Nonlinear Pharmacokinetics

References

1. Applied Biopharmaceutics and Pharmacokinetics, *7th Edition*
   - Leon Shargel and Andrew B. C. Yu
2. Basic Pharmacokinetics, *2nd Edition*
   - Sunil S. Jambhekar and Philip J. Breen

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Chapter Contents

Non-linear Pharmacokinetics (12 lectures). Introduction, drug elimination by capacity-limited pharmacokinetics: one compartment model (IV bolus injection), estimation of Michaelis-Menten parameters (V_{max} and K_m), determination of clearance, time dependent pharmacokinetics.

Chapter Objectives

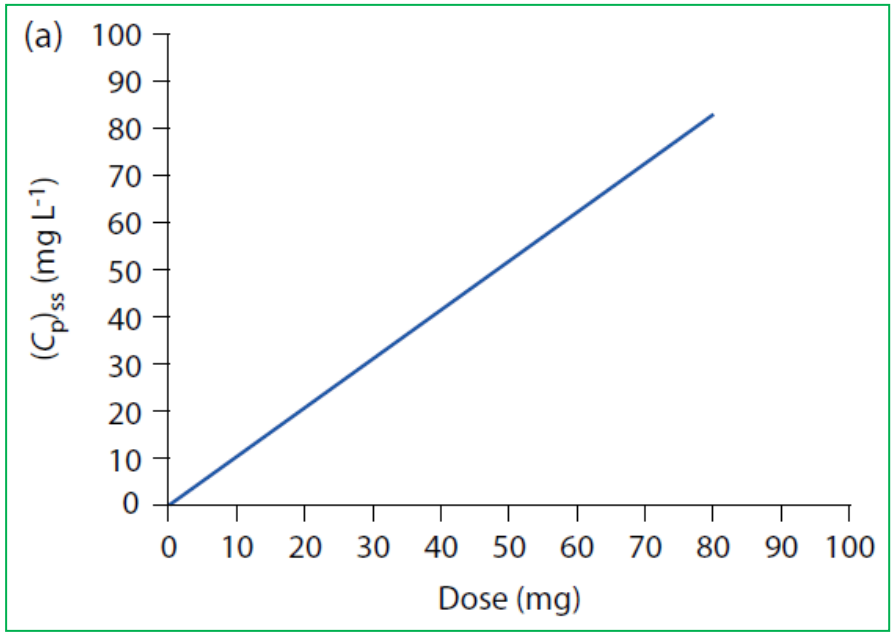
- Describe the differences between linear pharmacokinetics and nonlinear pharmacokinetics.
- Illustrate nonlinear pharmacokinetics with drug disposition examples.
- Explain how to detect nonlinear kinetics using AUC-versus-doses plots.
- Apply the appropriate equation and graphical methods, to calculate the V_{max} and K_M parameters after multiple dosing in a patient.
- Describe the use of the Michaelis–Menten equation to simulate the elimination of a drug by a saturable enzymatic process.

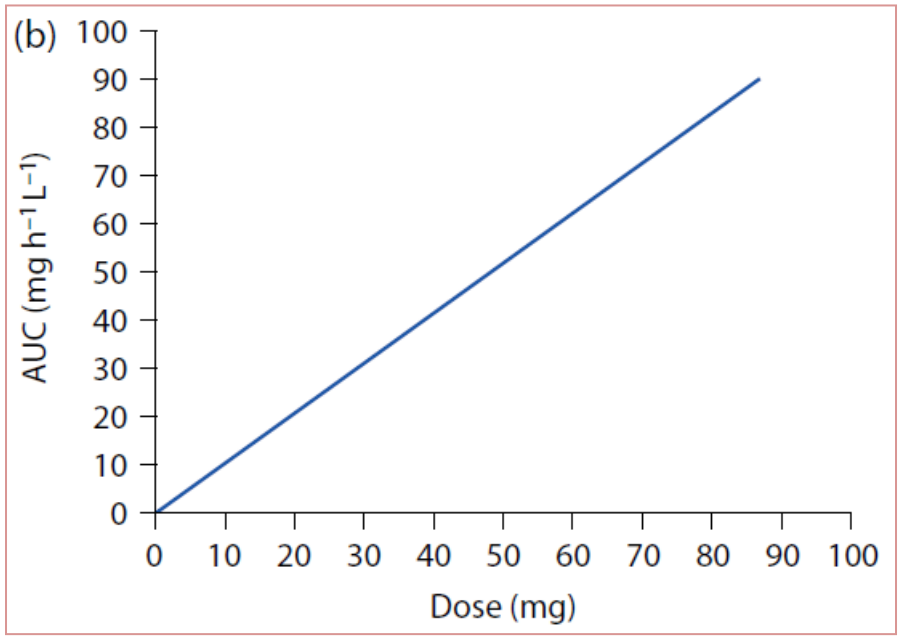
Assumptions of linear (dose-independent) pharmacokinetics models

- The course of drug disposition and action follow first-order kinetics.

