1/10/2024

# Excretion

Pharmacokinetics.

- passage out of systemically absorbed drug

- Excreted unchanged or as metabolites.
- major organ of excretion - kidney.

Routes of Excretion

- renal.
- Biliary } major.
- Alveolar

- sweat, saliva } minor routes of elimination.
- milk

## Renal Excretion.

kidney - most important organ of Excretion.

Net renal excretion =

(Glomerular filtration + tubular secretion) - tubular reabsorption.

3 principle processes.

→ glomerular filtration.

→ tubular secretion

→ tubular reabsorption.

## Glomerular filtration

- glomerular (capillaries) → large pores → Non protein bound drug filtered.
- Normal GFR → 125 ml/min

Glomerular filtration - factors.

- Molecular size. → inversly prop
- plasma protein binding → inversly prop.
- renal blood flow → directly prop.

- Driving force

→ capillary hydrostatic pressure.

## Tubular reabsorption.

- passive diffusion.

- lipid solubility → d prop.
- ionization of drug. → $\frac{1}{\text{ionization}}$ inversly prop.

imp

Alkalinization → Rx of poisoning of barbiturates & salicylate (acidic drugs).
(by sodium bicarbonate)

acidification → not practiced clinically, due to side effects.
(by vit c - but not done clinically cause it causes cardiotoxicity)

## Active tubular secretion

- site - PCT.
- transporters mediated.
- active transfer of organic acids and bases
- Energy dependent.
- depends on renal blood flow.

Transporters

| | |
|---|---|
| Organic acid transport | OATP. |
| organic base transport | OCT. |
| efflux transporters | p-glycoproteins, MRP2 |

- Organic Acid transport
- through OATP
- for acidic drugs.
- Penicillin, probenecid, uric acid, Salicylates, Nitrofurantoin, methotrexate.

Organic base transport

- through OCT.
- for basic drugs.
- Endogenous compounds. (reabsorbed).
- drugs & their metabolite, (secreted)

eg: furosemide, Thiazides, Amiloride.

Active tubular secretion

- Bidirectional.
- drugs utilizing same active transport compete with each other.

eg: Probenecid & uric acid & penicillin,

probenecid (uricosuric in gout) → high affinity for OATP, block active transport of both, reduce penicillin excretion & uric acid reabsorption.

## Enterohepatic circulation

- phenomenon of cycling of drug btw intestine & liver.

eg: cardiac glycosides, rifampicin, chloramphenicol, indomethacin.

Poobenol.

Biliary Excretion

- large molecules eliminated in bile.
- 90% reabsorbed.
- high polarity drugs } Excreted
- metabolites.
- active process.
- transporters.
- OATP, OCT, MRP2, P-gp.

eg: Erythromycin, ampicillin, rifampicin, OCP, tetracyclins.

advantages

- prolongation of drug action

eg: oral contraceptives, rifampicin (TB).

alveolar Excretion

- Simple diffusion.
- gases, volatile liquids (general anesthetics, alcohol)
- depends on:
  ✓ partial pressure in blood.

Saliva, sweat

- minor route.
- lithium, rifampicin, heavy metals (mainly)

## Milk excretion

- Small amounts only reach infant.
- passive diffusion.
- ⚠ lower pH (6.6), so basic drugs get concentrated in milk.

## 3 PK parameters

1. Bioavailability (F)
2. volume of distribution (Vd).
3. clearance.

## Clearance. ⚠ Imp Short note.

- measure of body's efficiency in eliminating drug from systemic circulation.
- theoretical volume of plasma from which the drug is completely removed in unit time.

$$Cl = \frac{\text{rate of elimination}}{\text{plasma concentration}}$$

## Vvimpt S.N. plasma half life ✓

- plasma half-life of a drug is the time taken for its plasma concentration to be reduced to half of its original value.
- Elimination

$$T_{1/2} = \frac{\text{natural logarithm of } 2}{K}$$

$$= \frac{0.693}{K}$$

K is elimination rate constant.

$$K = \frac{Cl}{Vd}$$

$$T_{1/2} = 0.693 \times \frac{Vd}{Cl}$$

- about 5 ($T_{1/2}$) are required for 97% elimination of the drug
- at end of 5 half lives almost 97% of drug is eliminated
- ≈ 3.125 is remaining.

