B.Pharmacy
Subject-Biopharmaceutics and pharmacokinetics
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Module-5

Non Linear Pharmacokinetics

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Objective of course:

Understand various pharmacokinetic parameters, their significance and application.

Learning Outcomes:

❖Students will learn about various factors causing non linear pharmacokinetics and tests to detect non linearity.

❖Students will learn about Michaelis-menton method to determine pharmacokinetic parameters.

CONTENTS

- Introduction
- Linear & Nonlinearity Pharmacokinetics
- Detection of non-linearity in pharmacokinetics
- Causes of nonlinearity
- Michaelis – Menten equation
- Estimation of K_m and V_{max}
- Estimation of K_m and V_{max} at steady-state concentration

LINEAR PHARMACOKINETICS

» At therapeutic doses, the change in the amount of drug in the body or the change in its plasma concentration due to absorption, distribution, binding, metabolism or excretion, is proportional to its dose, whether administered as a single dose or as multiple doses.

» In such situation the rate processes are said to follw first order or linear kinetics and all semilog plots of C Vs t for different doses when collected for dose administered, are superimposable.

» The important pharmacokinetic parameters viz. F, K_a, K_E, Vd, Cl_R, Cl_H which describes the time course of a drug in the body remain unaffected by the dose.

» Pharmacokinetics is dose independent.

NONLINEAR PHARMACOKINETICS

» The rate process of drug's ADME are depend upon carrier or enzymes that are substrate specific, have definite capacities and are susceptible to saturation at a high drug concentration.

» In such cases, an essentially first-order kinetics transform into a mixture of first-order and zero-order rate processes and the pharmacokinetic parameters are changed with the size of the administered dose.

» Pharmacokinetics of such drugs are said to be dose-dependent. Terms synonymous with it are mixed-order, nonlinear and capacity-limited kinetics.

DETECTION OF NON-LINEARITY IN PHARMACOKINETICS

- There are several tests to detect non –linearity in pharmacokinetics but the simplest ones are:

1) First test:- Determination of steady state plasma concentration at different doses.

2) Second test:- Determination of some important pharmacokinetic parameters such as fraction bioavailability, elimination half life or total systemic clearance at different doses of drug. Any change in these parameters is indicative to non-linearity which are usually constant.

CAUSES OF NON-LINEARITY

Drug absorption

- Three causes:- I) Solubility / dissolution of drug is rate-limited; Griseofulvin - at high concentration in intestine.

  II) Carrier - mediated transport system; Ascorbic acid - saturation of transport system.

  III)Presystemic gut wall / hepatic metabolism attains saturation; Propranolol.

- These parameters affected F, K_a, C_{max} and AUC.

- A decrease in these parameters is observed in former two causes and an increase in latter cause.

Drug distribution

At high doses non-linearity due to

- Two causes:- I) Binding sites on plasma proteins get saturated; Phenylbutazone.

  II) Tissue binding sites get saturated.

- In both cases there is increase in plasma drug concentration.

- Increase in $V_d$only in (I)

- Clearance with high ER get increased due to saturation of binding sites.

Drug metabolism

- Non-linearity occurs due to capacity limited metabolism, small changes in dose administration - large variations in plasma concentration at steady state - large intersubject variability.

- Two imp causes:- I) Capacity - limited metabolism - enzyme &/ cofactor saturation; Phenytoin, Alcohol.

  II) Enzyme induction - decrease in plasma concentration; Carbamazepine.

- Autoinduction in dose dependent concentration.
- Saturation of enzymes - decrease in Cl_H - increase in C_{ss}.
- In case of enzyme induction reverse condition.
- Other reasons includes saturation of binding sites, inhibitory effects of the metabolites on the action of enzymes.

Drug excretion

- Two active processes which are saturable,
  - I) Active tubular secretion - Penicillin G
  - II) Active tubular reabsorption - Water soluble vitamins & Glucose.

- Saturation of carrier systems - decrease in renal clearance in case of I & increase in II. Half life also increases.
- Other reasons like forced diuresis, change in urine pH, nephrotoxicity & saturation of binding sites.
- In case of biliary excretion non - linearity due to saturation - Tetracycline & Indomethacin.

Examples of drugs showing nonlinear pharmacokinetics

Causes	Drugs
GI absorption:-	
Saturable transport in gut wall	Riboflavin, Gabapentin
Saturable GI decomposition	Penicillin G, Omeprazole
Intestinal metabolism	Propranolol, Salicylamide
Distribution:-	
Saturable plasma protein binding	Phenylbutazone, Lidocaine
Tissue binding	Imipramine
Metabolism:-	
Saturable metabolism	Phenytion, Salicylic acid
Enzyme induction	Carbamazepine
Metabolite inhibition	Diazepam
Renal elimination:-	
Active secretion	Para- aminohippuric acid
Tubular reabsorption	Ascorbic acid, Riboflavin
Change in urine pH	Salicylic acid, Dextroamphetamine

MICHAELIS MENTEN ENZYME KINETICS

- It is also called as Capacity-limited metabolism or Mixed order kinetics.

$$E + D \longleftrightarrow ED \longrightarrow E + M$$

- Enzymes usually react with the substrate to form enzyme substrate complexes; then the product is formed. The enzyme can go back to react with another substrate to form another molecule of the product.

MICHAELIS MENTEN EQUATION

- The kinetics of capacity limited or saturable processes is best described by Michaelis-Menten equation.

$$-\frac{dC}{dt} = \frac{V_{max} \cdot C}{K_M + C} \quad \text{..... I}$$

Where ,

-dC/dt = rate of decline of drug conc. with time

V_{max}= theoretical maximum rate of the process

K_M= Michaelis constant

- Three situation can now be considered depending upon the value of K_m and C.

