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NONLINEAR PHARMACOKINETICS: INTRODUCTION

In previous chapters, linear pharmacokinetic models using simple first-order kinetics were introduced to describe the course of drug disposition and action. These linear models assumed that the pharmacokinetic parameters for a drug would not change when different doses or multiple doses of a drug were given. 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* pharmacokinetic behavior is also termed *dose-dependentpharmacokinetics.*

Many of the processes of drug absorption, distribution, biotransformation, and excretion involve enzymes or carrier-mediated systems. For some drugs given at therapeutic levels, one of these specialized processes may become saturated. As shown in , various causes of nonlinear pharmacokinetic behavior are theoretically possible. Besides saturation of plasma protein-binding or carrier-mediated systems, drugs may demonstrate nonlinear pharmacokinetics due to a pathologic alteration in drug absorption, distribution, and elimination. For example, aminoglycosides may cause renal nephrotoxicity, thereby altering renal drug excretion. In addition, gallstone obstruction of the bile duct will alter biliary drug excretion. In most cases, the main pharmacokinetic outcome is a change in the apparent elimination rate constant.

Table 9.1 Examples of Drugs Showing Nonlinear Kinetics

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

[a]Hypothermia, metabolic acidosis, altered cardiovascular function, and coma are additional causes of dose and time dependencies in drug overdose.

[b]In guinea pig and probably in some younger subjects.

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A number of drugs demonstrate *saturation* or *capacity-limitedmetabolism* in humans. Examples of these saturable metabolic processes include glycine conjugation of salicylate, sulfate conjugation of salicylamide, acetylation of *p*-aminobenzoic acid, and the elimination of phenytoin (). 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. However, the elimination half-life might decrease due to "self"-induction of liver biotransformation enzymes, as is observed for carbamazepine.

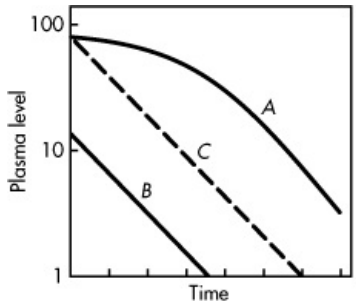
3. The area under the curve (AUC) is not proportional to the amount of bioavailable drug.

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

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

Because these drugs have a changing apparent elimination constant with larger doses, prediction of drug concentration in the blood based on a single small dose is difficult. Drug concentrations in the blood can increase rapidly once an elimination process is saturated. In general, metabolism (biotransformation) and active tubular secretion of drugs by the kidney are the processes most usually saturated. shows plasma level–time curves for a drug that exhibits *saturable* kinetics. When a large dose is given, a curve is obtained with an initial slow elimination phase followed by a much more rapid elimination at lower blood concentrations (curve *A*). With a small dose of the drug, apparent first-order kinetics are observed, because no saturation kinetics occur (curve *B*). If the pharmacokinetic data were estimated only from the blood levels described by curve *B*, then a twofold increase in the dose would give the blood profile presented in curve *C*, which considerably underestimates the drug concentration as well as the duration of action.

Figure 9-1.

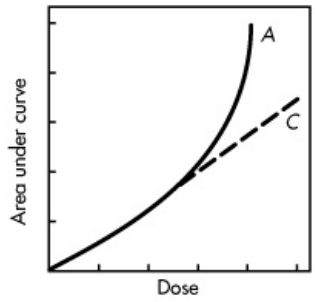


Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Plasma level–time curves for a drug that exhibits a saturable elimination process. Curves *A* and *B* represent high and low doses of durg, respectively, given in a single IV bolus. The terminal slopes of curves *A* and *B* are the same. Curve *C* represents the normal first-order elimination of a different drug.

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. The curves should exhibit parallel slopes if the drug follows dose-independent kinetics. Alternatively, a plot of the areas under the plasma level–time curves at various doses should be linear ().

Figure 9-2.



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Area under the plasma level–time curve versus dose for a drug that exhibits a saturable elimination process. 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*. If C_p is the concentration of drug in the plasma, then

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad (9.1)$$

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, 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 $0.5V_{max}$. The values for K_M and V_{max} are dependent on the nature of the drug and the enzymatic process involved.

The elimination rate of a hypothetical drug with a K_M of 0.1 µg/mL and a V_{max} of 0.5 µg/mL per hour is calculated in by means of Equation 9.1. Because the ratio of the elimination rate to drug concentration changes as the drug concentration changes (ie, dC_p/dt is not constant, Eq. 9.1), the rate of drug elimination also changes and is not a first-order or linear process. In contrast, a first-order elimination process would yield the same elimination rate constant at all plasma drug concentrations. At drug concentrations of 0.4–10 µg/mL, the enzyme system is not saturated and the rate of elimination is a mixed or nonlinear process (). At higher drug concentrations, 11.2 µg/mL and above, the elimination rate approaches the maximum velocity (V_{max}) of approximately 0.5 µg/mL per hour. At V_{max}, the elimination rate is a constant and is considered a zero-order process.

Table 9.2 Effect of Drug Concentration on the Elimination Rate and Rate Constant[a]

Drug Concentration (µg/mL)	Elimination Rate (µg/mL per hr)	Elimination Rate/Concentration[b] (hr^{-1})
0.4	0.400	1.000
0.8	0.444	0.556
1.2	0.462	0.385
1.6	0.472	0.294
2.0	0.476	0.238
2.4	0.480	0.200
2.8	0.483	0.172
3.2	0.485	0.152
10.0	0.495	0.0495
10.4	0.495	0.0476
10.8	0.495	0.0459
11.2	0.496	0.0442
11.6	0.496	0.0427

[a] K_M = 0.1 µg/mL, V_{max} = 0.5 µg/mL per hour.

[b] The ratio of the elimination rate to the concentration is equal to the rate constant.

Equation 9.1 describes a nonlinear enzyme process that encompasses a broad range of drug concentrations. When the 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 and Equation 9.1 becomes:

$$-\frac{dC_p}{dt} = \frac{V_{max} C_p}{C_p} = V_{max} \qquad (9.2)$$

Practice Problem

Using the hypothetical drug considered in (V_{max} = 0.5 µg/mL per hour, K_M = 0.1 µg/mL), how long would it take for the plasma drug concentration to decrease from 20 to 12 µg/mL?

Solution

Because 12 µg/mL is above the saturable level, as indicated in , elimination occurs at a zero-order rate of approximately 0.5 µg/mL per hour.

Time needed for the drug to decrease to 12 μg/mL

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

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. The data generated from Equation 9.2 ($C_p \leq 0.05$ µg/mL,) using $K_M = 0.8$ µg/mL and $V_{max} = 0.9$ µg/mL per hour shows that enzymatic drug elimination can change from a nonlinear to a linear process over a restricted concentration range. This is evident because the rate constant (or elimination rate/drug concentration) values are constant. At drug concentrations below 0.05 µg/mL, the ratio of elimination rate to drug concentration has a constant value of 1.1 hr^{-1}. Mathematically, when C_p is much smaller than K_M, C_p in the denominator is negligible and the elimination rate becomes first order.

$$-\frac{dC_p}{dt} = \frac{V_{max}C_p}{C_p + K_M} = \frac{V_{max}}{K_M}C_p \qquad (9.3)$$

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

Table 9.3 Effect of Drug Concentration on the Elimination Rate and Rate Constant[a]

		Elimination Rate
Drug Concentration (C_p) (µg/mL)	**Elimination Rate (µg/mL per hr)**	**Concentration (hr^{-1})[b]**
0.01	0.011	1.1
0.02	0.022	1.1
0.03	0.033	1.1
0.04	0.043	1.1
0.05	0.053	1.1
0.06	0.063	1.0
0.07	0.072	1.0
0.08	0.082	1.0
0.09	0.091	1.0

[a] $K_M = 0.8$ µg/mL, $V_{max} = 0.9$ µg/mL per hour.