- Pharmacokinetic parameters, such as elimination half life ($t_{1/2}$), the elimination rate constant (k), the apparent volume of distribution (V_D), and the systemic clearance (Cl) of most drugs are not change when different doses are administered and/or when the drug is administered via different routes as a single dose or multiple doses.

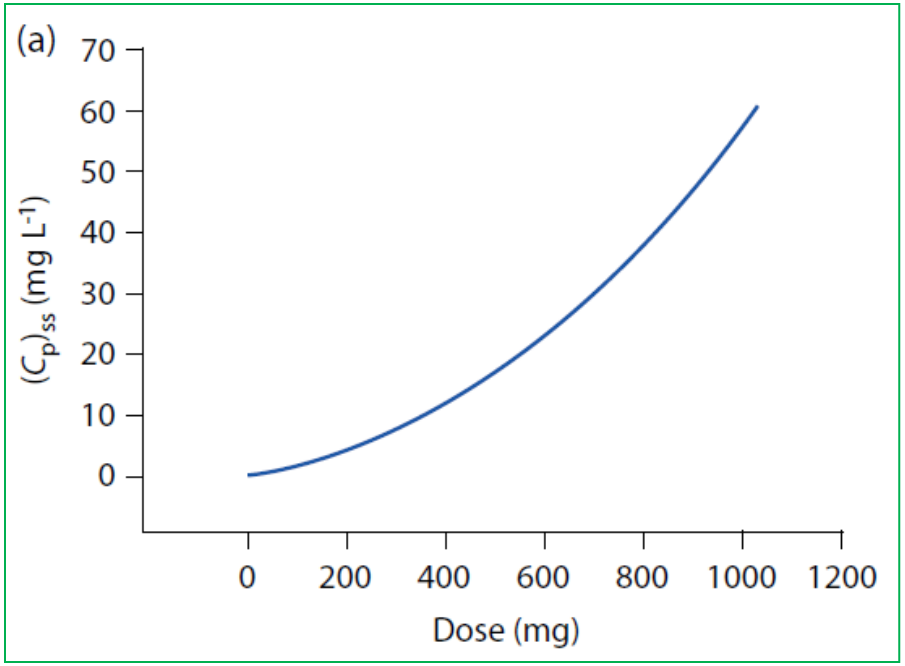
The term linear simply means that plasma concentration at a given time at steady state and AUC will both be directly proportional to the dose administered





Nonlinear (dose-dependent) pharmacokinetics

For drugs that exhibit nonlinear or dose-dependent kinetics, the fundamental pharmacokinetic parameters such as V_D, Cl, k and $t_{1/2}$ may vary depending on the administered dose.



