Nonlinear Pharmacokinetics

The linear models assumed that the pharmacokinetic parameters for a drug would not change when different doses or multiple doses of a drug were given. While with some drugs, increased doses or chronic medication can cause deviations from the linear pharmacokinetic profile previously observed with single low doses of the same drug. This *nonlinear* behavior is also termed *dose dependent pharmacokinetics*. In most cases, the main pharmacokinetic outcome is a change in the apparent elimination rate constant.

The causes of nonlinear pharmacokinetic behavior:

1. Saturation of plasma protein-binding or carrier-mediated systems or enzymes involved in the processes of drug absorption, distribution, biotransformation, and excretion

2.A pathologic alteration in drug absorption, distribution, and elimination. For example, aminoglycosides may cause renal nephrotoxicity, there by altering renal drug excretion. In addition, gallstone obstruction of the bile duct will alter biliary drug excretion.

Examples of nonlinear pharmacokinetic drugs

Cause	Drug
Absorption	
Saturable transport in gut wall	Riboflavin
Saturable intestinal metabolism	Propranolol
Distribution	
Saturable plasma protein binding	lidocaine
Saturable transport into or out of tissues	Methotrexate

Metabolism	
Saturable hepatic metabolism	Phenytoin
Enzyme induction	Carbamazepine
Altered hepatic blood flow	Propranolol
Renal Elimination	
Saturable active tubular secretion	Penicillin G
Saturable tubular reabsorption	Ascorbic acid
Change in urine pH	Salicylic acid

Drugs that demonstrate saturation kinetics usually show the following characteristics:

1. Elimination of drug does not follow simple first-order kinetics (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. However, the elimination half-life might decrease due to "self"-induction of liver biotransformation enzymes, as is observed for carbamazepine.

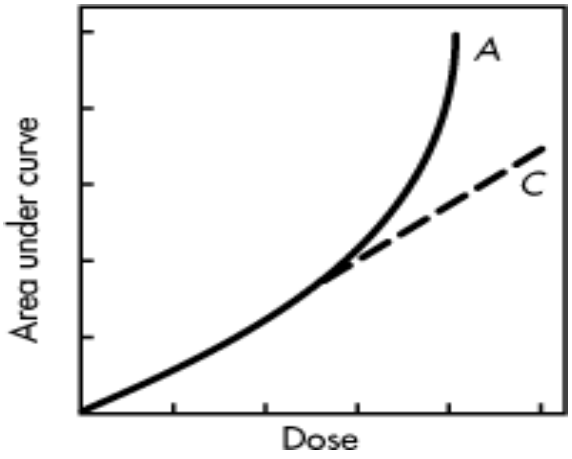
3. The area under the curve (AUC) is not proportional to the amount of bioavailable drug.

4. The saturation of capacity-limited processes may be affected by other drugs that require the same enzyme or carrier-mediated system (i.e., competition effects).

5. The composition and/or ratio of the metabolites of a drug may be affected by a change in the dose.

- In general, metabolism and active tubular secretion of drugs by the kidney are the processes most usually saturated.

- In order to determine whether a drug is following dose-dependent kinetics, the drug is given at various dosage levels and a plasma level time curve is obtained for each dose. A plot of the areas under the plasma level time curves at various doses should be linear if the drug follows dose-independent kinetics.



Curve *A* represents dose dependent or saturable elimination kinetics.
Curve *C* represents dose-independent kinetics

Saturable Enzymatic Elimination Processes

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

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p}$$

Where *V* max is the maximum elimination rate and *K* M is the Michaelis constant that reflects the *capacity* of the enzyme system. It is important to note that *K* M is not an elimination constant and it is equal to the drug concentration or amount of drug in the body at 0.5*V* max. The values for *K* M and *V* max are dependent on the nature of the drug and the enzymatic process involved.

When drug concentration *C* p is large in relation to *K* M (*C* p >> *K* m), saturation of the enzymes occurs and the value for *K* M is negligible.

The rate of elimination proceeds at a fixed or constant rate equal to *V*max. Thus, elimination of drug becomes a zero-order process

$$-\frac{dC_p}{dt} = \frac{V_{max} C_p}{C_p} = V_{max}$$

Practice Problem

Using the hypothetical drug (V max = 0.5 g/mL per hour, K M = 0.1 g/mL), how long would it take for the plasma drug concentration to decrease from 20 to 12 g/mL?