[b] The ratio of the elimination rate to the concentration is equal to the rate constant.

The first-order rate constant for a saturable process, k', can be calculated from Equation 9.3:

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

This calculation confirms the data in , because enzymatic drug elimination at drug concentrations below 0.05 µg/mL is a first-order rate process with a rate constant of 1.1 hr^{-1}. Therefore, the $t_{1/2}$ due to enzymatic elimination can be calculated:

$$t_{1/2} = \frac{0.693}{1.1} = 0.63\ hr$$

Practice Problem

How long would it take for the plasma concentration of the drug in to decline from 0.05 to 0.005 µg/mL?

Solution

Because drug elimination is a first-order process for the specified concentrations,

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

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

$$t = \frac{\log C - \log C_p^0}{k}$$

Because $C^0_p = 0.05$ µg/mL, $k = 1.1\ hr^{-1}$, and $C_p = 0.005$ µg/mL,

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

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 higher doses, and may approach zero-order with very 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. Equation 9.1 describes the elimination of a drug that distributes in the body as a single compartment and is eliminated by Michaelis–Menten or capacity-limited pharmacokinetics. If a single IV bolus injection of drug (D_0) is given at $t = 0$, the drug concentration (C_p) in the plasma at any time t may be calculated by an integrated form of Equation 9.1 described by

$$\frac{C_0 - C_p}{t} = V_{max} - \frac{K_M}{t} \ln \frac{C_0}{C_p} \qquad (9.4)$$

Alternatively, the amount of drug in the body after an IV bolus injection may be calculated by the following relationship. Equation 9.5 may be used to simulate the decline of drug in the body after various size doses are given, provided the K_M and V_{max} of drug are known.

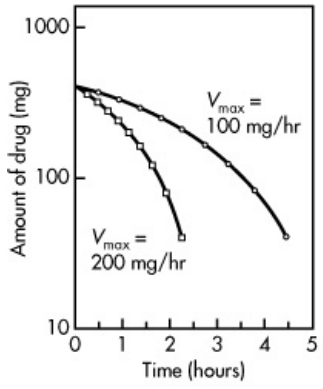
$$\frac{D_0 - D_t}{t} = V_{max} - \frac{K_M}{t} \ln \frac{D_0}{D_t} \qquad (9.5)$$

where D_0 is the amount of drug in the body at $t = 0$. In order to calculate the time for the dose of the drug to decline to a certain amount of drug in the body, Equation 9.5 must be rearranged and solved for time t:

$$t = \frac{1}{V_{max}}\left(D_0 - D_t + K_M \ln \frac{D_0}{D_t}\right) \qquad (9.6)$$

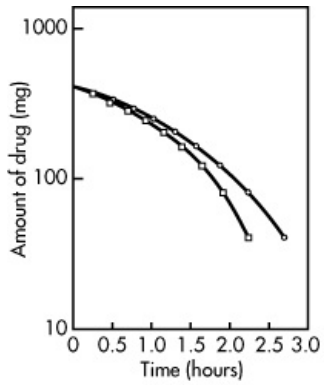
The relationship of K_M and V_{max} to the time for an IV bolus injection of drug to decline to a given amount of drug in the body is illustrated in and . Using Equation 9.6, the time for a single 400-mg dose given by IV bolus injection to decline to 20 mg was calculated for a drug with a K_M of 38 mg/L and a V_{max} that varied from 200 to 100 mg/hr (). With a V_{max} of 200 mg/hr, the time for the 400-mg dose to decline to 20 mg in the body is 2.46 hours, whereas when the V_{max} is decreased to 100 mg/hr, the time for the 400-mg dose to decrease to 20 mg is increased to 4.93 hours (). Thus, there is an inverse relationship between the time for the dose to decline to a certain amount of drug in the body and the V_{max} as shown in Equation 9.6.

Figure 9-3.



Amount of drug in the body versus time for a capacity-limited drug following an IV dose. Data generated using V_{max} of 100 (O) and 200 mg/hr (□). K_m is kept constant.

Figure 9-4.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Amount of drug in the body versus time for a capacity-limited drug following an IV dose. Data generated using K_M of 38 mg/L (□) and 76 mg/L (O). V_{max} is kept constant.

Table 9.4 Capacity-Limited Pharmacokinetics: Effect of V_{max} on the Elimination of Drug[a]

	Time for Drug Elimination (hr)	
Amount of Drug in Body (mg)	**V_{max} = 200 mg/hr**	**V_{max} = 100 mg/hr**
400	0	0
380	0.109	0.219
360	0.220	0.440
340	0.330	0.661
320	0.442	0.884
300	0.554	1.10
280	0.667	1.33
260	0.781	1.56
240	0.897	1.79
220	1.01	2.02
200	1.13	2.26
180	1.25	2.50
160	1.37	2.74
140	1.49	2.99
120	1.62	3.25
100	1.76	3.52
80	1.90	3.81
60	2.06	4.12
40	2.23	4.47
20	2.46	4.93

[a]A single 400-mg dose is given by IV bolus injection. The drug is distributed into a single compartment and is eliminated by capacity-limited pharmacokinetics. K_M is 38 mg/L. The time for drug to decline from 400 to 20 mg is calculated from Equation 9.6 assuming the drug has V_{max} = 200 mg/hr or V_{max} = 100 mg/hr.

Using a similar example, the effect of K_M on the time for a single 400-mg dose given by IV bolus injection to decline to 20 mg in the body is described in and . Assuming V_{max} is constant at 200 mg/hr, the time for the drug to decline from 400 to 20 mg is 2.46 hours when K_M is 38 mg/L; whereas when K_M is 76 mg/L, the time for the drug dose to decline to 20 mg is 3.03 hours. Thus, an increase in K_M (with no change in V_{max}) will increase the time for the drug to be eliminated from the body.

Table 9.5 Capacity-Limited Pharmacokinetics: Effects of K_M on the Elimination of Drug[a]

	Time for Drug Elimination (hr)	
Amount of Drug in Body (mg)	**K_M = 38 mg/L**	**K_M = 76 mg/L**

400	0	0
380	0.109	0.119
360	0.220	0.240
340	0.330	0.361
320	0.442	0.484
300	0.554	0.609
280	0.667	0.735
260	0.781	0.863
240	0.897	0.994
220	1.01	1.12
200	1.13	1.26
180	1.25	1.40
160	1.37	1.54
140	1.49	1.69
120	1.62	1.85
100	1.76	2.02
80	1.90	2.21
60	2.06	2.42
40	2.23	2.67
20	2.46	3.03

[a]A single 400-mg dose is given by IV bolus injection. The drug is distributed into a single compartment and is eliminated by capacity-limited pharmacokinetics. V_{max} is 200 mg/hr. The time for drug to decline from 400 to 20 mg is calculated from Equation 9.6 assuming the drug has K_M = 38 mg/L or K_M = 76 mg/L.

The one-compartment open model with capacity-limited elimination pharmacokinetics adequately describes the plasma drug concentration–time profiles for some drugs. The mathematics needed to describe nonlinear pharmacokinetic behavior of drugs that follow two-compartment models and/or have both combined capacity-limited and first-order kinetic profiles are very complex and have little practical application for dosage calculations and therapeutic drug monitoring.

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/hr. If 400 mg of the drug is given to a patient by IV bolus injection, calculate the time for the drug to be 50% eliminated. If 320 mg of the drug is to be given by IV bolus injection, calculate the time for 50% of the dose to be eliminated. Explain why there is a difference in the time for 50% elimination of a 400-mg dose compared to a 320-mg dose.

Solution

Use Equation 9.6 to calculate the time for the dose to decline to a given amount of drug in the body. For this problem, 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 partially saturated. Therefore, small changes in the dose will produce large differences in the time for 50% drug elimination. The parameters K_M and V_{max} determine when the dose is saturated.

