UNIT- V 07 Hours

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

Nonlinear Pharmacokinetics

In most cases, 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 situations, the rate processes are "Said to follow frrst-otder or linear kinetics and all semilog plots of C versus t for different doses when corrected for dose administered, a□e superimposable. This is called as **principle of superposition.** The important pharmacokinetic parameters viz. F, Ka, K_E, Vd, CI_R and CI_H which describe the time-course of a drug in the body remain unaffected by the dose i.e. the pharmacokinetics is dose independent.

In some instances, the rate process of a drug's ADME are dependent upon carrier or enzymes that are substrate specific, have definite capacities, ·and susceptible to saturation at high drug concentration. In such cases, an essentially first-order kinetics transfonn into a mixture of, frrst order and zero-order rate processes and the pharmacokinetic parameters change with the size of the administered dose. The pham1acokinetics of such drugs are said to be **dose-dependent.** Other terms synonymous with it are **mixed-order, nonlinear** and **capacity-limited** kinetics. Drugs exhibiting such a kinetic profile are sources of variability in pharmacologic response.

There are several *tests to detect nonlinearity* in pharmacokinetics but the simplest ones are:

1. Determination of steady-state plasma concentration at different doses. If the steady-state concentrations are directly proportional to the dose, ·then linearity in the kinetics exist. Such proportionality is not observable when there is nonlinearity.

2. Determination of some of the important phar1nacokinetic parameters such as fraction bioavailable, elimination half-life or total systemic clearance at different doses of the drug. Any change in these parameters which are usually constant, is indicative of nonlinearity.

CAUSES OF NONLINEARITY

Nonlinearities can occur in drug absorption, distribution, metabolism and excretion:

Drug 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. riboflavin, ascorbic acid, cyanocobalamin, etc. Saturation of the transport system at higher doses of these vitamins results in nonlinearity.

3. *When presystemic gut wall or hepatic metabolism attains saturation* e.g. propranolol.

The parameters affected will be F, Ka, 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. Nonlinearity in drug absorption is of little consequence unless availability is drastically affected.

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.

2. *Saturation of tissue binding sites.*

- In both cases, the free plasma drug concentration increases but Vd 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 pharmacologic response.

Drug .Metabolism

The nonlinear kinetics. of most clinical importance is capacity-limited metabolism since small changes in dose administered can produce large variations in plasma concentration at steady-state. It is a major source of large intersubject variability in pharmacologic response. Two important causes of nonlinearity in metabolism are:

l . *Capacity-limited metabolism due to enzyme and/or cofactor saturation.* Typical examples include phenytoin, alcohol, theophylline, etc.

2. *Enzyme induction* e.g. carbamazepine, where a decrease in peak plasma concentration has been observed on repetitive administration over a period of time. Autoinduction characterized in this case is also dose-dependent. Thus, enzyme induction is a common cause of both dose- and time-dependent kinetics.

Saturation of enzyme results in decreased CI_H and therefore increased C**ss.** Reverse is true for enzyme induction. Other causes of nonlinearity in biotransfor111ation include saturation of binding sites, inhibitory effect of the metabolite on enzyme and pathologic situations such as hepatotoxicity and changes in hepatic blood flow.

Drug Excretion

The two active processes in renal excretion of a drug that are saturable are:

l . *Active tubular secretion* e.g. penicillin G, and

2. *Active tubular reabsorption* e.g. water soluble vitamins and glucose.

After saturation of the carrier systems, a decrease in renal clearance in the former case and an increase in the latter situation is observed. Other sources of nonlinearity in renal excretion include forced diuresis, changes in urine pH, nephrotoxicity and saturation of binding sites.

Biliary secretion, which is also an active process, is also subject to saturation e.g. tetracycline and indomethacin.

MICHAELIS MENTEN EQUATION

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

$$-\frac{dC}{dt} = \frac{V_{max}\, C}{K_m + C}$$ 1

where -dC/dt = rate of decline of drug concentration with time,

V max = theoretical maximum rate of the process, and

Km = Michaelis constant.

Three situations can now be considered depending upon the values of Km, and C:

1. When Km = **C:** Under this situation, the equation1 reduces to:

$$-\frac{dC}{dt} = \frac{V_{max}}{2}$$ 2

i.e. the rate of process is equal to one-half its maximum rate (Fig. 1).

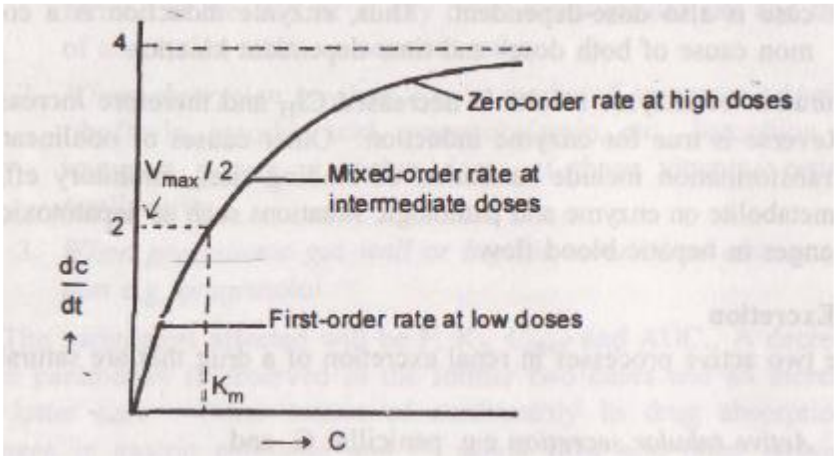

Fig. 1 A plot of Michaelis-Menten equation (elimination rate dC/dt versus concentration C). Initially, the rate increases linearly (first-order) with concentration, becomes mixed-order at higher concentrationand then reaches maximum (Vmax) beyond which it proceeds at a constant rate (zero-order).

