General Pharmacology

- Pharmacokinetics
- Pharmacodynamics
- Drug-drug interactions

EXCRETION OF DRUGS

Kidney is the most important organ for excretion. Excretion occurs through:

1. Glomerular filtration:
   All free drug molecules whose size is less than the glomerular pores are filtered into bowman's capsule.
2. Proximal convoluted tubules (PCT):

- Secretion of drugs occurs primarily in the PCT by energy-dependent active transport systems.
- Active secretion occurs either through acid carrier e.g. for penicillin, probenicid & salicylic acid or basic carrier for amphetamine &quinine.

3. Distal convoluted tubules:

- Lipophilic drugs may be reabsorbed back to systemic circulation.
- Alkalinization of urine (by $NaHCO_3$) keeps acidic drugs ionized and increases their excretion.
- Acidification of urine (by ascorbic acid "Vit.C" or ammonium chloride) leads to ionization of weak bases and enhancement of their excretion.

Other sites of excretion:

1. **Bile: with enterohepatic recycling** e.g. rifampicin, doxycycline, ciprofloxacin & azithromycin, or without enterohepatic recycling e.g. ceftriaxone and cefoperazone.
   - Biliary excretion of these drugs increased their efficacy in treatment of enteric and biliary diseases.
2. Lungs e.g. volatile anesthetics.
3. Saliva e.g. iodides.
4. Sweat e.g. rifampicin.
5. **Milk:** this is important in lactaaing mothers.

Examples of drugs contraindicated during breast feeding:

1. **Antibiotics:** chloramphenicol, tetracyclines & sulfonamides.
2. **CNS drugs:** Narcotics, benzodiazepines, alcohol & nicotine.
3. **Laxatives:** Cascara & senna.
4. **Corticosteroids:** They suppress baby's growth and immunity.
5. **Bromocreptine:** It suppresses lactation.
6. **Sex hormones:** Contraceptive pills suppress lactation.

Note: To decrease risk to infants, lactating mothers should take drugs immediately after nursing or 3 – 4 hours before next feeding.

Note: pH of milk is more acidic than that of plasma basic drugs accumulate in milk. Also, milk contains more fat which leads to retention of lipid-soluble drugs e.g. cytotoxic drugs, metronidazole, morphine and laxatives.

PARAMETERS OF ELIMINATION

(1) KINETICS ORDERS

1- First order kinetics (for most drugs):

1. Rate of elimination is directly proportionate to the blood concentration of drugs i.e. constant percentage of the drug is eliminated per unit of time.
2. Constant "$t_{1/2}$" (elimination half life)
3. Repeated dosing increases drug concentration and accordingly the rate of elimination increases till the rate of administration equals the rate of elimination. At this point Css (steady state concentration) is reached.
4. After 4 – 5 $T_{1/2}$ more than 95% of Css is reached.
5. Css is directly proportionate to the dose (↑ dose → ↑ Css).
6. Most drugs obey 1st order kinetics.

2- Zero-order kinetics: (Example: *digitalis glycosides)*

1. Rate of drug elimination is constant i.e. constant amount of drug is eliminated per unit of time.
2. "$t_{1/2}$" (half life) is not constant.

3. No Css is reached by repeated dosing.
4. Any change of the dose may cause toxicity.

Note: some drugs follow 1st order kinetics in small dose and zero order kinetic at large doses i.e. the elimination mechanism is said to be saturated (saturation kinetics).