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

As in Practice Problem 1, use Equation 9.6 to calculate the time for the amount of drug in the body at zero time (D0) to decline 50%.

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. For 10- and 5-mg doses the amount of drug in the body is much less than the K_M of 100 mg. Therefore, the amount of drug in the body is well below saturation of the elimination process and the drug declines at a first-order rate.

Determination of K_M and V_{max}

Equation 9.1 relates the rate of drug biotransformation to the concentration of the drug in the body. The same equation may be applied to determine the rate of enzymatic reaction of a drug *in vitro* (Eq. 9.7). When an experiment is performed with solutions of various concentration of drug C, a series of reaction rates (v) may be measured for each concentration. Special plots may then be used to determine K_M and V_{max} (see also).

Equation 9.7 may be rearranged into Equation 9.8.

$$v = \frac{V_{max} C}{K_M + C} \qquad (9.7)$$

$$\frac{1}{v} = \frac{K_M}{V_{max}} \frac{1}{C} + \frac{1}{V_{max}} \qquad (9.8)$$

Equation 9.8 is a linear equation when $1/v$ is plotted against $1/C$. The y-intercept for the line is $1/V_{max}$, and the slope is K_M/V_{max}. An example of a drug reacting enzymatically with rate (v) at various concentrations C is shown in and . A plot of $1/v$ versus $1/C$ is shown in . A plot of $1/v$ versus $1/C$ is linear with an intercept of 0.33 mmol. Therefore,

$$\frac{1}{V_{max}} = 0.33 \text{ min mL}/\mu\text{mol}$$

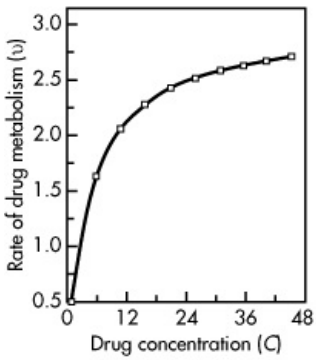
$$V_{max} = 3 \ \mu\text{mol/mL min}$$

because the slope = 1.65 = K_M/V_{max} = $K_M/3$ or K_M = 3 x 1.65 µmol/mL = 5 µmol/mL. Alternatively, K_M may be found from the x intercept, where $-1/K_M$ is equal to the x intercept. (This may be seen by extending the graph to intercept the x axis in the negative region.)

Table 9.6 Information Necessary for Graphic Determination of V_{max} and K_M

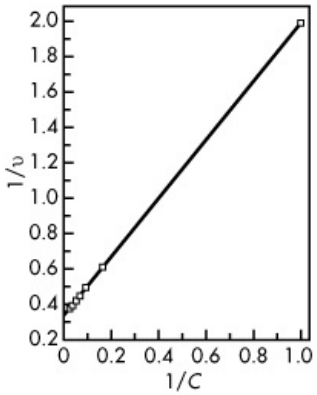
Observation Number	C (µM/mL)	V (µM/mL per min)	$1/V$ (mL per min/µM)	$1/C$ (mL/µM)
1	1	0.500	2.000	1.000
2	6	1.636	0.611	0.166
3	11	2.062	0.484	0.090
4	16	2.285	0.437	0.062
5	21	2.423	0.412	0.047
6	26	2.516	0.397	0.038
7	31	2.583	0.337	0.032
8	36	2.504	0.379	0.027
9	41	2.673	0.373	0.024
10	46	2.705	0.369	0.021

Figure 9-5.



Plot of rate of drug metabolism at various drug concentrations. (K_M = 0.5 μmol/mL, V_{max} = 3 μmol/mL per minute.)

Figure 9-6.



Plot of 1/*v* versus 1/*C* for determining K_M and V_{max}.

With this plot (), the points are clustered. Other methods are available that may spread the points more evenly. These methods are derived from rearranging Equation 9.8 into Equations 9.9 and 9.10.

$$\frac{C}{v} = \frac{1}{V_{max}} C + \frac{K_M}{V_{max}} \qquad (9.9)$$

$$v = -K_M \frac{v}{C} + V_{max} \qquad (9.10)$$

A plot of *C*/*v* versus *C* would yield a straight line with $1/V_{max}$ as slope and K_M/V_{max} as intercept (Eq. 9.9). A plot of *v* versus *v*/*C* would yield a slope of $-K_M$ and an intercept of V_{max} (Eq. 9.10).

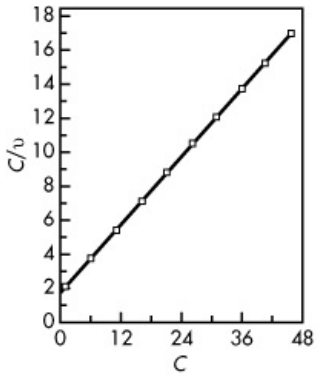
The necessary calculations for making the above plots are shown in . The plots are shown in and . It should be noted that the data are spread out better by the two latter plots. Calculations from the slope show that the same K_M and V_{max} are obtained as in . When the data are more scattered, one method may be more accurate than the other. A simple approach is to graph the data and examine the linearity of the graphs. The same basic type of plot is used in the clinical literature to determine K_M and V_{max} for individual patients for drugs that undergo capacity-limited kinetics.

Table 9.7 Calculations Necessary for Graphic Determination of K_M and V_{max}

C (μM/mL)	*v* (μM/mL per min)	*C*/*v* (min)	*v*/*C* (1/min)
1	0.500	2.000	0.500
6	1.636	3.666	0.272
11	2.062	5.333	0.187
16	2.285	7.000	0.142

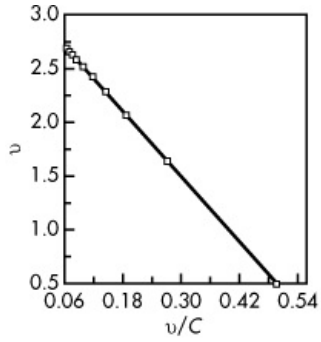
21	2.423	8.666	0.115
26	2.516	10.333	0.096
31	2.583	12.000	0.083
36	2.634	13.666	0.073
41	2.673	15.333	0.065
46	2.705	17.000	0.058

Figure 9-7.



Plot of C/v versus C for determining K_M and V_{max}.

Figure 9-8.



Plot of v versus v/C for determining K_M and V_{max}.

Determination of K_M and V_{max} in Patients

Equation 9.7 shows that the rate of drug metabolism (v) is dependent on the concentration of the drug (C). This same basic concept may be applied to the rate of drug metabolism of a capacity-limited drug in the body (). The body may be regarded as a single compartment in which the drug is dissolved. The rate of drug metabolism will vary depending on the concentration of drug C_p as well as on the metabolic rate constants K_M and V_{max} of the drug in each individual.

An example for the determination of K_M and V_{max} is given for the drug phenytoin. Phenytoin undergoes capacity-limited kinetics at therapeutic drug concentrations in the body. To determine K_M and V_{max}, two different dose regimens are given at different times, until steady state is reached. The steady-state drug concentrations are then measured by assay. At steady state, the rate of drug metabolism (v) is assumed to be the same as the rate of drug input R (dose/day). Therefore Equation 9.11 may be written for drug metabolism in the body similar to the way drugs are metabolized *in vitro* (Eq. 9.7). However, steady state will not be reached if the drug input rate, R, is greater than the V_{max}; instead, drug accumulation will continue to occur without reaching a steady-state plateau.

$$R = \frac{V_{max} C_{SS}}{K_M + C_{SS}} \qquad (9.11)$$

where R = dose/day or dosing rate; C_{SS} = steady-state plasma drug concentration, V_{max} = maximum metabolic rate constant in the body, and K_M = Michaelis–Menten constant of the drug in the body.