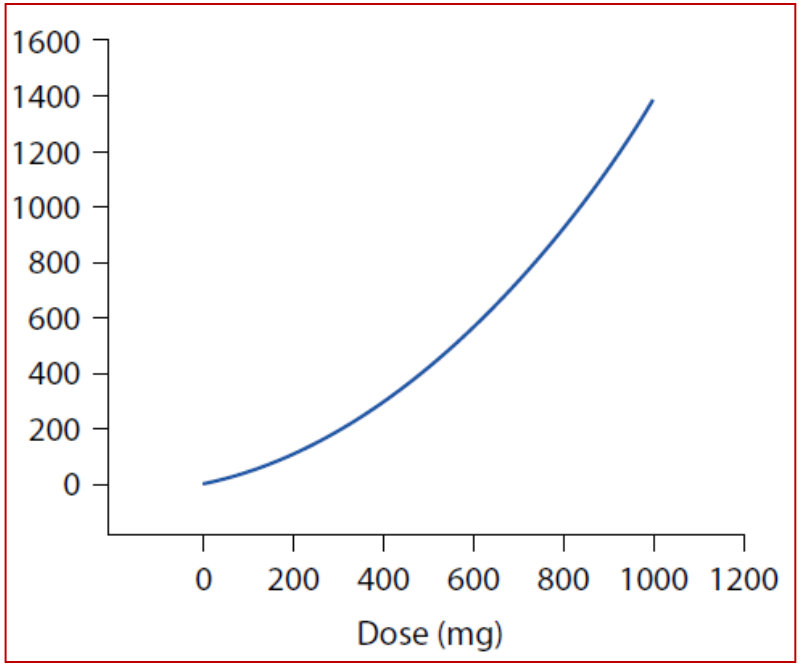
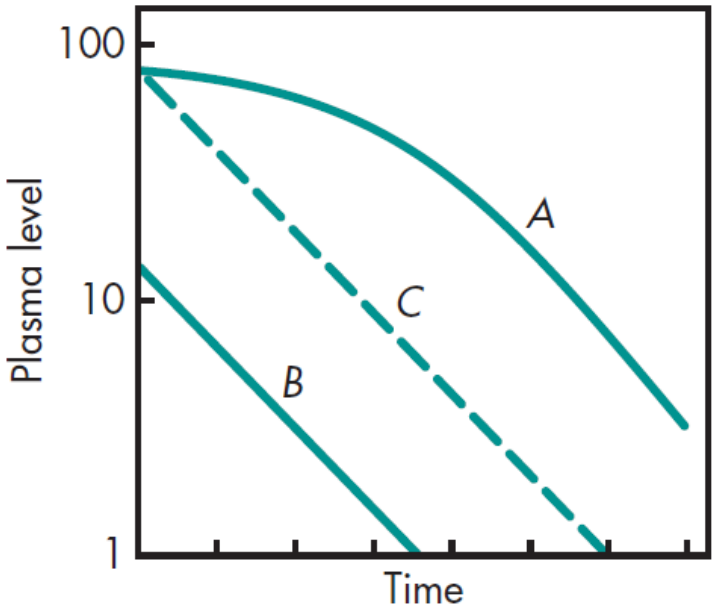


FIGURE: Plasma level–time curves for a drug that exhibits a saturable elimination process.



- Curves *A* and *B* represent high and low doses of drug, 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.

Causes behind nonlinear pharmacokinetics

- Saturation of carrier-mediated systems: 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.

- Pathologic alteration: 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.

- Gallstone obstruction: Gallstone obstruction of the bile duct will alter biliary drug excretion.

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

Contents

- Saturable enzymatic elimination processes
- Drug elimination by capacity-limited pharmacokinetics
- Determination of K_M and V_{max}

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

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

where V_{max} is the maximum elimination rate and K_M is the Michaelis constant that reflects the capacity of the enzyme system.