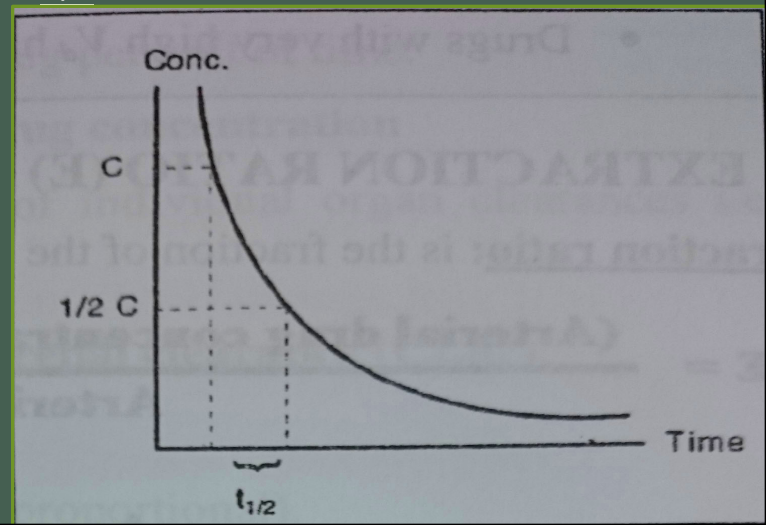
Importance of saturation kinetics:

1. Modest change in dose or bioavailability may cause unexpected toxicity.
2. Drug-drug interactions are common.
3. Drugs obeying saturation kinetic : phenytoin, salicylate and theophylline.
4. These drugs need monitoring of their plasma levels to avoid toxicity.

(2) ELIMINATION HALF LIFE ($t_{1/2}$)

It is the time required to reduce the plasma concentration of the drug to half the initial concentration (the time required for drug concentration to be changed by 50%).

$$t_{1/2} = 0.693 \ V_d / CLs$$



Importance of elimination $t_{1/2}$:

1- It determines the dosage interval (T).

- if T = "$t_{1/2}$"
- if T < "$t_{1/2}$" → drug accumulation may occur.
- if T > "$t_{1/2}$" → drug concentration decreases between doses.

2- It indicates time required to attain Css (about 4-5 $T_{1/2}$) :

- If the drug is aadministered every "$t_{1/2}$" :
  - After the 1st "$t_{1/2}$" , drug concentration reaches 50% of the final Css.
  - After the 2nd "$t_{1/2}$" , drug concentration reaches 75% Css.
  - After the 3rd "$t_{1/2}$" , drug concentration reaches 87.5% Css.
  - After the 4th "$t_{1/2}$" , drug concentration reaches 93.75% & 96.87% Css .
- Therefore, one can assume that if the if the drug is given every "$t_{1/2}$". Css will be reached after 4-5 "$t_{1/2}$"s.

3- If "$t_{1/2}$" is very short (seconds or minutes), the drug should be given by IV infusion (e.g. dobamine, dobutamine, esmolol).

4- If "$t_{1/2}$" is very long , the drug should be administered in loading dose to reach the desired Css rapidly followed by maintenance dose to maintain the desired Css.

Factors affecting elimation "$t_{1/2}$" :

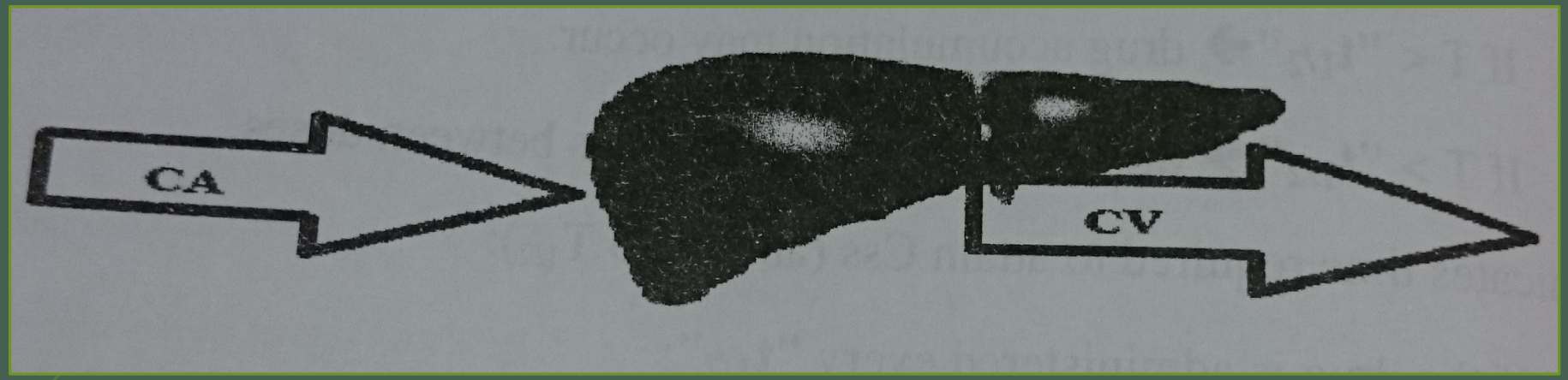
1. State eliminating organs i.e. liver & kidney function.
2. Delivery of drugs to the eliminating organs:
   - Plasma protein binding limits drug elimination.
   - Drugs with very high V_d have limited elimination.