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 a steady-state concentration of 11.3 mg/L?

Solution

There are three methods for solving this problem, all based on the same basic equation (Eq. 9.11).

Method A

Inverting Equation 9.11 on both sides yields

$$\frac{1}{R} = \frac{K_M}{V_{max}} \frac{1}{C_{SS}} + \frac{1}{V_{max}} \qquad (9.12)$$

Multiply both sides by $C_{SS} V_{max}$.

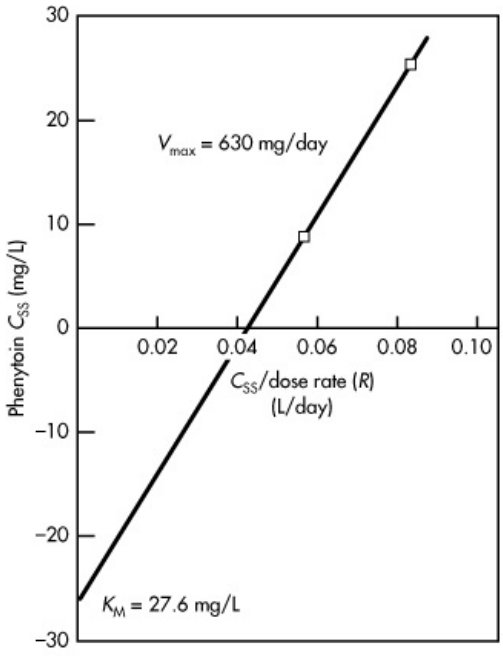
$$\frac{V_{max} C_{SS}}{R} = K_M + C_{SS}$$

Rearrange.

$$C_{SS} = \frac{V_{max} C_{SS}}{R} - K_M \qquad (9.13)$$

A plot of C_{SS} versus C_{SS}/R is shown in . V_{max} is equal to the slope, 630 mg/day, and K_M is found from the y intercept, 27.6 mg/L (note the negative intercept).

Figure 9-9.



Plot of C_{SS} versus C_{SS}/R (method *A*).

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Method B

From Equation 9.11,

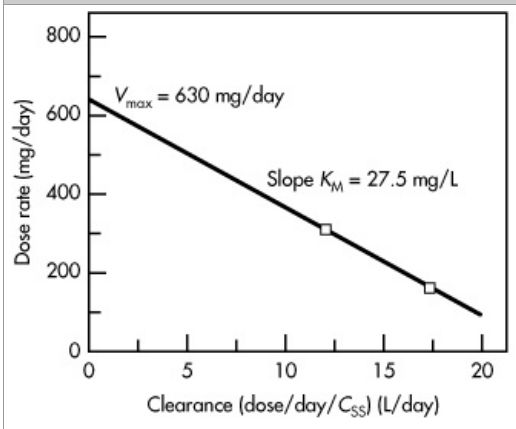
$$RK_M + RC_{SS} = V_{max}C_{SS}$$

Dividing both sides by C_{SS} yields

$$R = V_{max} - \frac{K_M R}{C_{SS}} \qquad (9.14)$$

A plot of R versus R/C_{SS} is shown in . The K_M and V_{max} found are similar to those by the previous method ().

Figure 9-10.



Plot of R versus R/C_{SS} or clearance (method *B*).

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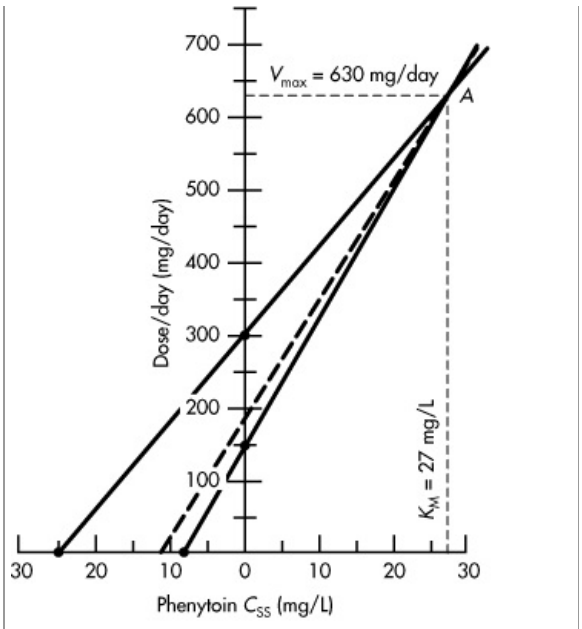
Method C

A plot of R versus C_{SS} is shown in . To determine K_M and V_{max}:

1. Mark points for R of 300 mg/day and C_{SS} of 25.1 mg/L as shown. Connect with a straight line.
2. Mark points for R of 150 mg/day and C_{SS} of 8.6 mg/L as shown. Connect with a straight line.
3. Where lines from the first two steps cross is called point *A*.
4. From point *A*, read V_{max} on the *y* axis and K_M on the *x* axis. (Again, V_{max} of 630 mg/day and K_M of 27 mg/L are found.)

Figure 9-11.



Plot of R versus C_{SS} (method *C*).

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This V_{max} and K_M can be used in Equation 9.11 to find an *R* to produce the desired C_{SS} of 11.3 mg/L. Alternatively, join point *A* on the graph to meet 11.3 mg/L on the *x* axis; *R* can be read where this line meets the *y* axis (190 mg/day).

To calculate the dose needed to keep steady-state phenytoin concentration of 11.3 mg/L in this patient, use Equation 9.7.

$$R = \frac{(630\ \text{mg/day})\,(11.3\ \text{mg/L})}{27\ \text{mg/L} + 11.3\ \text{mg/L}} = \frac{7119}{38.3} = 186\ \text{mg/day}$$

This answer compares very closely with the value obtained by the graphic method. All three methods have been used clinically. introduced a method that allows for an estimation of phenytoin dose based on steady-state concentration resulting from one dose. This method is based on a statistically compiled nomogram that makes it possible to project a most likely dose for the patient.

Determination of K_M and V_{max} by Direct Method

When steady-state concentrations of phenytoin are known at only two dose levels, there is no advantage in using the graphic method. K_M and V_{max} may be calculated by solving two simultaneous equations formed by substituting C_{SS} and *R* (Eq. 9.11) with C_1, R_1, C_2, and R_2. The equations contain two unknowns, K_M and V_{max}, and may be solved easily.

$$R_1 = \frac{V_{max} C_1}{K_M + C_1}$$

$$R_2 = \frac{V_{max} C_2}{K_M + C_2}$$

Combining the two equations yields Equation 9.15.

$$K_M = \frac{R_2 - R_1}{(R_1/C_1) - (R_2/C_2)} \qquad (9.15)$$

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. To calculate K_M and V_{max}, use Equation 9.15 with the values C_1 = 8.6 mg/L, C_2 = 25.1 mg/L, R_1 = 150 mg/day, and R_2 = 300 mg/day. The results are

$$K_M = \frac{300 - 150}{(150/8.6) - (300/25.1)} = 27.3\ \text{mg/L}$$

Substitute K_M into either of the two simultaneous equations to solve for V_{max}.