$$V_0 = \frac{V_{max}[S]}{K_m + [S]}$$

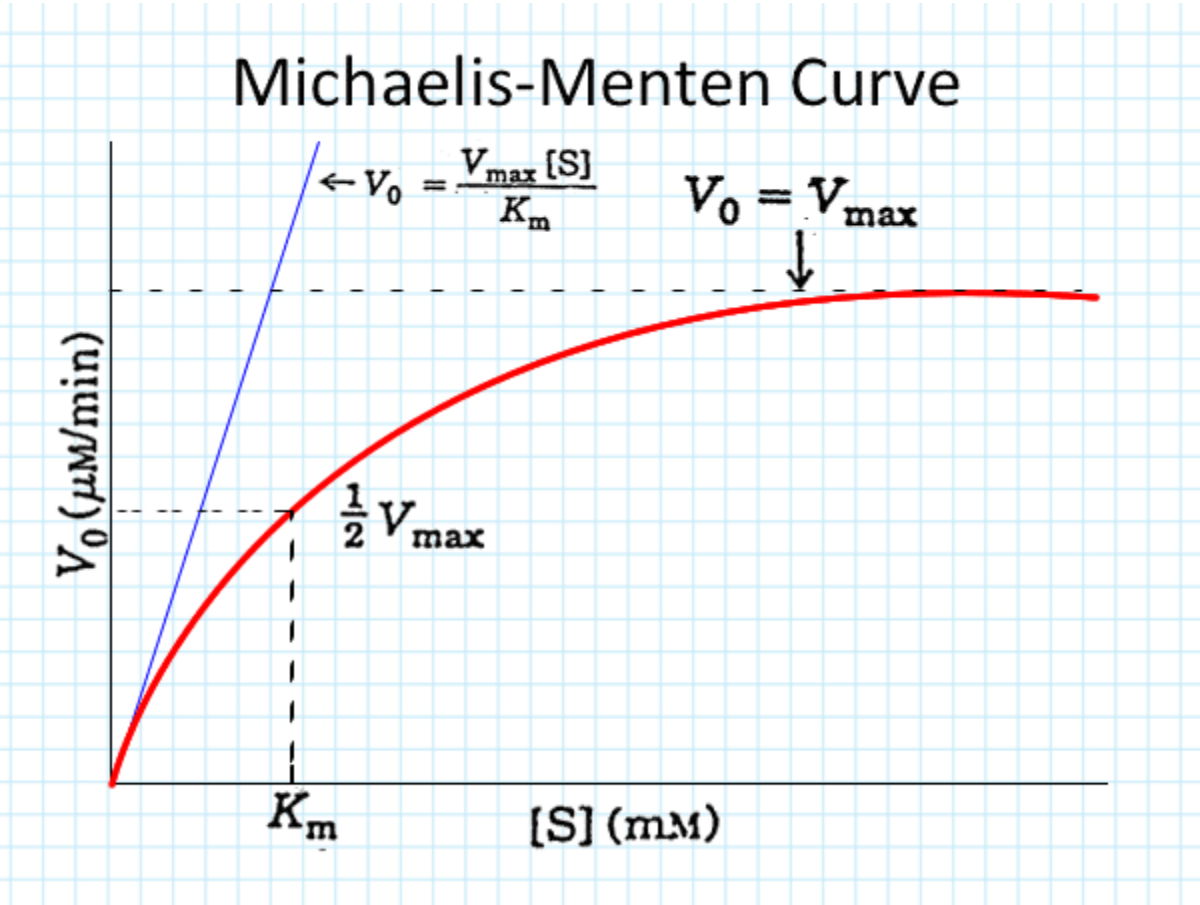


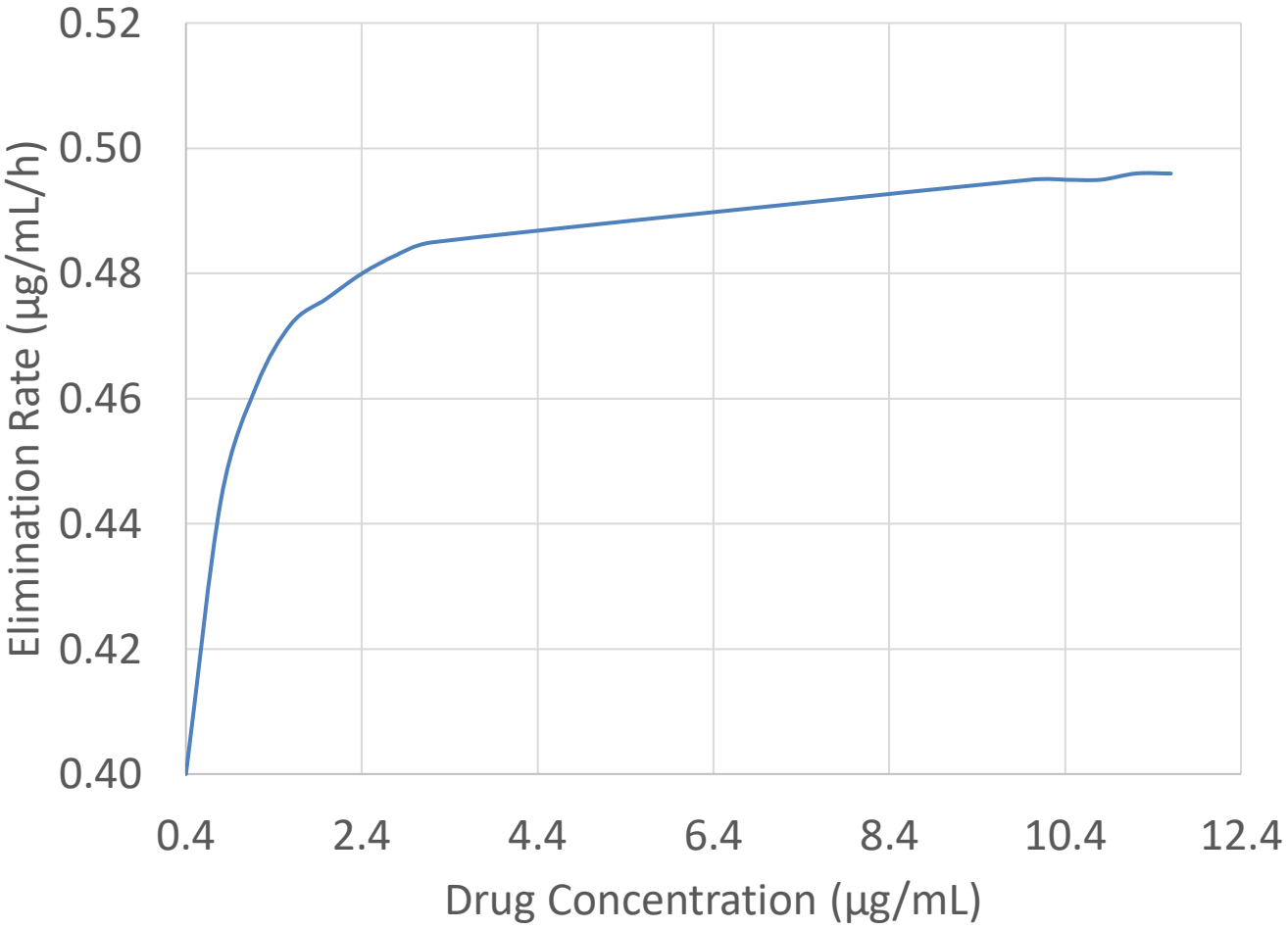
Table 10-2 Effect of Drug Concentration on the Elimination Rate and Rate Constant[a]