Solution

Because 12 g/mL is above the saturable level, elimination occurs ata zero-order rate of approximately 0.5 g/mL per hour.

$$\text{Time} = \frac{20 - 12\ \mu g}{0.5\ \mu g/hr} = 16\ hr$$

A saturable process can also exhibit linear elimination when drug concentrations are much less than enzyme concentrations. When the drug concentration *C* p is small in relation to the *K* M, the rate of drug elimination becomes a first-order process.

$$-\frac{dC_p}{dt} = \frac{V_{max} C_p}{C_p + K_M} = \frac{V_{max}}{K_M} C_p$$

$$-\frac{dC_p}{dt} = k' C_p$$

$$k' = \frac{V_{max}}{K_M}$$

Where *k*' the first-order rate constant for a saturable process.

Practice Problem

How long would it take for the plasma concentration of the drug (K M = 0.8 g/mL, V max = 0.9 g/mL per hr) to decline from 0.05 to 0.005 g/mL?

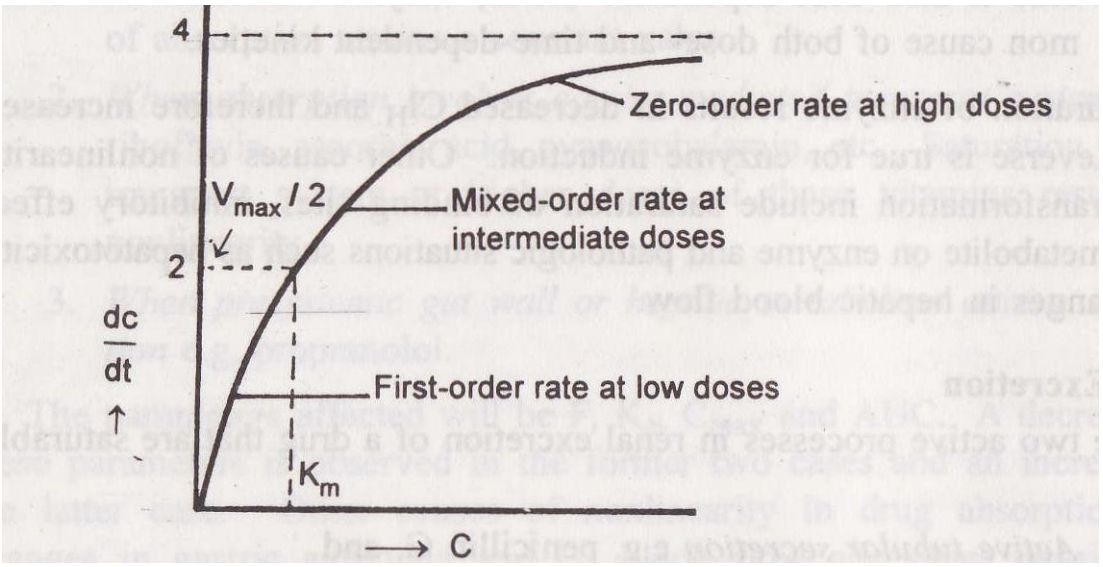
Solution

$$k' = \frac{V_{max}}{K_M} = \frac{0.9}{0.8} = \sim 1.1 \text{ hr}^{-1}$$

$$C_P = C_P^0 e^{-kt}$$

$$\log C_P = \log C_P^0 - \frac{kt}{2.3}$$

$$t = \frac{2.3(\log 0.05 - \log 0.005)}{1.1} = \frac{2.3(-1.30 + 2.3)}{1.1} = \frac{2.3}{1.1} = 2.09 \text{ hr}$$



Michaelis-Menten kinetics plot

When given in therapeutic doses, most drugs produce plasma drug concentrations well below *K* M for all carrier-mediated enzyme systems affecting the pharmacokinetics of the drug. Therefore, most drugs at normal therapeutic concentrations follow first-order rate processes. Only a few drugs, such as salicylate and phenytoin, tend to saturate the hepatic mixed-function oxidases at higher therapeutic doses. With these drugs, elimination kinetics are first-order with very small doses, mixed order at intermediate doses, and may approach zero-order with high therapeutic doses.

Drug Elimination by Capacity-Limited Pharmacokinetics: One-Compartment Model, IV Bolus Injection

The rate of elimination of a drug that follows capacity-limited pharmacokinetics is governed by the *V* max and *K*M of the drug.