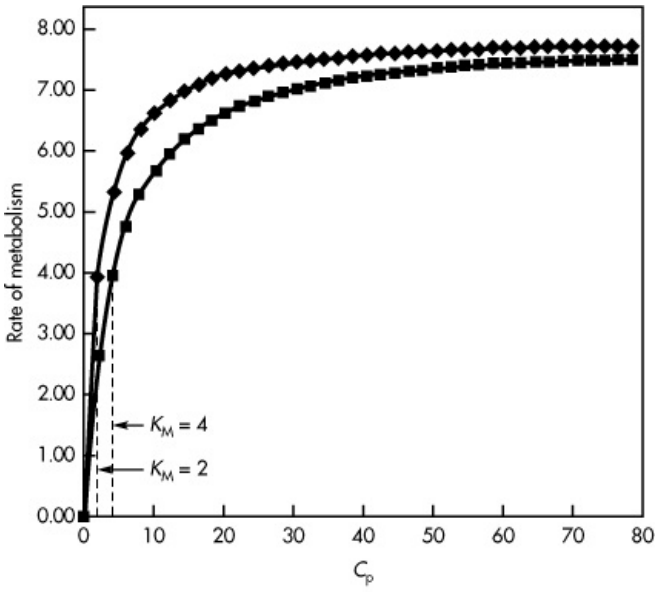
$$150 = \frac{V_{max}(8.6)}{27.3 + 8.6}$$

$$V_{max} = 626 \text{ mg/day}$$

Interpretation of K_M and V_{max}

An understanding of Michaelis–Menten kinetics provides insight into the nonlinear kinetics and helps to avoid dosing a drug at a concentration near enzyme saturation. For example, in the above phenytoin dosing example, since K_M occurs at $0.5V_{max}$, K_M = 27.3 mg/L, the implication is that at a plasma concentration of 27.3 mg/L, enzymes responsible for phenytoin metabolism are eliminating the drug at 50% V_{max}, ie, 0.5 x 626 mg/day or 313 mg/day. When the subject is receiving 300 mg of phenytoin per day, the plasma drug concentration of phenytoin is 8.6 mg/L, which is considerably below the K_M of 27.3 mg/L. In practice, the K_M in patients can range from 1 to 15 mg/L, V_{max} can range from 100 to 1000 mg/day. Patients with a low K_M tend to have greater changes in plasma concentrations during dosing adjustments. Patients with a smaller K_M (same V_{max}) will show a greater change in the rate of elimination when plasma drug concentration changes compared to subjects with a higher K_M. A subject with the same V_{max}, but different K_M, is shown in . (For another example, see the slopes of the two curves generated in).

Figure 9-12.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Diagram showing the rate of metabolism when V_{max} is constant (8 µg/mL/hr) and K_M is changed (K_M = 2 µg/mL for top curve and K_M = 4 µg/mL for bottom curve). Note the rate of metabolism is faster for the lower K_M, but saturation starts at lower concentration.

Dependence of Elimination Half-Life on Dose

For drugs that follow linear kinetics, the elimination half-life is constant and does not change with dose or drug concentration. For a drug that follows nonlinear kinetics, the elimination half-life and drug clearance both change with dose or drug concentration. Generally, the elimination half-life becomes longer, clearance becomes smaller, and the area under the curve becomes disproportionately larger with increasing dose. The relationship between elimination half-life and drug concentration is shown in Equation 9.16. The elimination half-life is dependent on the Michaelis–Menten parameters and concentration.

$$t_{1/2} = \frac{0.693}{V_{max}}(K_M + C_p) \qquad (9.16)$$

Some pharmacokineticists prefer not to calculate the elimination half-life of a nonlinear drug because the elimination half-life is not constant. Clinically, if the half-life is increasing as plasma concentration increases, and there is no apparent change in metabolic or renal function, then there is a good possibility that the drug may be metabolized by nonlinear kinetics.

Dependence of Clearance on Dose

The total body clearance of a drug given by IV bolus injection that follows a one-compartment model with Michaelis–Menten elimination kinetics changes with respect to time and plasma drug concentration. Within a certain drug concentration range, an average or mean clearance (Cl_{av}) may be determined. Because the drug follows Michaelis–Menten kinetics, Cl_{av} is dose-dependent. Cl_{av} may be estimated from the area under the curve and the dose given ().

According to the Michaelis–Menten equation,

$$\frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} \qquad (9.17)$$

Inverting Equation 9.17 and rearranging yields

$$C_p dt = \frac{K_M}{V'_{max}} dC_p - \frac{C_p}{V'_{max}} dC_p \qquad (9.18)$$

The area under the curve, $[AUC]^{\infty}_{0}$, is obtained by integration of Equation 9.18 (ie, $[AUC]^{\infty}_{0} = \int^{\infty}_{0} C_p dt$).

$$\int_0^{\infty} C_p dt = \int_{C_p^0}^{\infty} \frac{K_M}{V'_{max}} dC_p + \int_{C_p^0}^{\infty} \frac{C_p}{V'_{max}} dC_p \qquad (9.19)$$

where V'_{max} is the maximum velocity for metabolism. Units for V'_{max} are mass/compartment volume per unit time. $V'_{max} = V_{max}/V_D$; used V_{max} in Equation 9.20 as mass/time to be consistent with biochemistry literature, which considers the initial mass of the substrate reacting with the enzyme.

Integration of Equation 9.18 from time 0 to infinity gives Equation 9.20.

$$[AUC]^{\infty}_{0} = \frac{C_p^0}{V_{max}/V_D}\left(\frac{C_p^0}{2} + K_M\right) \qquad (9.20)$$

where V_D is the apparent volume of distribution.

Because the dose $D_0 = C^0_p V_D$, Equation 9.20 may be expressed as

$$[AUC]^{\infty}_{0} = \frac{D_0}{V_{max}}\left(\frac{C_p^0}{2} + K_M\right) \qquad (9.21)$$

To obtain mean body clearance, Cl_{av} is then calculated from the dose and the AUC.

$$Cl_{av} = \frac{D_0}{[AUC]^{\infty}_{0}} = \frac{V_{max}}{(C_p^0/2) + K_M} \qquad (9.22)$$

$$Cl_{av} = \frac{V_{max}}{(D_0/2V_D) + K_M} \qquad (9.23)$$

Alternatively, dividing Equation 9.17 by C_p gives Equation 9.24, which shows that the clearance of a drug that follows nonlinear pharmacokinetics is dependent on the plasma drug concentration C_p, K_M, and V_{max}.

$$Cl = \frac{V_D(dC_p/dt)}{C_p} = \frac{V_{max}}{K_M + C_p} \qquad (9.24)$$

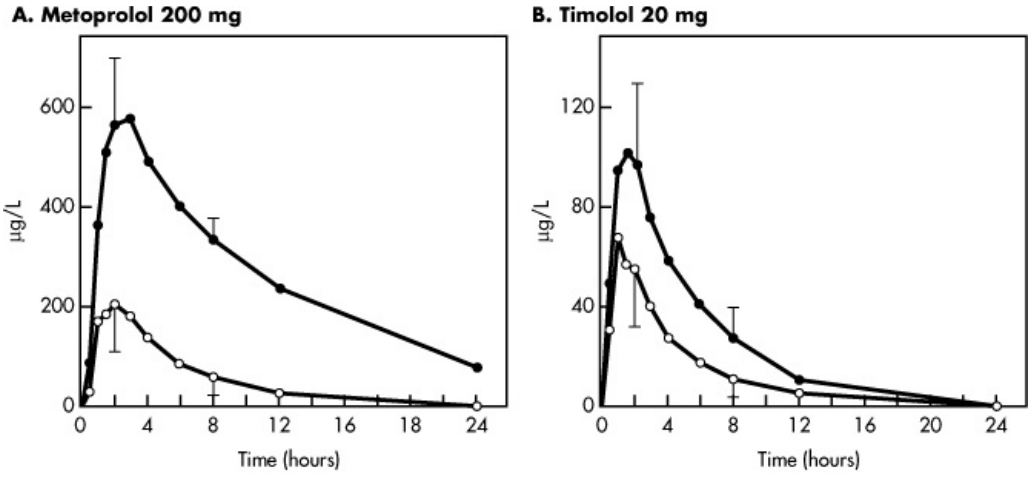
Equation 9.22 or 9.23 calculates the average clearance Cl_{av} for the drug after a single IV bolus dose over the entire time course of the drug in the body. For any time period, clearance may be calculated according to (Eq. 12.10) as

$$Cl_T = \frac{dD_E/dt}{C_p} \qquad (9.25)$$

In , the physiologic model based on blood flow and intrinsic clearance is used to describe drug metabolism. The extraction ratios of many drugs are listed in the literature. Actually, extraction ratios are dependent on dose, enzymatic system, blood flow, and for practical purposes, they are often assumed to be constant at normal doses.

