PHARMACOKINETICS: V (Elimination)

- **Objectives**

At the end of session the students should be able to:

- Explain the dug clearance by renal, hepatic and other routes
- Compare and contrast between first order and zero order kinetics

- Estimate the loading dose ,maintenance and steady state concentration dose of a drug.
- Enumerate methods of prolonging drug action

Drug Elimination

Elimination of a drug is defined as the process where by drugs or metabolites are irreversibly transferred from internal to external environment through renal or non renal route.

Excretion of unchanged or intact drug is needed in termination of its pharmacological action. Excretion of a drug is the passage out of systemically absorbed drug.

Route Of Drug Elimination

- Renal Elimination
- Non Renal Elimination
  - Biliary elimination
  - Pulmonary elimination
  - Salivary elimination.

- Mammary elimination.
- Skin / Dermal elimination.
- Gastrointestinal elimination.

Kidneys are the principal organ of drug elimination

Most drugs are excreted in urine either as unchanged or drug metabolites .

Net renal excretion= (glomerular filteration+ tubular secretion)-tubular reabsorption

Glomerular filteration:

Glomerular capillaries have pores larger than usual. Non protein bound drug are filtered.

Normal glomerular filteration rate is 125ml/min.

Tubular reabsorption:

Occurs by passive diffusion

Depends on lipid solubility and ionization of drug at urinary pH.

"*Ion trapping*" by acidifying or alkalinising the urine.

Tubular secretion

Mainly occurs in the proximal tubules

Occurs by active transport processes.

Excretion of protein bound drug.

- Factors effecting renal elimination of drug

Physiochemical properties of drug
Urine pH
Blood flow to the kidneys
Biological factors(age ,sex etc.)
Renal diseases
Drug interaction eg. penicillin and probenicid

Drug elimination by the kidney

- Biliary Elimination of Drug

Phenomenon of enterohepatic circulation.

Mainly the drug metabolites are eliminated in bile rather than parent drug. Example: chloramphenicol, indomethacin, morphine

Kinetics of elimination

- First order kinetics:

Rate of Elimination of the drug is directly proportional to the concentration of the drug in the body. A constant fraction of the drug present in the body is eliminated per unit time.

Most drug follow first order kinetics.

Elimination Constant and Half-life

Half-life = the time it takes for the plasma concentration to be reduced by ½

Half life = 0.693/Ke

Calculating a drug's half-life makes the Elimination constant more practical and accessible

Clinical Application of Half-Life

You walk in to your patient's room and she appears sedated. You remember that she received a dose of dilaudid at 8 am, but it was now 6 pm. You wonder whether the dilaudid could still be in her system

so you look up the half life to determine how much of the dose is likely to remain in her system. You check micromedex to find that the $T_{1/2}$ is 2 hours. Since it has been 10 hours, 5

half-lives have elapsed. How much of the original dose remains?

Clinical Application

After 1 half life

50% remains

2 half lives

25% remains

3 half lives

12.5% remains

4 half lives

6.25% remains

5 half lives

3.125% remains

Effects of the dose of a single intravenous injection of drugs om plasma levels
Drug concentrations in serum after a single injection of drug at time =0
Data are plotted on a log scale
$T_{0.5}$= 0.693/Ke

- Zero order kinetics:

Rate of elimination remains constant and is independent of the concentration of the drug in the body.

A constant amount of drug is eliminated in unit time.
E.g.ethanol.

Zero-Order elimination occurs in overdose situations when the various processes by which drugs get eliminated are saturated.

- Clearance(CL):

Theoretical volume of plasma from which the drug is removed in unit time.

Clearance(CL) of drug is calculated by formula:

CL=rate of elimination ÷plasma concentration

(unit-volume per unit time)

First order kinetics-CL is constant

CL depends upon drug and condition of the organ eliminating the drug.

Dosage Regimen:

A plan of drug administration over a period of time.

Achievement of therapeutic levels of drug in the blood

without exceeding the minimum toxic level.
Loading dose
Maintenance dose

➢ **Loading Dose:**

This is a single or few quickly repeated doses given in the beginning to attain target concentration rapidly.

A **loading dose** is an initial higher dose of a drug that may be given at the beginning of a course of treatment before dropping down to a lower **maintenance dose.**

Loading dose

=($\mathbf{V_D}$)Xdesired plasma conc/Bioavailability

Maintenance Dose:

This dose is the one that is to be repeated at specified intervals after the attainment of desire plasma concentration of the drug.

Dosing rate(average dose per unit time)

=(**CL**)Xdesired plasma conc/Bioavailability

CL=clearance; if CL is in ml/min

Daily dose=dose per minX60(min/h)X24(hr/d)

Steady State Concentration

Steady state is achieved when the amount of drug coming into the body is equal to the amount of drug coming out of the

body during each dosing interval.

Loading dose=Vd X C_{ss}

Maintenance dose= Cl X Css

THANK YOU