2. **When K >>C:** Here, Km + C = Km and the equation 1 reduces to:

$$-\frac{dC}{dt} = \frac{V_{max}\, C}{K_m}$$ 3

The above equation is identical to the one that describes first-order elimination of a drug where V max/Km = KE. This means that the drug· concentration in the body that results from usual dosage regimens of most drugs is well below the Km of the elimination process with certain exceptions such as phenytoin and alcohol.

3. When Km << **C:** Under this condition, Km + C = C and the equation 1 will become:

$$-\frac{dC}{dt} = V_{max}$$ 4

The above equation is identical to the one that describes a zero-order process i.e. the rate process occurs at a constant rate V max and is independent of drug concentration e.g. metabolism of ethanol.

Estimation of Km and V max

The parameters of capacity-limited processes like metabolism, renal tubular secretion and biliary excretion can be easily defmed by assuming one-compartment kinetics for the drug and that elimination involves only a single capacity-limited process.

The parameters Km and V max can be accessed from the plasma concentration-time data collected after i. v. bolus administration of a drug with nonlinear elimination characteristics.

Rewriting equation 1

$$-\frac{dC}{dt} = \frac{V_{max}\, C}{K_m + C}$$

Integration of above equation followed by conversion to log base 10 yields:

$$\log C = \log C_o + \frac{(C_o - C)}{2.303\ K_m} - \frac{V_{max}\ t}{2.303\ K_m}$$ -------5

A semilog plot of C versus t yields a curve with a terminal linear portion having slope -V max12.303Km and when back extrapolated to time zero gives Y-intercept log C0 *(see* Fig. 2). The equation that describes this line is:

$$\log C = \log \overleftarrow{C_o} - \frac{V_{max}\ t}{2.303\ K_m}$$ **....6**

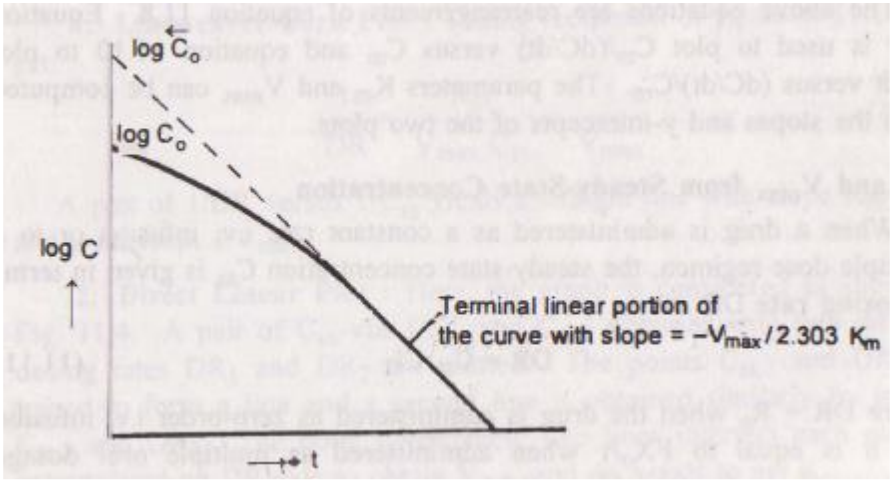

Fig. 2 Semilog plot of a drug given as i. v. Bolus with nonlinear elimination and that fits one- compartment kinetics.

At low plasma concentrations, equations 5 and 6 are identical.

Equating the two and simplifying further, we get:

$$\frac{(C_o - C)}{2.303\ K_m} = \log \frac{\overleftarrow{C_o}}{C_o}$$ 7

Km can thus be obtained from above equation. V max can be computed by substituting the value of K m in the slope value.

An alternative approach of estimating Vmax and Km is determining the rate of change of plasma drug concentration at different times and using the reciprocal of the equation 1. Thus:

$$\frac{1}{dC/dt} = \frac{K_m}{V_{max}\ C_m} + \frac{1}{V_{max}}$$ 8

where Cm = plasma= concentration at midpoint of the sampling interval. A double reciprocal plot or the **Lineweaver-Burk plot** of 1/(dC/dt) versus 1/Cm of the above equation yields a straight line with slope = Km / Vmax and y-mtercept = 1/ Vmax·

There are several limitations of Km and V max estimated by assuming one-compartment system and a single capacity-limited process. More complex equations will result and the computed Km and V max will usually be larger when:

1. The drug is eliminated by more than one capacity-limited process.

2. The drug exhibits parallel capacity-limited and first-order elimination processes.

3. The drug follows multicompartment kinetics.

However, Km and V max obtained under such circumstances have little practical applications in dosage calculations.

Drugs that -behave nonlinearly within the therapeutic range (for example, **phenytoin** shows saturable metabolism) yield less predictable results in drug therapy and possess greater potential in precipitating toxic effects.