Except for phenytoin, there is a paucity of K_M and V_{max} data defining the nature of nonlinear drug elimination in patients. However, abundant information is available supporting variable metabolism due to genetic polymorphism (). The clearance (apparent) of many of these drugs in patients who are slow metabolizers changes with dose, although these drugs may exhibit linear kinetics in subjects with the "normal" phenotype. Metoprolol and many β-adrenergic antagonists are extensively metabolized. The plasma levels of metoprolol in slow metabolizers () were much greater than other patients, and the AUC, after equal doses, is several times greater among slow metabolizers of metoprolol (). A similar picture is observed with another β-adrenergic antagonist, timolol. These drugs have smaller clearance than normal.

Figure 9-13.



Mean plasma drug concentration versus time profiles following administration of single oral doses of **(A)** metoprolol tartrate 200 mg to 6 extensive metabolizers (EMs) and 6 poor metabolizers (PMs). **(B)** timolol maleate 20 mg to 6 EMs (O) and 4 PMs (●).

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EXAMPLE

The dose-dependent pharmacokinetic of sodium valproate (VPA) was studied in guinea pigs at 20, 200, and 600 mg/kg by rapid intravenous infusion. The area under the plasma concentration–time curve increased out of proportion at the 600-mg/kg dose level in all groups (). The total clearance (Cl_T) was significantly decreased and the beta elimination half-life ($t_{1/2}$) was significantly increased at the 600-mg/kg dose level. The dose-dependent kinetics of VPA were due to saturation of metabolism. Metabolic capacity was greatly reduced in young guinea pigs.

Clinically, it is not uncommon to observe similar enzymatic saturation in infants and in special patient populations, whereas drug metabolism may be linear with dose in normal subjects. These patients have lower V_{max} and longer elimination half-life. Variability in drug metabolism is described in and .

EQUATIONS FOR DRUGS DISTRIBUTED AS ONE-COMPARTMENT MODEL AND ELIMINATED BY NONLINEAR PHARMACOKINETICS

The equations presented thus far in this chapter have been for drugs given by IV bolus, distributed as a one-compartment model, and eliminated only by nonlinear pharmacokinetics. The following are useful equations describing other possible routes of drug administration and including mixed drug elimination, by which the drug may be eliminated by both nonlinear (Michaelis–Menten) and linear (first-order) processes.

Mixed Drug Elimination

Drugs may be metabolized to several different metabolites by parallel pathways. At low drug doses corresponding to low drug concentrations at the site of the biotransformation enzymes, the rates of formation of metabolites are first order. However, with higher doses of drug, more drug is absorbed and higher drug concentrations are presented to the biotransformation enzymes. At higher drug concentrations, the enzyme involved in metabolite formation may become saturated, and the rate of metabolite formation becomes nonlinear and approaches zero order. For example, sodium salicylate is metabolized to both a glucuronide and a glycine conjugate (hippurate). The rate of formation of the glycine conjugate is limited by the amount of glycine available. Thus, the rate of formation of the glucuronide continues as a first-order process; whereas the rate of conjugation with glycine is capacity limited.

The equation that describes a drug that is eliminated by both first-order and Michaelis–Menten kinetics after IV bolus injection is given by

$$-\frac{dC_P}{dt} = kC_P + \frac{V'_{max}C_P}{K_M + C_P} \qquad (9.26)$$

where k is the first-order rate constant representing the sum of all first-order elimination processes, while the second term of Equation 9.26 represents the saturable process. V'_{max} is simply V_{max} expressed as concentration by dividing by V_D.

Zero-Order Input and Nonlinear Elimination

The usual example of zero-order input is constant IV infusion. If the drug is given by constant IV infusion and is eliminated only by nonlinear pharmacokinetics, then the following equation describes the rate of change of the plasma drug concentration:

$$\frac{dC_P}{dt} = \frac{k_0}{V_D} - \frac{V'_{max}C_P}{K_M + C_P} \qquad (9.27)$$

where k_0 is the infusion rate and V_D is the apparent volume of distribution.

First-Order Absorption and Nonlinear Elimination

The relationship that describes the rate of change in the plasma drug concentration for a drug that is given extravascularly (eg, orally), absorbed by first-order absorption, and eliminated only by nonlinear pharmacokinetics, is given by the following equation. C_{GI} is concentration in the GI tract.

$$\frac{dC_p}{dt} = k_a C_{GI} e^{-k_a t} - \frac{V'_{max} C_p}{K_M + C_p} \qquad (9.28)$$

where k_a is the first-order absorption rate constant.

If the drug is eliminated by parallel pathways consisting of both linear and nonlinear pharmacokinetics, Equation 9.28 may be extended to Equation 9.29.

$$\frac{dC_p}{dt} = k_a C_{GI} e^{-k_a t} - \frac{V'_{max} C_p}{K_M + C_p} - kC_p \qquad (9.29)$$

where k is the first-order elimination rate constant.

CHRONOPHARMACOKINETICS AND TIME-DEPENDENT PHARMACOKINETICS

Chronopharmacokinetics broadly refers to a temporal change in the rate process (such as absorption or elimination) of a drug. The temporal changes in drug absorption or elimination can be cyclical over a constant period (e.g., 24-hour interval), or they may be noncyclical, in which drug absorption or elimination changes over a longer period of time. Chronopharmacokinetics is an important consideration during drug therapy.

Time-dependent pharmacokinetics generally 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. For example, have shown that repeated doses of carbamazepine induce the enzymes responsible for its elimination (ie, auto-induction), thereby increasing the clearance of the drug. Auto-inhibition may occur during the course of metabolism of certain drugs (). In this case, the metabolites formed increase in concentration and further inhibit metabolism of the parent drug. In biochemistry, this phenomenon is known as *product inhibition*. Drugs undergoing time-dependent pharmacokinetic have variable clearance and elimination half-lives. The steady-state concentration of a drug that causes auto-induction may be due to increased clearance over time. Some anticancer drugs are better tolerated at certain times of the day; for example, the antimetabolite drug, fluorouracil (FU) was least toxic when given in the morning to rodents (). A list of drugs that demonstrate time dependence is shown in . In pharmacokinetics, it is important to recognize that many isozymes (CYPs) are involved in drug metabolisms. A drug may competitively influence the metabolism of another drug within the same CYP subfamily. Sometimes, an unrecognized effect from the presence of another drug may be misjudged as a time-dependent pharmacokinetic. Drug metabolism and pharmacogenetics are discussed more extensively in .

Table 9.8 Drugs Showing Circadian or Time-Dependent Disposition

Cefodizime	Fluorouracil	Ketoprofen	Theophylline
Cisplatin	Heparin	Mequitazine	

From .

Circadian Rhythms and Influence on Drug Response

C*ircadian rhythms* are rhythmic or cyclical changes in plasma drug concentrations that may occur daily, due to normal changes in body functions. Some rhythmic changes that influence body functions and drug response are controlled by genes and subject to modification by environmental factors. The mammalian circadian clock is a self-sustaining oscillator, usually within a period of ~24 hours, that cyclically controls many physiological and behavioral systems. The biological clock attempts to synchronize and respond to changes in length of the daylight cycle and optimize body functions.

Circadian rhythms are regulated through periodic activation of transcription by a set of clock genes. For example, melatonin onset is associated with onset of the quiescent period of cortisol secretion that regulates many functions. Some well-known circadian physiologic parameters are core body temperature (CBT), heart rate (HR), and other cardiovascular parameters. These fundamental physiologic factors can affect disease states, as well as toxicity and therapeutic response to drug therapy. The toxic dose of a drug may vary as much as several-fold, depending on the time of drug administration—during either sleep or wake cycle.