1) when K_M= C:

under this situation , eq I reduces to,

- $-dC/dt = V_{max}/2$.....II
- The rate of process is equal to half of its maximum rate.
- This process is represented in the plot of dc/dt vs. C. shown in fig. 1
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2) If a drug at low conc. undergoes a saturable biotransformation then $K_M >> C$:

- here , $K_M + C = K_M$ and eq. I reduces to,

$$-dC/dt = V_{max} C / K_M \ldots\ldots\ldots\ldots\ldots\ldots III$$

- above eq. is identical to the one that describe first order elimination of drug, where $V_{max}/K_M = K_E$.

3) When $K_M << C$:

- Under this condition ,$K_M + C = C$ and eq. I will become,

$$-dC/dt = V_{max} \ldots\ldots\ldots\ldots\ldots IV$$

above eq. is identical to the one that describe a zero order process i.e. the rate process occurs at constant rate V_{max} and is independent of drug conc.

E.g. metabolism of ethanol

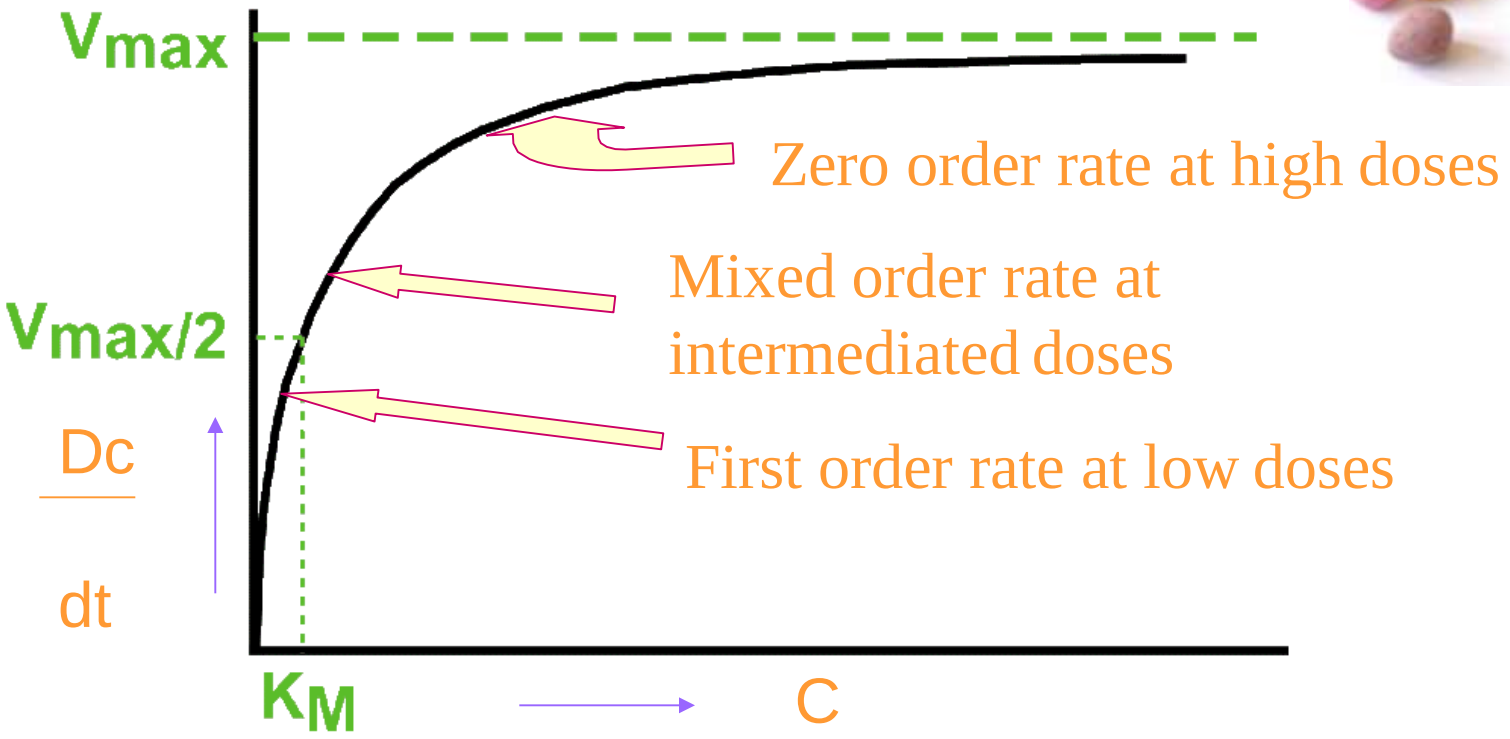

Figure 1

A plot of MME

CALCULATION OF K_M & V_{MAX} STEADY- STATE CONCENTRATION

- If drug is administered for constant rate IV infusion/ in a multiple dosage regimen, the steady-state conc. is given in terms of dosing rate (DR):

$$DR = C_{ss}Cl_T \qquad \text{..... (1)}$$

- If the steady-state is reached, then the dosing rate = the rate of decline in plasma drug conc. & if the decline occurs due to a single capacity-limited process then eq. I become as:

$$DR = \frac{V_{max}\, C_{ss}}{K_M + C_{ss}} \qquad \text{..... (2)}$$

- From a plot of C_{ss} vs. DR, a typical curve having a shape of hocky-stick is obtained which is shown in fig. 5.

Thanks