## Uses of half life.

- As a guide for the time taken for a drug to get eliminated from the body
- As a guide for the time to reach steady state.
- As a guide to the relationship btw loading dose & maintenance dose.

### T½ of some representative drug

paracetamol – 2hr.

digoxin – 40hr.

penicillin – G – 30min

digitoxin – 7days.

Impt

## Zero order kinetics. - ∇ alcohol is only drug that follows zero order kinetics

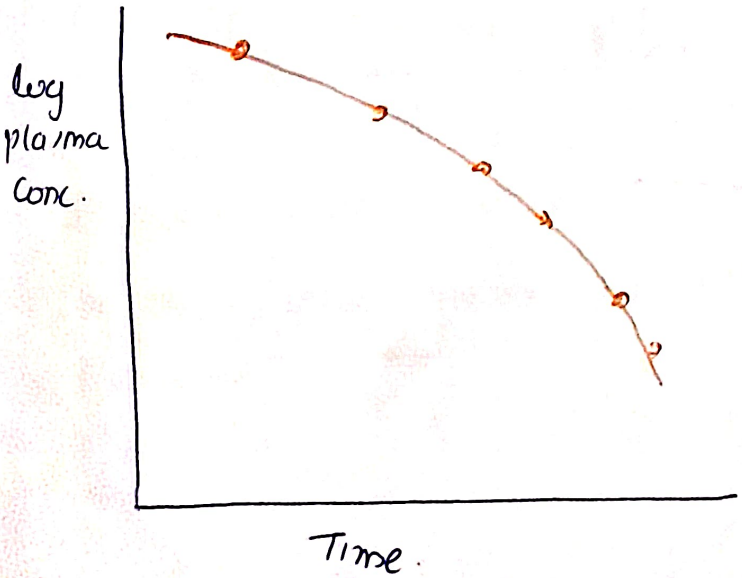
- Constant amount of drug is eliminated in unit time.
- rate of elimination is constant irrespective of drug conc → cumulative toxicity
- $T_{1/2}$ is never constant: changes with plasma concentration.
- CL decreases with increase in, concentration.

Eg: alcohol.

- 200 $\xrightarrow[50mg]{2hr.}$ 150 $\xrightarrow[50mg.]{2hr.}$ 100 $\xrightarrow[50mg.]{2hr.}$ 50.

- $T_{1/2}$ is never constant; changes.
- Non linear
- michaelis menten elimination.
- capacity limited elimination.

Zero order kinetics

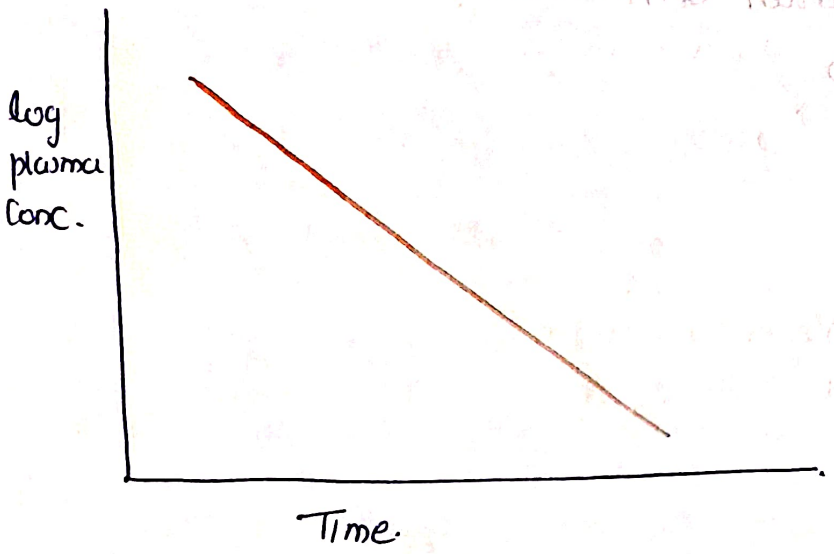



Non linear

## First Order Kinetics. ☆Imp

- Constant fraction of drugs eliminated in unit time
- Rate of elimination ∝ to drug concentration.
- T1/2 remains constant ✓
- Clearance – constant ✓
- eg: majority of drugs (paracetamol, penicillin)

200 —2h, 50%→ 100 —2h, 50%→ 50




→ linear.