Drug Concentration (μg/mL)	Elimination Rate (μg/mL/h)	Elimination Rate/ Concentration[b] (h^{-1})
0.4	0.400	1.0000
0.8	0.444	0.5560
1.2	0.462	0.3850
1.6	0.472	0.2940
2	0.476	0.2380
2.4	0.480	0.2000
2.8	0.483	0.1720
3.2	0.485	0.1520
10	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/h.

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

Figure 10-2 Effect of Drug Concentration on the Elimination Rate and Rate Constant[a]



[a] K_M = 0.1 μg/mL, V_{max} = 0.5 μg/mL/h.
[b] The ratio of the elimination rate to the concentration is equal to the rate constant.

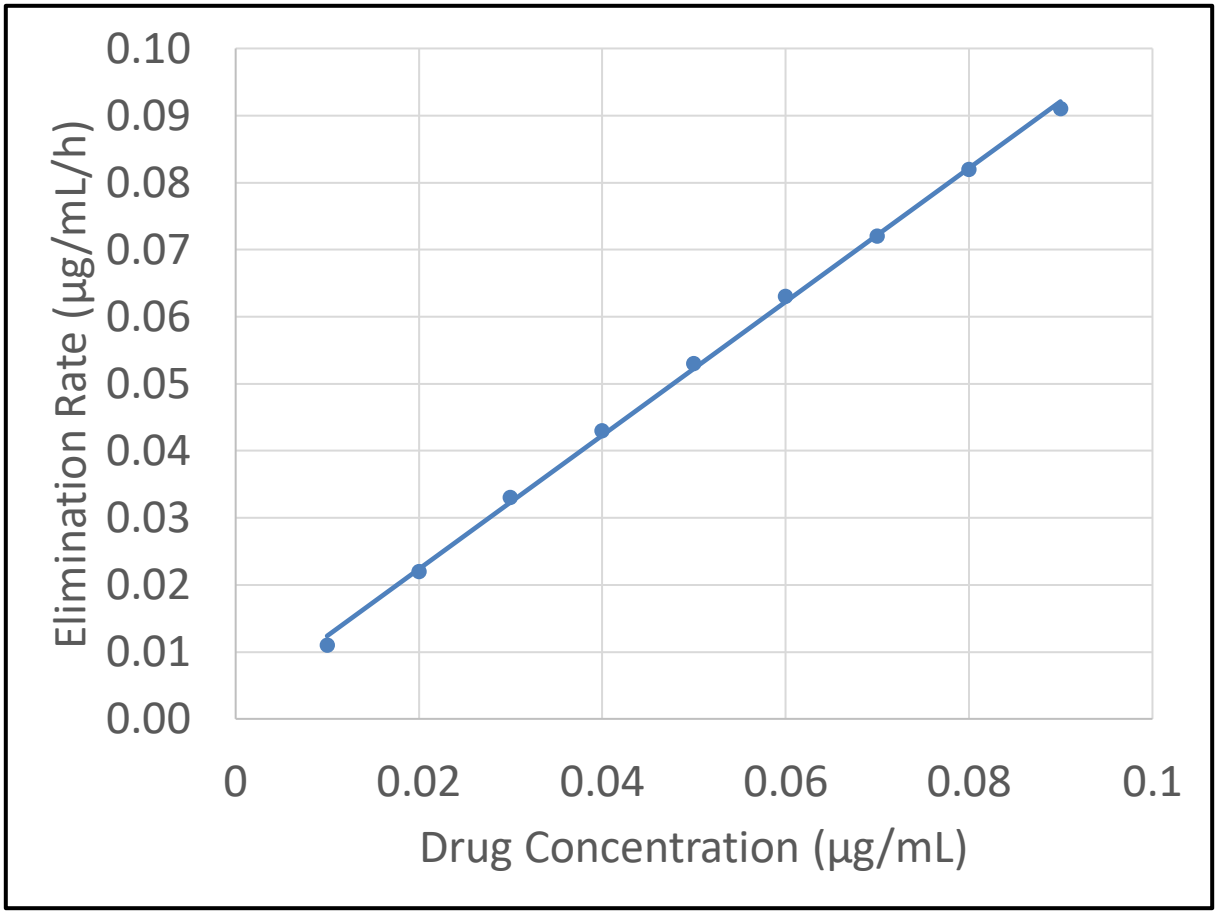
When the drug concentration C_p is small in relation to the K_M, the rate of drug elimination becomes a first-order process.

