Date

NON - LINEAR PHARMACOKINETICS :

- It is also called as "Dose-dependant kinetics" or "Mixed order kinetics."

- The rate process of drug's ADME are dependant upon carriers or enzymes that are substrate specific.

- Hence here, the first order kinetics transform into mixture of zero-order and first-order rate processes.

- The pharmacokinetic parameter change with the administered dose size. Hence, it is called as "Dose-dependant kinetics" or "Non-linear kinetics."

- These pharmacokinetics show variability in pharmacological response.

⇒ Determination of non-linear kinetics :

(1) Determination of steady state plasma concentration at different doses.

If,

steady state conc. $\propto$ dose = Linearity

steady state conc. $\propto \frac{1}{\text{dose}}$ = ~~Non-linearity~~

Date

(2) Determination of some important pharmacokinetic parameter such as elimination half-life, total systemic clearance or fractional bioavailability at different doses of drug.

⇒ ~~(3)~~ Factors causing Non-linearity:
Non-linearity can occur in absorption, distribution, metabolism and excretion.

(1) Drug absorption -
(a) when absorption is solubility or dissolution rate limited:
Eg: Griseofulvin.
- At higher doses, saturated solution of drug is formed in GIT or at any other G.V. site.
- Rate of absorption attains a constant value.

(b) When absorption involves any carrier-mediated transport systems:
Eg: Riboflavin, Ascorbic acid, cyanocobalamin etc.
- At high doses, saturation of transport systems of these vitamins result in non-linearity.

#

Date

(c) When presystemic gut wall or hepatic metabolism attains saturation -

Eg : Propranolol

- F, Ka, Cmax and AUC are increased

(2) Drug Distribution -

(a) saturation of binding sites on plasma proteins

Eg : Phenyl butazone.

- Free plasma drug conc. and Vd. are increased.

(b) saturation of tissue binding sites:

- Free plasma drug concs is ↑
- Vd is ↓.

(3) Drug Metabolism -

(a) capacity - limited metabolism due to enzyme or co-factor saturation:

Eg : Phenytoin
Alcohol
Theophylline.

(b) Enzyme induction

Eg : Carbamazepine

- ↓ Cl_H and ↑ Css → (a)
- ↑ Cl_H and ↓ Css → (b)

(4) Drug excretion :

(a) Active tubular secretion

Eg : Penicillin - G

#

Date

(b) Active tubular reabsorption.

Eg: Water - soluble vitamins and Glucose.

Date

MICHAELIS - MENTON EQUATION :

Kinetics of capacity - limited or saturable process is given by -

$$-\frac{dc}{dt} = \frac{V_{max} + C}{\cdot km + C} \quad \text{---- (1)}$$

Where,

$-\frac{dc}{dt}$ = rate of decline of drug conc. with time

V_{max} = Theoretical maximum of the rate process

km = Michaelis constant.

Three situations can be considered depending on values of km and C :

(1) $km = C$

$$-\frac{dc}{dt} = \frac{V_{max}}{2} \quad \text{---- (2)}$$

(2) $km >> C$

Here, $km + C = km$ and eqn (1) is reduced to :

$$-\frac{dc}{dt} = \frac{V_{max}\, C}{km} \quad \text{---- (3)}$$

#

Date

(3) when $K_m \ll C$

under this condition, $K_m + C \approx C$

and eqn (1) will become:

$$-\frac{dC}{dt} = V_{max} \quad \text{---} (4)$$