Name of Unit	Nonlinear Pharmacokinetics
Course/Subject Name	Biopharmaceutics and Pharmacokinetics
Course/Subject Code	BP604T
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Learning Outcome of Unit-5

LO	Learning Outcome(LO)	Course Outcome Code
LO1	Students will learn about the capacity limited kinetics and various factors causing Non Linear Kinetics.	BP604.4
LO2	Students will learn about the kinetics govern the Non Linear Kinetics.	BP604.4

CONTENT OF MODULE

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

INTRODUCTION:

In some cases, 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 transform into a mixture of first- order and zero-order rate processes and the pharmacokinetic parameters change with the size of the administered dose. The pharmacokinetics 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 pharmacological response.

Drugs that demonstrate saturation kinetics usually show the following characteristics:

1. Elimination of drug does not follow simple first-order kinetics— that is, elimination kinetics are nonlinear.
2. The elimination half-life changes as dose is increased. Usually, the elimination half-life increases with increased dose due to saturation of an enzyme system.
3. The area under the curve (AUC) is not proportional to the amount of bioavailable drug.
4. The saturation of capacity-limited processes may be affected by other drugs that require the same enzyme or carrier-mediated system (ie, competition effects).
5. The composition and/or ratio of the metabolites of a drug may be affected by a change in the dose.

Factors causing Non-linearity:

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

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.
3. 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.
4. 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.
5. 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.

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 pharmacological response.

Two important causes of nonlinearity in metabolism are –

Capacity-limited metabolism due to enzyme and/or cofactor saturation. Typical examples include phenytoin, alcohol, theophylline, etc.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 ClH and therefore increased Css. Reverse is true for enzyme induction. Other causes of nonlinearity in biotransformation 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 –

1. Active tubular secretion e.g. penicillin G. After saturation of the carrier system, a decrease in renal clearance occurs.
2. Active tubular reabsorption e.g. water soluble vitamins and glucose. After saturation of the carrier system, an increase in renal clearance occurs.
3. Other sources of nonlinearity in renal excretion include forced diuresis, changes in urine pH, nephrotoxicity and saturation of binding sites.
4. Biliary secretion, which is also an active process, is also subject to saturation e.g. tetracycline and indomethacin.

Cause[a]	Drug
GI Absorption	
Saturable transport in gut wall	Riboflavin, gebapentin, L-dopa, baclofen, ceftibuten
Intestinal metabolism	Salicylamide, propranolol
Drugs with low solubility in GI but relatively high dose	Chorothiazide, griseofulvin, danazol
Saturable gastric or GI decomposition	Penicillin G, omeprazole, saquinavir
Distribution	
Saturable plasma protein binding	Phenylbutazone, lidocaine, salicylic acid, ceftriaxone, diazoxide, phenytoin, warfarin, disopyramide
Cellular uptake	Methicillin (rabbit)
Tissue binding	Imiprimine (rat)
CSF transport	Benzylpenicillins
Saturable transport into or out of tissues	Methotrexate
Renal Elimination	
Active secretion	Mezlocillin, para-aminohippuric acid
Tubular reabsorption	Riboflavin, ascorbic acid, cephapirin
Change in urine pH	Salicylic acid, dextroamphetamine
Metabolism	
Saturable metabolism	Phenytoin, salicyclic acid, theophylline, valproic acid[b]
Cofactor or enzyme limitation	Acetaminophen, alcohol
Enzyme induction	Carbamazepine
Altered hepatic blood flow	Propranolol, verapamil
Metabolite inhibition	Diazepam
Biliary Excretion	
Biliary secretion	Iodipamide, sulfobromophthalein sodium
Enterohepatic recycling	Cimetidine, isotretinoin

TABLE -Examples of Drugs Showing Nonlinear Kinetics

Michaelis–Menten kinetics:

The elimination of drug by a saturable enzymatic process is described by *Michaelis–Menten kinetics*.

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

Where, –dC/dt = rate of decline of drug concentration with time,

Vmax= is the maximum elimination rate

Km = Michaelis constant that reflects the *capacity* of the enzyme system. It is important to note that *K*m is not an elimination constant, but is actually a hybrid rate constant in enzyme kinetics, representing both the forward and backward reaction rates and equal to the drug concentration or amount of drug in the body at 0.5Vmax. The values for Km and Vmax are dependent on the nature of the drug and the enzymatic process involved.