TABLE 10-3 Effect of Drug Concentration on the Elimination Rate and Rate Constant[a]

Drug Concentration (μg/mL)	Elimination Rate (μg/mL/h)	Elimination Rate/ Concentration (h^{-1})
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/h.

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


0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Elimination Rate (µg/mL/h)
0
0.02
0.04
0.06
0.08
0.1
Drug Concentration (µg/mL)

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

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.

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

Thus, elimination of drug becomes a zero-order process.

When C_p is much smaller than K_M, C_p in the denominator is negligible and the elimination rate becomes first order.

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

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

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

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

DRUG ELIMINATION BY CAPACITY-LIMITED PHARMACOKINETICS: ONE-COMPARTMENT MODEL, IV BOLUS INJECTION

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

$$\frac{C_0 - C_p}{t} = V_{max} - \frac{K_M}{t} \ln \frac{C_0}{C_p}$$

The following equation may be used to simulate the decline of drug in the body after various size IV doses are given

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

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, the equation is rearranged and solved for time t:

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

PRACTICE PROBLEM

Using the hypothetical drug considered in Table 10-2 ($V_{max} = 0.5$ 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 Table 10-2, elimination occurs at a zero-order rate of approximately 0.5 μg/mL per hour.

Time needed for the drug to decrease to

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

PRACTICE PROBLEM

How long would it take for the plasma concentration of the drug in Table 10-3 to decline from 0.05 to 0.005 μg/mL?

Solution

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

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

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

$$t = \frac{2.3(\log C_p^0 - \log C_p)}{k}$$

$$t = \frac{2.3(\log 0.05 - \log 0.005)}{1.1}$$

$$= \frac{2.3(-1.30 + 2.3)}{1.1}$$

$$= \frac{2.3}{1.1} = 2.09 \text{ h}$$

Determination of K_M and V_{max}

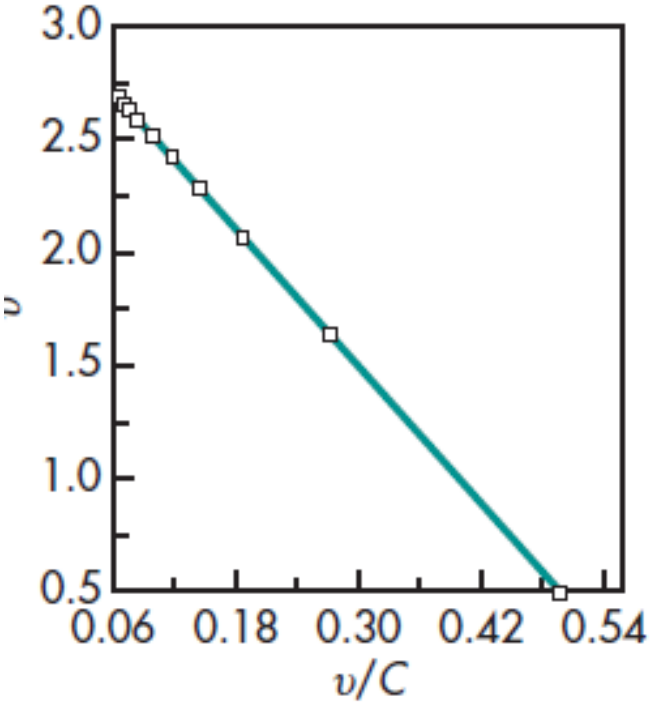
$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_M + C_p} = v$$

