Destruction* of drug within GIT lumen by gastric acid, bacteria, ...
    - ✓ *Faulty manufacturing* of the dosage form



- It can be reduced due to *decrease in the absorption* of the drug, because:
  - The drug is **too hydrophilic** (**atenolol**) and so it can't cross the lipid membrane
  - The drug is **too lipophilic** (**acyclovir**) and so it can't dissolve in water and so can't reach membranes
  - The presence of **reverse transporters** (**P-glycoproteins**) which pumps the drug out (efflux) the gut wall back to the gut lumen
    - ✓ **Grapefruit juice** *increases bioavailability* by inhibiting:
      - Reverse transporters effect which increases drug absorption and bioavailability
      - The presystemic elimination of some drugs

- First Pass and Enterohepatic cycling of drugs
  - After oral administration, the drug reaches the **gut** then the **liver** and then can be bound to bile:
    - ✓ It can either get back to the intestine and reabsorbed with bile into the liver
    - ✓ Excreted with bile into the feces

- It *reduces the bioavailability*
- *Increases the half-life* of elimination

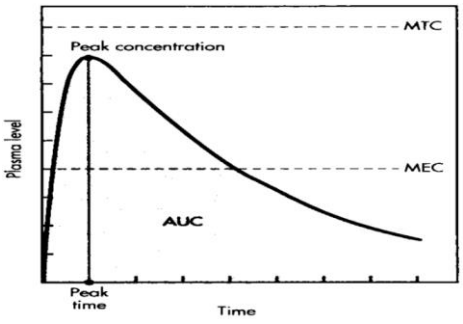


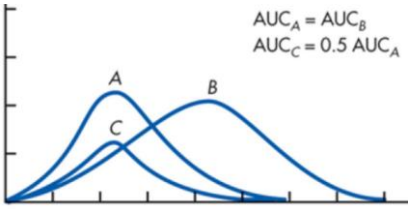
- ***Activated charcoal*** is used in the cases of <u>drug overdose</u> to enhance the elimination of drugs and reduce half-life
  - It can bind (absorb) drugs and chemicals (except ionized and petroleum distillates) and prevent their reabsorption into the systemic circulation

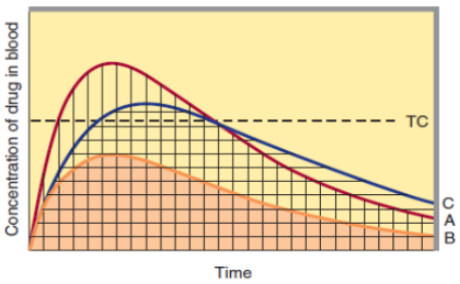
- ***Extraction ration (ER)*** it is the ratio of the drug excreted <u>by the hepatic first pass</u> effect
  - 1 – ER is the amount of the drug that avoids the first pass effect
  - ***Bioavailability (F) = f . (1 – ER)***
  - *f* is the percentage of incomplete absorption

- Example: What is the bioavailability of morphine which is completely absorbed but having a 0.67 ER?
  - Answer: 33%

- Blood concentration versus time curve
  - Bioavailability (*extent of absorption*) represents the *area under the curve (AUC)*
  - C_{max} is the *peak concentration* reached
  - T_{max} is the *time* in which the C_{max} reached
  - ***Absorption rate*** is measured by C_{max} and T_{max}
  - ***Bioequivalence:*** It is a term used to ***compare*** the rate and extent of absorption of different formulations (or dosage forms) of the same active drug







Volume of Distribution (VD)

- 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
- If the apparent volume of distribution is ***large*** that means that the drug is ***highly distributed*** into the tissues

• In a normal 70 Kg man, the volume of:		• But the volume of distribution for:	
Plasma	= 2.8 L	Aspirin	= 11 L
Blood	= 5.6 L	Ampicillin	= 20 L
ECF	= 14 L	Phenobarbital	= 40 L
TBW	= 42 L	Digoxin	= 640 L
Fat	= 14 - 25 L	Imipramine	= 1600 L
		Chloroquine	= 13000 L

- If it is a ***small*** number, that means that the drug is ***restricted in the plasma*** due to:
  - Binding to *plasma proteins*
  - *Highly ionized* state in the plasma

- V_D = amount of the drug in the body (Ab, dose) / concentration in the plasma (Cp)

Drug binding in the plasma

- The binding to plasma proteins is reversible
- Examples of plasma proteins:
  - *Albumin* (the most important)
  - *α1-Acid glycoprotein* is important for binding some basic drugs

Drug + Protein ⟷ Drug-Protein complex

D + P ⟷ DP

- The ***free unbound*** drug fraction (D) is responsible for the pharmacological *action* and for *elimination*
  - The ***bound drug*** fraction (DP) is not available, and it represents a *reservoir* for the drug
  - The plasma protein binding help interpretation of measured plasma drug concentration of such drugs

- When the *plasma protein concentration is lower* than normal
  - The *total drug* concentration will be *lower* than expected
  - The *free concentration* may *not be affected* because the drug will distribute, and its rate of elimination will increase, so its plasma concentration will NOT increase dramatically

- 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 Clearance (CL)