(3) EXTRACTION RATIO (E) & HEPATIC CLEARANCE (CL_{liver})

Extraction ratio: is the fraction of the drug eliminated by the liver.

$$E = \frac{(Arterial\ drug\ concentration) - (Venons\ drug\ concentration)}{Arterial\ drug\ concentration}$$

$$Extraction\ ratio = \frac{amount\ extracted}{amount\ entered} = \frac{Q\ X\ (CA-CV)}{Q\ X\ CA}$$



Amount entered = Q X C_A Amount exit = Q X C_V

Amount extracted = Q (C_A – C_V)

Q: blood flow – C_A : Atreial concentration – C_V: Venous concentration.

- When E > 0.6 ➔ Clearance is nearly flow-dependent e.g. propranolol.
- When E < 0.2 ➔ Clearance is nearly enzyme-dependent e.g. warfarine.
- When E is 0.2 – 0.6 ➔ Clearance depends on both flow and enzymaticdegradation e.g. acetaminophen & chloramphenicol.

Hepatic clearance (Cl_{liver}): is the volume of blood cleared from the drug per unit of time.

CL_{liver} = Extranction ratio (E) X hepatic blood flow (Q)

(4) SYSTEMIC CLEARANCE (CL_S)

- It is the volume of fluid cleared from the drug per unit of time.

CLs = Rate of elimination/Drug concentration

- Systemic clearance is equal to the sum of individual organ clearances i.e. clearance by liver, kidney, lungs…

CLs = Renal clearance (CL_r) + non-renal clearance (CLnr)

Factors affecting drug clearance:

1. Blood flow to the clearing organs (directly proportional).
2. Plasma protein binding of the drug (inversely proportional).
3. Activity of clearing processes e.g. hepatic enzyme, glomerular filtration and secretory processes (directly proportional).

Significance of clearance :

1. Calculation of the maintenance dose (MD) = **CLs X Css.**
2. The dosing regimen of drug eliminated by glomerular filtration can be guided by creatinine clearance e.g. dosing of gentamicin:
   - If kidney function is normal (Cr CL = 120 ml/min.) → dose is 80 mg 3times/day.
   - If kidney function is impaired, you can reduce the dose or increase the dosage interval according to Cr CL:
     - If Cr CL = 60 ml/min, give half the usual dose (40 mg 3times/day).
     - If Cr CL = 30 ml/min, give one quarter the usual dose (20 mg 3times/day) or give the usual dose every 32 hours.

How to icrease duration of action of drugs:

1- ***Delay absorption:***

- Add vasoconstrictor e.g. adrenaline to local anaesthetics.
- Use S.C. pellet implantation.
- Use sustained-release (SR) preparations.
- Add oil to vasopressin.
- Use moderately soluble preparations e.g. protamine zinc insulin suspension.

2- *Decrease metabolism:* use enzyme inhibitors.

3- *Decrease excretion:* probenicid →↓renal secretion of penicillin.

Notes:

- **Loading dose:** The dose required to achieve a desired plasma concentration (desired Css) rapidly, followed by routine maintenance dose.

Loading dose = Vd x desired Css

- **Maintenance dose :** The dose given to maintain the desired Css. i.e. maintenance dose equal eliminated drug in certain period of time.

Maintenance dose = clearance x desired Css

- **Changing the dose** not change the time needed to reach Css but changes Css.
- **Increasing dosing frequency** reduces the amplitude of swings and troughs in drug concentration but the value of Css is constant.