The above equation can be rearranged as

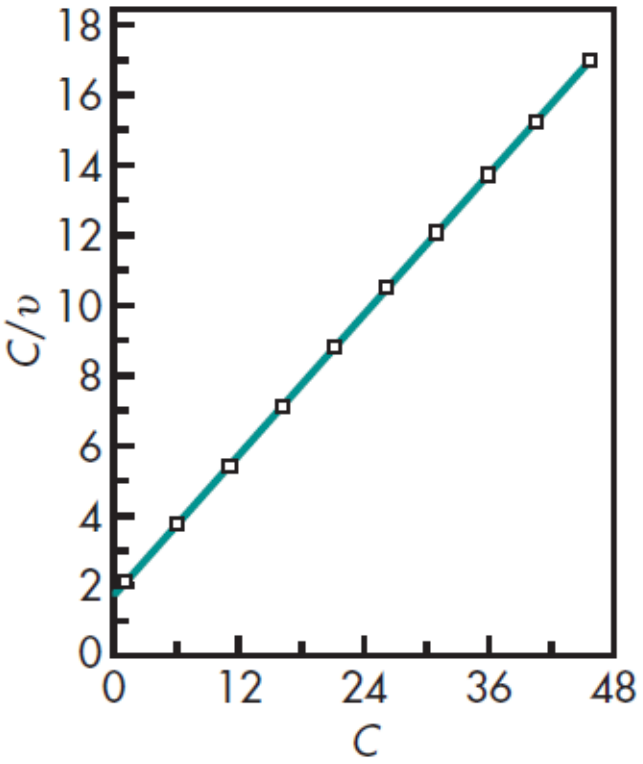
$$v = \frac{V_{max} C}{K_M + C}$$

$$\frac{1}{v} = \frac{K_M}{V_{max}} \frac{1}{C} + \frac{1}{V_{max}}$$

$$v = -K_M \frac{v}{C} + V_{max}$$



$$\frac{C}{v} = \frac{1}{V_{max}} C + \frac{K_M}{V_{max}}$$



Lecture-3

Contents

- Determination Of K_M And V_{max} in Patients
- Clearance
- Determination Of Renal Clearance

Determination of K_M and V_{max} in Patients

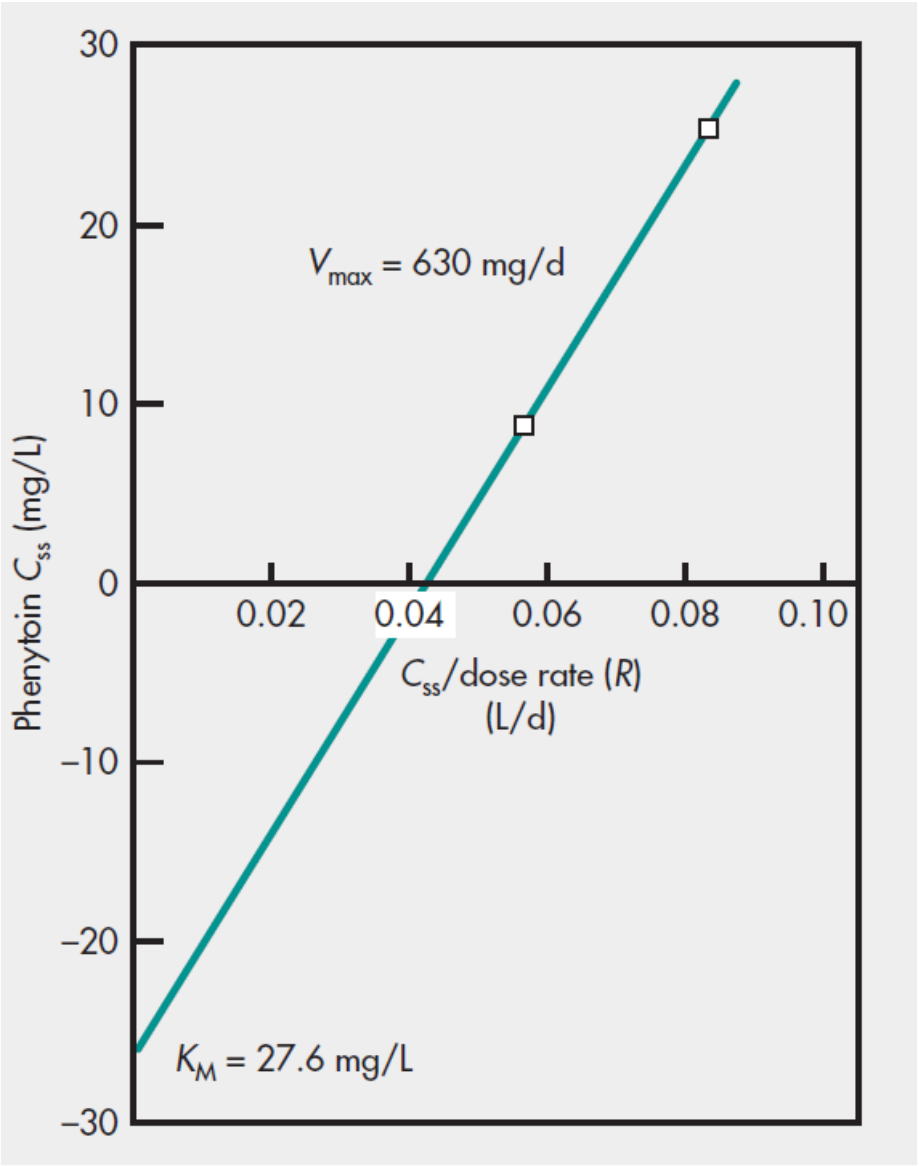
- To determine K_M and V_{max}, two different dose regimens are given at different times, until steady state is reached.
- The steady-state drug concentrations (C_{ss}) are then measured by assay. At steady state, the rate of drug metabolism (v) is assumed to be the same as the rate of drug input R (dose/day).