For example, the effects of aminoglycoside administration timing on serum aminoglycoside levels and the incidence of nephrotoxicity were studied in 221 patients (). Each patient received an IV injection of 2–4 mg/kg gentamicin or tobramycin once daily at: (1) between midnight and 7:30 AM, (2) between 8 AM and 3:30 PM, or (3) between 4 PM and 11:30 PM. In this study, no

statistically significant differences in drug trough levels (0–4.2 mg/L) or peak drug levels (3.6–26.8 mg/L) were found for the three time periods of drug administration. However, nephrotoxicity occurred significantly more frequently when the aminoglycosides were given during the rest period (midnight to 7:30 AM). Many factors contribute to nephrotoxicity were discussed; the time of administration was considered to be an independent risk factor in the multivariate statistical analysis. Time-dependent pharmacokinetics/pharmacodynamics are important, although it is not always possible to detect the difference in drug concentration clinically because of multivariates.

Another example of circadian changes on drug response involves observations with chronic obstructive pulmonary disease (COPD) patients. Symptoms of hypoxemia may be aggravated in some COPD patients due to changes in respiration during the sleep cycle. Prominent circadian variations have been reported involving the incidence of acute myocardial infarction, sudden cardiac death, and stroke, the leading causes of death in the United States. Platelet aggregation favoring coagulation is increased after arising in the early morning hours, coincident with the peak incidence of these cardiovascular events, although much remains to be elucidated.

Time-dependent pharmacokinetic and physiologic functions are important considerations in the treatment of certain hypertensive subjects, in whom early-morning rise in blood pressure may increase the risk of stroke or hypertensive crisis. Verapamil is a commonly used antihypertensive. The diurnal pattern of forearm vascular resistance (FVR) between hypertensive and normotensive volunteers was studied at 9 PM on 24-hour ambulatory blood pressure monitoring, and the early-morning blood pressure rise was studied in 23 untreated hypertensives and 10 matched, normotensive controls. The diurnal pattern of FVR differed between hypertensives and normotensives, with normotensives exhibiting an FVR decline between 2 PM and 9 PM, while FVR rose at 9 PM in hypertensives. Verapamil appeared to minimize the diurnal variation in FVR in hypertensives, although there were no significant differences at any single time point. Verapamil effectively reduced ambulatory blood pressure throughout the 24-hour period, but it did not blunt the early-morning rate of blood pressure rise despite peak S-verapamil concentrations in the early morning ().

Another example of time-dependent pharmacokinetics involves ciprofloxacin. Circadian variation in the urinary excretion of ciprofloxacin was investigated in a crossover study in 12 healthy male volunteers, ages 19–32 years. A significant decrease in the rate and extent of the urinary excretion of ciprofloxacin was observed following administrations at 22:00 versus 10:00 hour, indicating that the rate of excretion during the night time was slower ().

Clinical and Adverse Toxicity Due to Nonlinear Pharmacokinetics

The presence of nonlinear or dose-dependent pharmacokinetics, whether due to saturation of a process involving absorption, first-pass metabolism, binding, or renal excretion, can have significant clinical consequences. However, nonlinear pharmacokinetics may not be noticed in drug studies that use a narrow dose range in patients. In this case, dose estimation may result in disproportionate increases in adverse reactions, but insufficient therapeutic benefits. Nonlinear pharmacokinetics can occur anywhere above, within, or below the therapeutic window.

The problem of nonlinear dose relationship in population pharmacokinetics analysis has been investigated using simulations (, ;). For example, nonlinear fluvoxamine pharmacokinetics were reported () to be present even at subtherapeutic doses. By using simulated data and applying nonlinear mixed-effects models using NONMEM, the authors also demonstrated that use of nonlinear mixed-effect models in population pharmacokinetics has an important application in the detection and characterization of nonlinear processes (pharmacokinetic and pharmacodynamic). Both first-order (FO) and FO conditional estimation (FOCE) algorithms were used for the population analyses. Population pharmacokinetics are discussed further in .

BIOAVAILABILITY OF DRUGS THAT FOLLOW NONLINEAR PHARMACOKINETICS

The bioavailability of drugs that follow nonlinear pharmacokinetics is difficult to estimate accurately. As shown in , each process of drug absorption, distribution, and elimination is potentially saturable. Drugs that follow linear pharmacokinetics follow the principle of superposition (). The assumption in applying the rule of superposition is that each dose of drug superimposes on the previous dose. Consequently, the bioavailability of subsequent doses is predictable and not affected by the previous dose. In the presence of a saturable pathway for drug absorption, distribution, or elimination, drug bioavailability will change within a single dose or with subsequent (multiple) doses. An example of a drug with dose-dependent absorption is chlorothiazide ().

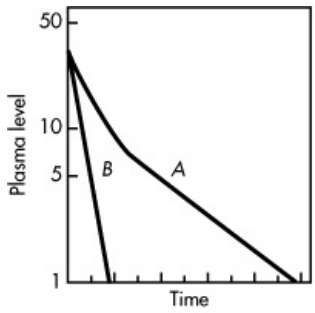
The extent of bioavailability is generally estimated using $[AUC]_0^\infty$. If drug absorption is saturation limited in the gastrointestinal tract, then a smaller fraction of drug is absorbed systemically when the gastrointestinal drug concentration is high. A drug with a saturable elimination pathway may also have a concentration-dependent AUC affected by the magnitude of K_M and V_{max} of the enzymes involved in drug elimination (Eq. 9.21). At low C_p, the rate of elimination is first order, even at the beginning of drug absorption from the gastrointestinal tract. As more drug is absorbed, either from a single dose or after multiple doses, systemic drug concentrations increase to levels that saturate the enzymes involved in drug elimination. The body drug clearance changes and the AUC increases disproportionately to the increase in dose ().

NONLINEAR PHARMACOKINETICS DUE TO DRUG–PROTEIN BINDING

Protein binding may prolong the elimination half-life of a drug. Drugs that are protein bound must first dissociate into the free or nonbound form to be eliminated by glomerular filtration. The nature and extent of drug–protein binding affects the magnitude of the deviation from normal linear or first-order elimination rate process.

For example, consider the plasma level–time curves of two hypothetical drugs given intravenously in equal doses (). One drug is 90% protein bound, whereas the other drug does not bind plasma protein. Both drugs are eliminated solely by glomerular filtration through the kidney.

Figure 9-14.



Plasma curve comparing the elimination of two drugs given in equal IV doses. Curve *A* represents a drug 90% bound to plasma protein. Curve *B* represents a drug not bound to plasma protein.

The plasma curves in demonstrate that the protein-bound drug is more concentrated in the plasma than a drug that is not protein bound, and the protein-bound drug is eliminated at a slower, nonlinear rate. Because the two drugs are eliminated by identical mechanisms, the characteristically slower elimination rate for the protein-bound drug is due to the fact that less free drug is available for glomerular filtration in the course of renal excretion.

The concentration of free drug, C_f, can be calculated at any time, as follows.

$$C_f = C_p\,(1 - \text{fraction bound}) \qquad (9.30)$$

For any protein-bound drug, the free drug concentration (C_f) will always be less than the total drug concentration (C_p).

A careful examination of shows that the slope of the bound drug decreases gradually as the drug concentration decreases. This indicates that the percent of drug bound is not constant. *In vivo*, the percent of drug bound usually increases as the plasma drug concentration decreases (see). Since protein binding of drug can cause nonlinear elimination rates, pharmacokinetic fitting of protein-bound drug data to a simple one-compartment model without accounting for binding results in erroneous estimates of the volume of distribution and elimination half-life. Sometimes plasma drug data for drugs that are highly protein bound have been inappropriately fitted to two-compartment models.