If a single IV bolus injection of drug (*D* 0) is given at $t = 0$, the amount of drug in the body may be calculated by the following relationship:

$$\frac{D_0 - D_t}{t} = V_{max} - \frac{K_M}{t} \ln \frac{D_0}{D_t}$$

The time for the dose of the drug to decline to a certain amount is:

$$t = \frac{1}{V_{max}}\left(D_0 - D_t + K_M \ln \frac{D_0}{D_t}\right)$$

Practice Problems

1. *A drug eliminated from the body by capacity-limited pharmacokinetics has a K M of 100 mg/L and a V max of 50 mg/L per hr. If 400 mg and 320 mg of the drug is given to a patient by IV bolus injection, calculate the time for the drug to be 50% eliminated for each dose. Explain why there is a difference in the time for 50% elimination of a 400-mg dose compared to a 320-mg dose.*

Solution

D t is equal to 50% of the dose *D* 0. If the dose is 400 mg

$$t = \frac{1}{50}\left(400 - 200 + 100 \ln \frac{400}{200}\right) = 5.39 \text{ hr}$$

If the dose is 320 mg,

$$t = \frac{1}{50}\left(320 - 160 + 100 \ln \frac{320}{160}\right) = 4.59 \text{ hr}$$

For capacity-limited elimination, the elimination half-life is dose dependent, because the drug elimination process is saturated. Therefore, small changes in the dose will produce large differences in the time for 50% drug elimination.

2. *Using the same drug as in Problem 1, calculate the time for 50% elimination of the dose when the doses are 10 and 5 mg. Explain why the times for 50% drug elimination are similar even though the dose is reduced by one-half.*

Solution

If the dose is 10 mg,

$$t = \frac{1}{50}\left(10 - 5 + 100 \ln \frac{10}{5}\right) = 1.49 \text{ hr}$$

If the dose is 5 mg,

$$t = \frac{1}{50}\left(5 - 2.5 + 100 \ln \frac{5}{2.5}\right) = 1.44 \text{ hr}$$

Whether the patient is given a 10- or a 5-mg dose by IV bolus injection, the times for the amount of drug to decline 50% are approximately the same because the amount of drug in the body is much less than the K M of 100 mg.

Determination of *K* M and *V* max in patients

The rate of elimination of a capacity-limited drug in the body is dependent on the drug concentration as well as on the metabolic rate constants *K* M and *V* max of the drug in each individual.

At steady state, the rate of drug elimination is assumed to be the same as the rate of drug input *R*.

$$R = \frac{V_{max} C_{SS}}{K_M + C_{SS}}$$

Where *R* = dose/day or dosing rate**.**

$$K_M = \frac{R_2 - R_1}{(R_1/C_1) - (R_2/C_2)}$$

Where *C* 1 is steady-state plasma drug concentration after dose 1, *C* 2 is steady-state plasma drug concentration after dose 2, *R* 1 is the first dosing rate, and *R* 2 is the second dosing rate.

Example

Phenytoin was administered to a patient at dosing rates of 150 and 300 mg/day, respectively. The steady-state plasma drug concentrations were 8.6 and 25.1 mg/L, respectively. Find the K M and V max of this patient. What dose is needed to achieve steady-state concentration of 11.3 mg/L?

*** Generally, for a drug that follows nonlinear kinetics, the elimination half-life becomes longer, clearance becomes smaller, and the AUC becomes disproportionately larger with increasing dose.

$$t_{1/2} = \frac{0.693}{V_{max}} (K_M + C_p)$$

*** The total body clearance of a drug given by IV bolus injection that follows a one-compartment model with Michaelis -Menten elimination kinetics may be calculated according to:

$$Cl = \frac{V_{max}}{K_M + C_p}$$

Chronopharmacokinetics refers to a temporary change in the rate process (such as absorption or elimination) of a drug. The temporary changes in drug absorption or elimination can be cyclical over a constant period (e.g., 24-hour interval) as a result of circadian rhythm, or they may be noncyclical, in which drug absorption or elimination changes over a longer period oftime.

Time-dependent pharmacokinetics refers to a noncyclical change in the drug absorption or drug elimination rate process over a period of time. Time-dependent pharmacokinetics leads to nonlinear pharmacokinetics. Unlike dose-dependent pharmacokinetics, which involves a change in the rate process when the dose is changed, time dependent pharmacokinetics may be the result of alteration in the physiology or biochemistry in an organ or a region in the body that influences drug disposition. Time-dependent pharmacokinetics may be due to auto-induction or auto-inhibition of biotransformation enzymes. Drugs undergoing time-dependent pharmacokinetic have variable clearance and elimination half-lives.