The frequency of administration of a drug in a particular dose is called dosage regimen.

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

$$\frac{1}{R} = \frac{K_M}{V_{max}} \frac{1}{C_{ss}} + \frac{1}{V_{max}}$$

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



Phenytoin was administered to a patient at dosing rates of 150 and 300 mg/d, 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?

CLEARANCE

Clearance (Cl) is a measure of drug elimination from the body without identifying the mechanism or process.

Mathematically,

$$Cl = \frac{\text{Elimination rate}}{\text{Plasma concentration } (C_p)} = \frac{dD_E/dt}{C_p}$$

$$= \frac{kC_pV_D}{C_p} = kV_D$$

Unit of Clearance

$$Cl = \left(\frac{dD_E/dt}{C_p}\right) = \frac{\mu g/\text{min}}{\mu g/\text{mL}} = \text{mL/min}$$

In general,
unit of *Cl* is volume/time

Clearance remains constant for linear PK

Clearance, $$Cl = \left(\frac{dD_E/dt}{C_p} \right) = \frac{kC_pV_D}{C_p} = kV_D$$

- Therefore, Clearance is the product of a volume of distribution, V_D, and a rate constant, k, both of which are constants when the PK is linear.
- As the plasma drug concentration decreases during elimination, the rate of drug elimination, dD_E/dt, decreases accordingly, but clearance remains constant. Clearance is constant as long as the rate of drug elimination is a first-order process.

EXAMPLE ▶▶▶

Penicillin has a Cl of 15 mL/min. Calculate the elimination rate for penicillin when the plasma drug concentration, C_p, is 2 μg/mL.

Solution

Elimination rate $= C_p \times Cl$ (from Equation 7.5)

$$\frac{dD_E}{dt} = 2\ \mu\text{g/mL} \times 15\ \text{mL/min} = 30\ \mu\text{g/min}$$

Clearance Processes

Renal Clearance, Cl_R

- Renal clearance is the removal of the drug from the body by the kidneys.
- It is dependent on a number of factors, including: renal blood flow, and the rates of glomerular filtration and tubular secretion compared to the rate of passive diffusion.
- Anything which impacts on these factors may impact on drug clearance, either speeding it up or slowing it down.

Hepatic Clearance, Cl_H

- Metabolic - or hepatic - clearance is the conversion of the parent drug into a different chemical entity by liver enzymes.
- It is dependent on a number of factors, including: hepatic blood flow, the rate of liver enzyme activity and the rate of secretion into the bile.
- Anything which impacts on these factors may, in turn, impact on drug clearance, either speeding it up or slowing it down.

Other Pathways

- Other pathways for drug excretion may include the excretion of drug into bile, sweat, saliva, milk (via lactation), or other body fluids.
- Volatile drugs, such as gaseous anesthetics, alcohol, or drugs with high volatility, are excreted via the lungs into expired air.

DETERMINATION OF RENAL CLEARANCE

For a drug that is excreted slowly through the kidney,

$$Cl_R = \frac{dD_u/dt}{C_p} \qquad (1)$$

Multiplying both sides by C_p gives

$$Cl_R \times C_p = dD_u/dt \qquad (2)$$

By rearranging Equation 2 and integrating, one obtains

$$[D_u]_{0\text{-}t} = Cl_R \times \mathrm{AUC}_{0\text{-}t} \qquad (3)$$

A graph is then plotted of cumulative drug excreted in the urine versus the area under the concentration-time curve. Renal clearance is obtained from the slope of the curve.