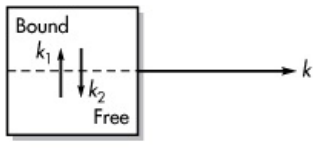
Valproic acid (Depakene) shows nonlinear pharmacokinetics that may be due partially to nonlinear protein binding. The free fraction of valproic acid is 10% at a plasma drug concentration of 40 µg/mL and is 18.5% at a plasma drug level of 130 µg/mL. In addition, higher than expected plasma drug concentrations occur in the elderly, hyperlidemic patients, and in patients with hepatic or renal disease.

One-Compartment Model Drug with Protein Binding

The process of elimination of a drug distributed in a single compartment with protein binding is illustrated in . The one compartment contains both free drug and bound drug, which are dynamically interconverted with rate constants k_1 and k_2. Elimination of drug occurs only with the free drug, at a first-order rate. The bound drug is not eliminated. Assuming a saturable and instantly reversible drug-binding process, where P = protein concentration in plasma, C_f = plasma concentration of free drug, $k_d = k_2/k_1$ = dissociation constant of the protein drug complex, C_p = total plasma drug concentration, and C_b = plasma concentration of bound drug,

$$\frac{C_b}{P} = \frac{(1/k_d)C_f}{1 + (1/k_d)C_f} \qquad (9.31)$$

Figure 9-15.



One-compartment model with drug–protein binding.

This equation can be rearranged as follows:

$$C_b = \frac{PC_f}{k_d + C_f} = C_p - C_f \qquad (9.32)$$

Solving for C_f,

$$C_f = \frac{1}{2}\left[-(P + k_d - C_p) + \sqrt{(P + k_d - C_p)^2 + 4k_dC_p}\right] \qquad (9.33)$$

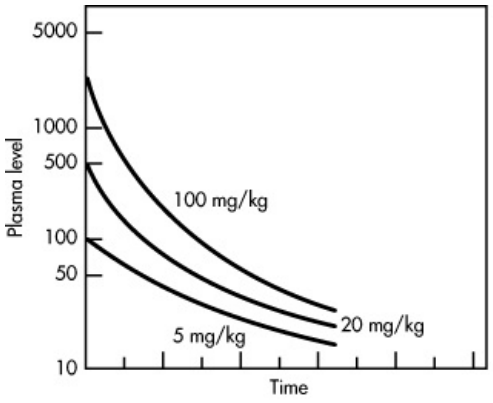
Because the rate of drug elimination is dC_p/dt,

$$\frac{dC_p}{dt} = -kC_f$$

$$\frac{dC_p}{dt} = \frac{-k}{2}\left[-(P + k_d - C_p) + \sqrt{(P + k_d - C_p)^2 + 4k_dC_p}\right] \qquad (9.34)$$

This differential equation describes the relationship of changing plasma drug concentrations during elimination. The equation is not easily integrated but can be solved using a numerical method. shows the plasma drug concentration curves for a one-compartment protein-bound drug having a volume of distribution of 50 mL/kg and an elimination half-life of 30 minutes. The protein concentration is 4.4% and the molecular weight of the protein is 67,000 Da. At various doses, the pharmacokinetics of elimination of the drug, as shown by the plasma curves, range from linear to nonlinear, depending on the total plasma drug concentration.

Figure 9-16.



Plasma drug concentrations for various doses of a one-compartment model durg with protein binding.

()

Nonlinear drug elimination pharmacokinetics occur at higher doses. Because more free drug is available at higher doses, initial drug elimination occurs more rapidly. For drugs demonstrating nonlinear pharmacokinetics, the free drug concentration may increase slowly at first, but when the dose of drug is raised beyond the protein-bound saturation point, free plasma drug concentrations may rise abruptly. Therefore, the concentration of free drug should always be calculated to make sure the patient receives a proper dose.

FREQUENTLY ASKED QUESTIONS

1. Most drugs follow linear pharmacokinetics at therapeutic doses. Why is it important to monitor drug level carefully for dose dependency?

2. What are the main differences in pharmacokinetic parameters between a drug that follows linear and a drug that follows nonlinear pharmacokinetic?

3. What are the main differences between a model based on Michaelis–Menten kinetic (V_{max} and K_M) and the physiologic model that describes hepatic metabolism based on clearance?

4. What is the cause of nonlinear pharmacokinetics that is not dose related?

LEARNING QUESTIONS

1. Define *nonlinear pharmacokinetics*. How do drugs that follow nonlinear pharmacokinetics differ from drugs that follow linear pharmacokinetics?

a. What is the rate of change in the plasma drug concentration with respect to time, dC_p/dt, when $C_p << K_M$?

b. What is the rate of change in the plasma drug concentration with respect to time, dC_p/dt, when $C_p >> K_M$?

2. What processes of drug absorption, distribution, and elimination may be considered "capacity limited," "saturated," or "dose dependent?"

3. Drugs, such as phenytoin and salicylates, have been reported to follow dose-dependent elimination kinetics. What changes in pharmacokinetic parameters, including $t_{1/2}$, V_D, AUC, and C_p, could be predicted if the amounts of these drugs administered were increased from low pharmacologic doses to high therapeutic doses?

4. A given drug is metabolized by capacity-limited pharmacokinetics. Assume K_M is 50 µg/mL, V_{max} is 20 µg/mL per hour, and the apparent V_D is 20 L/kg.

a. What is the reaction order for the metabolism of this drug when given in a single intravenous dose of 10 mg/kg?

b. How much time is necessary for the drug to be 50% metabolized?

5. How would induction or inhibition of the hepatic enzymes involved in drug biotransformation theoretically affect the pharmacokinetics of a drug that demonstrates nonlinear pharmacokinetics due to saturation of its hepatic elimination pathway?

6. Assume that both the active parent drug and its inactive metabolites are excreted by active tubular secretion. What might be the consequences of increasing the dosage of the drug on its elimination half-life?

7. The drug isoniazid was reported to interfere with the metabolism of phenytoin. Patients taking both drugs together show higher phenytoin levels in the body. Using the basic principles in this chapter, do you expect K_M to increase or decrease in patients taking both drugs? (*Hint:* see .)

8. Explain why K_M is often seen to have units of mM/mL and sometimes mg/L.

9. The V_{max} for metabolizing a drug is 10 mmol/hr. The rate of metabolism (v) is 5 µmol/hr when drug concentration is 4 µmol. Which of the following statements is/are true?

a. K_M is 5 µmol for this drug.

b. K_M cannot be determined from the information given.

c. K_M is 4 µmol for this drug.

10. Which of the following statements is/are true regarding the pharmacokinetics of diazepam (98% protein bound) and propranolol (87% protein bound)?

a. Diazepam has a long elimination half-life because it is difficult to be metabolized due to extensive plasma–protein binding.

b. Propranolol is an example of a drug with high protein binding but unrestricted (unaffected) metabolic clearance.

c. Diazepam is an example of a drug with low hepatic extraction.

d. All of the above.

e.a and **c.**

f.b and **c.**

11. Which of the following statements describe(s) correctly the properties of a drug that follows nonlinear or capacity-limited pharmacokinetics?

a. The elimination half-life will remain constant when the dose changes.

b. The area under the plasma curve (AUC) will increase proportionally as dose increases.

c. The rate of drug elimination = $C_p \times K_M$.

d. All of the above.

e.a and **b.**

f. None of the above.

12. The hepatic intrinsic clearances of two drugs are

Drug A: 1300 mL/min

Drug B: 26 mL/min

Which drug is likely to show the greatest increase in hepatic clearance when hepatic blood flow is increased from 1 L/min to 1.5 L/min?

a. Drug A

b. Drug B

c. No change for both drugs

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