→ constant rate of decline.

## Saturation kinetics

- Mixed order kinetics / Non-linear elimination.
- Elimination of some drugs approach saturation over therapeutic range.
- Due to saturation of metabolising enzymes or elimination process.
- Kinetics change from 1st order to zero order at higher doses.

eg: phenytoin, warfarin, Theophylline, tolbutamide, digoxin

Steady state plasma concentration (Css).

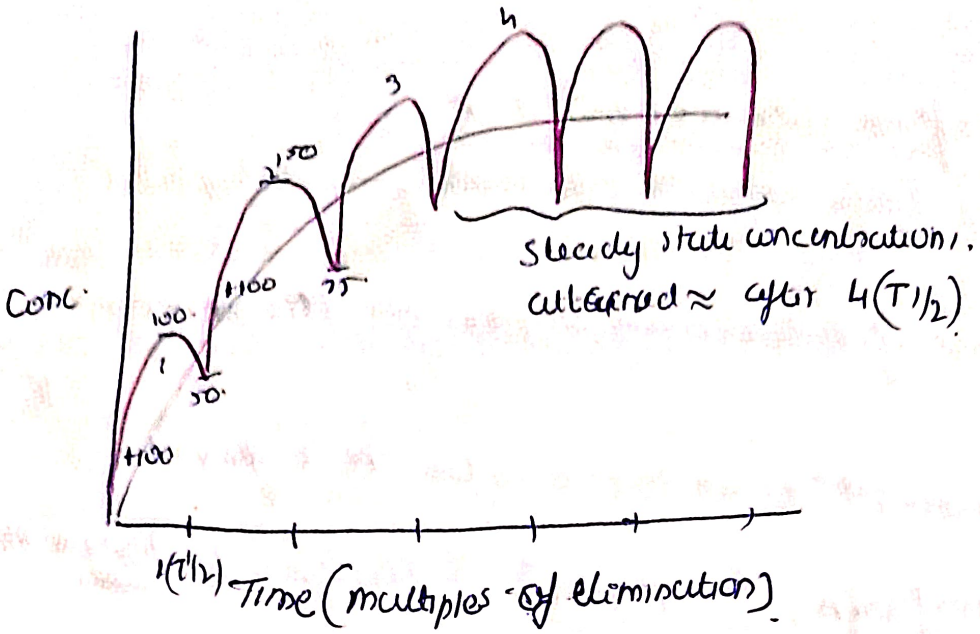
— Plateau principle.

- Is the plasma concentration of the drug at which rate of ~~absorption~~ administration equals rate of elimination.

$$Css = \frac{dose\ rate}{CL}$$

⚠ Css is achieved after 4-5 $T_{1/2}$

- In steady state, plasma conc. rises and falls within the therapeutic range.




## Loading Dose

- This is a single or few quickly repeated doses given in the beginning to attain target concentration rapidly.
- mainly for drugs with high Vd
- does not depend on clearance.

$$\text{Loading dose} = \left(\frac{\text{target plasma conc} \times Vd}{F}\right)$$

## maintenance dose.

- The dose is to be repeated at specified intervals after the attainment of Cpss, to maintain the same by balancing elimination.
- depend on clearance.

$$\text{Dose rate} = \frac{\text{target Cpss} \times C_L}{F}$$

# Therapeutic Drug monitoring (TDM)

→ Tailoring the dosage regimen for an individual patient either for cure, alleviation or prevention of illness or adverse effects by maintaining the blood or plasma concentration of the drug within the target therapeutic range.

## Indications (Learn any 3 atleast)

- Drugs with very low safety margin.
- If individual variations are large.
- potentially toxic drugs in case of renal failure
- poisoning
- to check non compliance of patient
- therapeutic failure eg: Antimicrobials.

## TDM – no value.

In – drugs whose response is easily measurable.

eg: Antihypertensive, hypoglycemics.

- prodrugs eg: Levodopa.
- 'Hit & run drugs' – eg: pantoprazole.
- drugs with irreversible action

eg: Organophosphates.

## VV impt Questions

- drug interaction btw penicillin & probenecid.
- Enterohepatic circulation.
- clearance
- ★ plasma half life ✓
- First order kinetics.
- ★ Zero order kinetics ✓
- Mixed order kinetics.
- Steady state plasma conc.
- TDM.