Unit-5

Biopharmaceutics and Pharmacokinetics

B.Pharma 6th Sem Notes

Unit: 5

Nonlinear Pharmacokinetics:

a. Introduction,
b. Factors causing Non-linearity.
c. Michaelis-menton method of estimating parameters, Explanation with example of drugs.

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Nonlinear Pharmacokinetics

Introduction

- **Pharmacokinetics** deals with the study of absorption, distribution, metabolism, and excretion (ADME) of drugs.
- When the **plasma concentration** of a drug **changes disproportionately** with the change in dose, the process is said to follow **nonlinear pharmacokinetics** (also called **dose-dependent pharmacokinetics**).
- In other words, **a twofold increase in dose does not produce a twofold increase in plasma concentration or AUC.**
- This usually happens because one or more pharmacokinetic processes (like absorption, metabolism, or excretion) become **saturated** at therapeutic or higher concentrations.

Detection Of Non-Linearity In Pharmacokinetics:

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

1. 1First 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:

During absorption

- Nonlinearity in drug absorption can arise from 3 important sources –

1. When absorption is solubility or dissolution rate-limited e.g. griseofulvin.At higher doses, a saturated solution of the drug is formed in the GIT or at any other extravascular site and the rate of absorption attains a constant value.

2. When absorption involves carrier-mediated transport systems e.g. absorption of riboflavin, ascorbic acid, cyanocobalamin, etc. Saturation of the transport system at higher doses of these vitamins results in nonlinearity.

3. When absorption involves carrier-mediated transport systems e.g. absorption of riboflavin, ascorbic acid, cyanocobalamin, etc. Saturation of the transport system at higher doses of these vitamins results in nonlinearity. When presystemic gut wall or hepatic metabolism attains saturation e.g. propranolol, hydralazine and verapamil. Saturation of presystemic metabolism of these drugs at high doses leads to increased bioavailability. The parameters affected will be F, K_2, Cmax and AUC. A decrease in these parameters is observed in the former two cases and an increase in the latter case. Other causes of nonlinearity in drug absorption are changes in gastric emptying and GI blood flow and other physiologic factors.

Drug Distribution:

Nonlinearity in distribution of drugs administered at high doses may be due to

1. Saturation of binding sites on plasma proteins e.g. phenylbutazone and naproxen. There is a finite number of binding sites for a particular drug on plasma proteins and, theoretically, as the concentration is raised, so too is the fraction unbound.
2. Saturation of tissue binding sites e.g. thiopental and fentanyl. With large single bolus doses or multiple dosing, saturation of tissue storage sites can occur.

In both cases, the free plasma drug concentration increases but Va increases only in the former case whereas it decreases in the latter.

Clearance is also altered depending upon the extraction ratio of the drug. Clearance of a drug with high ER is greatly increased due to saturation of binding sites.

Unbound clearance of drugs with low ER is unaffected and one can expect an increase in pharmacological response.

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) II) Enzyme induction - decrease in plasma concentration; Carbamazepine. • Autoinduction in dose dependent concentration. • Saturation of enzymes - decrease in ClH - increase in Css.

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

Michaelis Menten Enzyme Kinetics:

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

The concentration of the enzyme along with the substrate concentration is what describes the reaction when they are catalyzed by an enzyme – Michaelis-Menten kinetics. To form a final product that can release the enzyme and hence start the reaction again, there is a substrate in an enzyme-substrate reaction where it binds irreversibly to the enzyme which forms an enzyme-substrate complex (ES).

S + E ⇌ ES → P + E

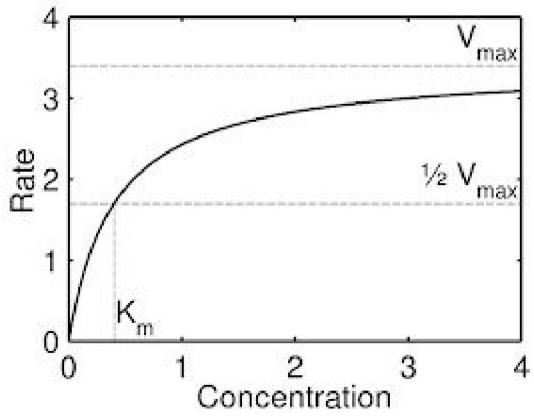
A Michaelis-Menten kinetics equation consists of two terms:

Vmax- As the enzyme's active sites become saturated with substrate, the reaction rate reaches its maximum.

Michaelis constant Km – this term refers to the term where it describes the concentration of the substrate at which 50% of the maximum rate of reaction occurs. As Km measures the affinity of enzymes for their substrates, the lower the value of Km, the more efficient are the enzymes in carrying out their functions while working with a lower substrate concentration.

$$v = \frac{V_{max}[S]}{K_M + [S]}$$

There is an effect on the initial reaction rate due to the initial substrate concentration according to the equation. An ES concentration is considered to remain constant where a steady-state is assumed in the reaction. With an increase in the substrate concentration (1st order kinetics), the rate linearly increases when the rate of reaction is plotted against the substrate concentration. As the enzyme active sites have been saturated with the substrate (0 order kinetics), this time the rate is plateaued, and hence the increasing amount of substrate concentration will not increase the velocity of the reaction.

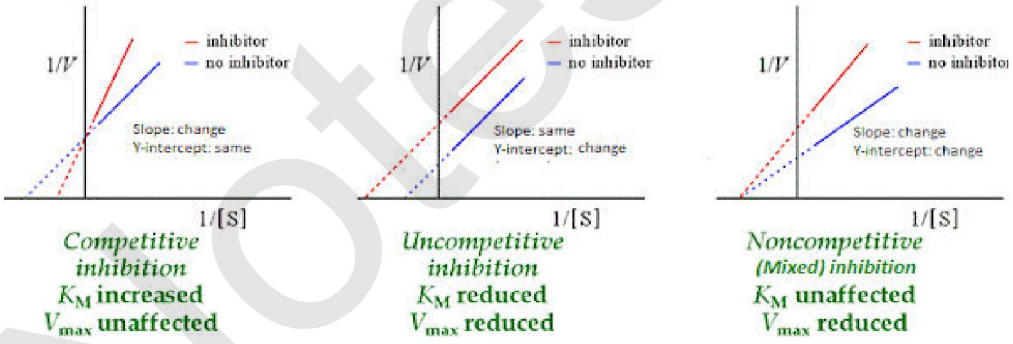


The plot of substrate concentration against the rate of reaction resembles a rectangular hyperbola. To visualize Michaelis-Menten kinetics practically, Lineweaver-Burk plot is the easiest way to do it as it plots the inverse of the reaction rate (1/r) against the inverse of substrate concentration (1/[S]). This plot was generated using the equation:

$$\frac{1}{V} = \frac{K_m}{V_{max}}\frac{1}{S} + \frac{1}{V_{max}}$$

In this way, a straight line is created, providing the user with a much easier way to interpret different quantities and values. Vmax, for instance, is equivalent to the y-intercept of the graph. It is also useful to compare the effect of protein inhibition on Km and Vmax by using the Lineweaver-Burk plot.

Lineweaver-Burk plots for enzyme inhibition



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