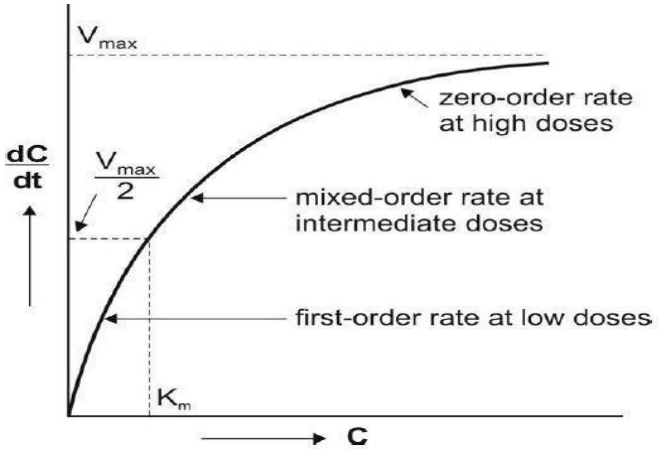

Fig. A plot of Michaelis-Menten equation (elimination rate dC/dt versus concentration C).

Initially, the rate increases linearly (first-order) with concentration, becomes mixed-order at higher concentration and then reaches maximum (Vmax) beyond which it proceeds at a constant rate (zero-order).

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

1. **When Km = C**

Under this situation, the equation reduces to:

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

i.e. the rate of process is equal to one-half its maximum rate

2. When Km >> C

Here, Km + C = Km and the equation reduces to:

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

The above equation is identical to the one that describes first-order elimination of a drug where Vmax/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 will become:

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

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

Estimation of K_m and V_{max}

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

The parameters K_m and V_{max} can be assessed from the plasma concentration-time data collected after i.v. bolus administration of a drug with nonlinear elimination characteristics.

Rewriting equation:

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

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

$$\log C = \log C_0 + \frac{C_0 - C}{2.303 K_m} - \frac{V_{max}}{2.303 K_m}$$

A semilog plot of C versus t yields a curve with a terminal linear portion having slope – $V_{max}/2.303K_m$ and when back extrapolated to time zero gives *Y*-intercept log $\underline{\text{Bar}}C_0$. The equation that describes this line is:

$$\log C = \log \bar{C}_0 - \frac{V_{max}}{2.303 K_m}$$

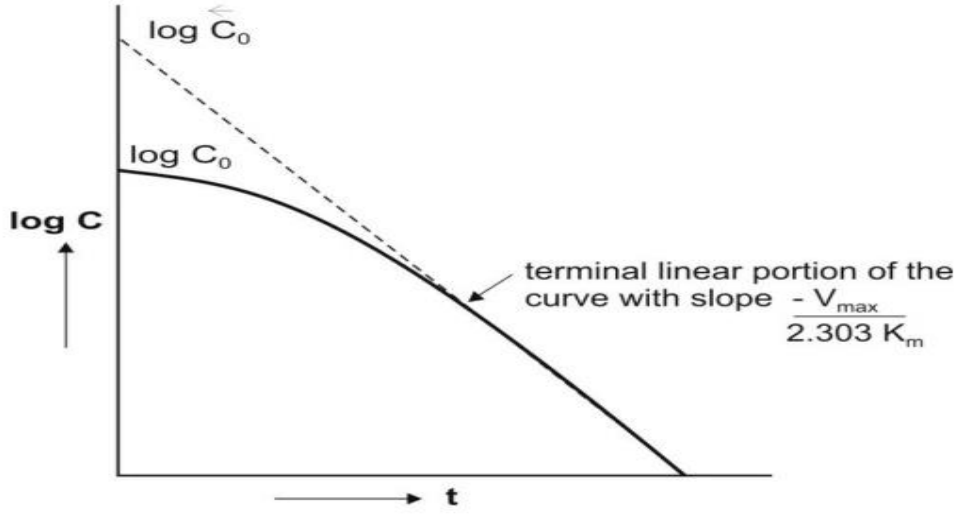

Fig. *Semilog plot of a drug given as i.v. bolus with nonlinear elimination and that fits one-compartment kinetics.*

IMPORTANT QUESTIONS

1. Define dose-dependent kinetics. Quote simple tests by which it can be detected in a rate process.
2. Why are drugs that show nonlinearity in pharmacokinetics considered sources of variability in pharmacological response?
3. What processes of drug ADME are known to show nonlinearity? Give examples.
4. When administered at high doses, how does the pharmacokinetic parameters — t½, Vd , Cmax, etc. change for drugs known to undergo capacity-limited elimination?
5. What are the limitations in calculating Km and Vmax by assuming one-compartment model and a single capacity-limited process?