- 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

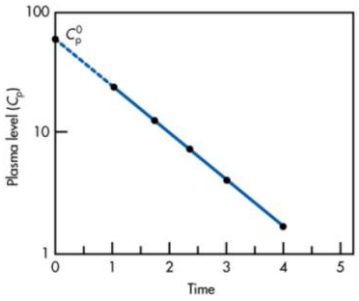
- Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration:
  - ***CL = Rate of elimination / Plasma concentration (Cp)***

- 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?
  - 10 L/hr

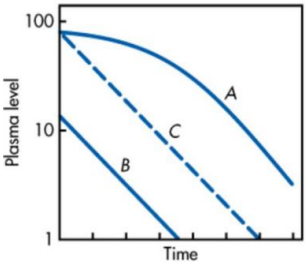
- *Renal clearance* $(CL_R) = C_u . V/Cp$
- *Hepatic clearance* $(CL_H) = Q . (Ci – Co)/ Ci = Q . ER$

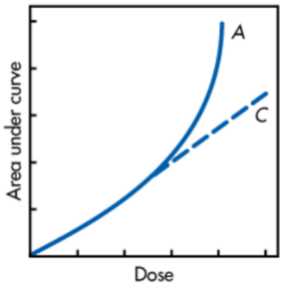
C_u (concentration of drug in urine)
V (urine flow rate)
C_i (concentration of drug going to liver)
C_o (concentration of drug leaving the liver)
Q (Blood Flow)

- Elimination can be either:
  - *First order elimination*
    - ✓ The rate of drug elimination is *directly proportional* to the amount of drug in the body
    - ✓ Constant **fraction (percentage)** of drug is eliminated per unit time
    - ✓ The elimination rate constant is designated as **k** (the unit is 1/time)
    - ✓ Occurs for many drugs at the therapeutic concentration



  - *Zero-Order Elimination*
    - ✓ Elimination rate is *NOT proportional* to the amount of drug in the body
    - ✓ **Constant amount** is removed per unit time because it is saturable
    - ✓ Occurs with few drugs (*aspirin*, *phenytoin*, *ethanol*)
    - ✓ Rate of elimination = V_{max} . C / K_m + C
      - C (drug concentration), V_{max} (maximum elimination), Km (Concentration of the drug at 0.5 V_{max})





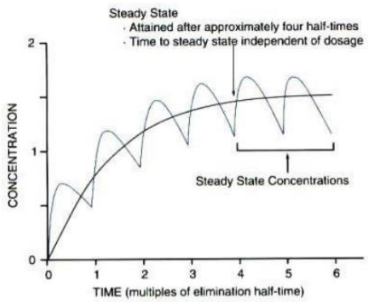
- **High-extraction ratio drugs**
  - Drugs ***cleared very rapidly*** where most of their amount is eliminated by ***first pass*** through the liver
  - Such as Morphine, Lidocaine, propranolol, verapamil

- *Half-Life ($t_{½}$) of Elimination*
  - For first order elimination:
    - ✓ It is the time required for the amount of drug in the body or the plasma concentration of the drug to drop by 50%
    - ✓ *After ~ 4 half-lives*, most of the drug will be eliminated from the body
    - ✓ In the first order elimination:
      - k * $t_{½}$ = 0.693
      - CL = k . V_d

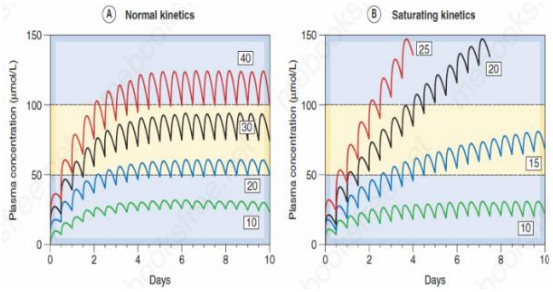
Half-lives	% of drug removed
1	50
2	75
3	87.5
4	93.75

  - For zero order elimination:
    - ✓ It is related to dose and plasma concentration for drugs undergoing zero-order kinetics, and is *NOT constant*
    - ✓ The higher the concentration, the longer the half-life of elimination and vice versa

- ***Steady-State:*** a *constant peak*, *trough*, and *average* drug concentrations are achieved
  - Is a condition achieved following repeated drug administration as occurs in clinical practice
  - Achieved following repeated drug administration where the rate of *administration* is *equal* to rate of *elimination*



- Steady-state (SS) is achieved after *approximately 4 half-lives* of repeated drug administration.
  - **50%** of SS is achieved after ***one half-life*** of administration
  - Our aim during drug therapy is to attain a steady-state drug concentration (Css) within the therapeutic range, NOT subtherapeutic or toxic



- **Loading Dose (LD)**
  - A **large** initial dose to reach the steady state
  - When the half-life is too long, steady-state will take a long time to be achieved so we need to give a loading dose to achieve drug concentration within the therapeutic range sooner (target concentration)
  - It could be given **orally** or **IV** and should be given **gradually** to avoid toxicity

- **Maintenance Dose (MD)**
  - To attain and **maintain** a desired SS concentration (Css) of a drug (target concetration)
  - **MD = CL. Css**

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