Reference Texts:

Applied Clinical Pharmacokinetics, Second Edition, 2008 by Larry A. Bauer.

Additional references include but not limited to the following:

Clinical Pharmacokinetics Concepts and Applications, Third Edition, 1995 by Malcolm Rowland and Thomas Tozer;

No	Lecture title	Hours
1	Course Overview	1
2	Review of basic pharmacokinetic (PK)-	2
3	Review of basic pharmacodynamic (PD)	1
4	Clinical PK equations and calculations	3
5	Clinical PK in special population and cases	3
6	Clinical PK/PD for Antibiotics (e.g., Aminoglycosides, Vancomycin	4
7	Clinical PK/PD for Cardiovascular agents (e.g., Digoxin, Lidocaine, Procainamide/N-Acetyl Procainamide	4
8	Clinical PK/PD for Anticonvulsants (e.g., Phenytoin, Carbamazepine, Valproic Acid, Phenobarbitone/Primidone, Ethosuxsimide	6
9	Clinical PK/PD for Immunossprasants (e.g., Cyclosporine, Tacrolimus	2
10	Clinical PK/PD of other drugs (e.g., Lithium, Theophylline, Anticancer agents, Anticoagulats	4

Principles of basic clinical pharmacokinetic parameters

Clinical pharmacokinetics

- Clinical pharmacokinetics is the application of pharmacokinetic concepts and principles in humans in order to :

1. Design individualized dosage regimens which optimize the therapeutic response of a medication.
2. Minimizing the chance of an adverse drug reaction.
3. Monitor medications with a narrow therapeutic index.
4. Development and evaluation of new drugs.

- Pharmacokinetics is the study of the ***absorption***, ***distribution, metabolism,*** and ***excretion*** of drugs.

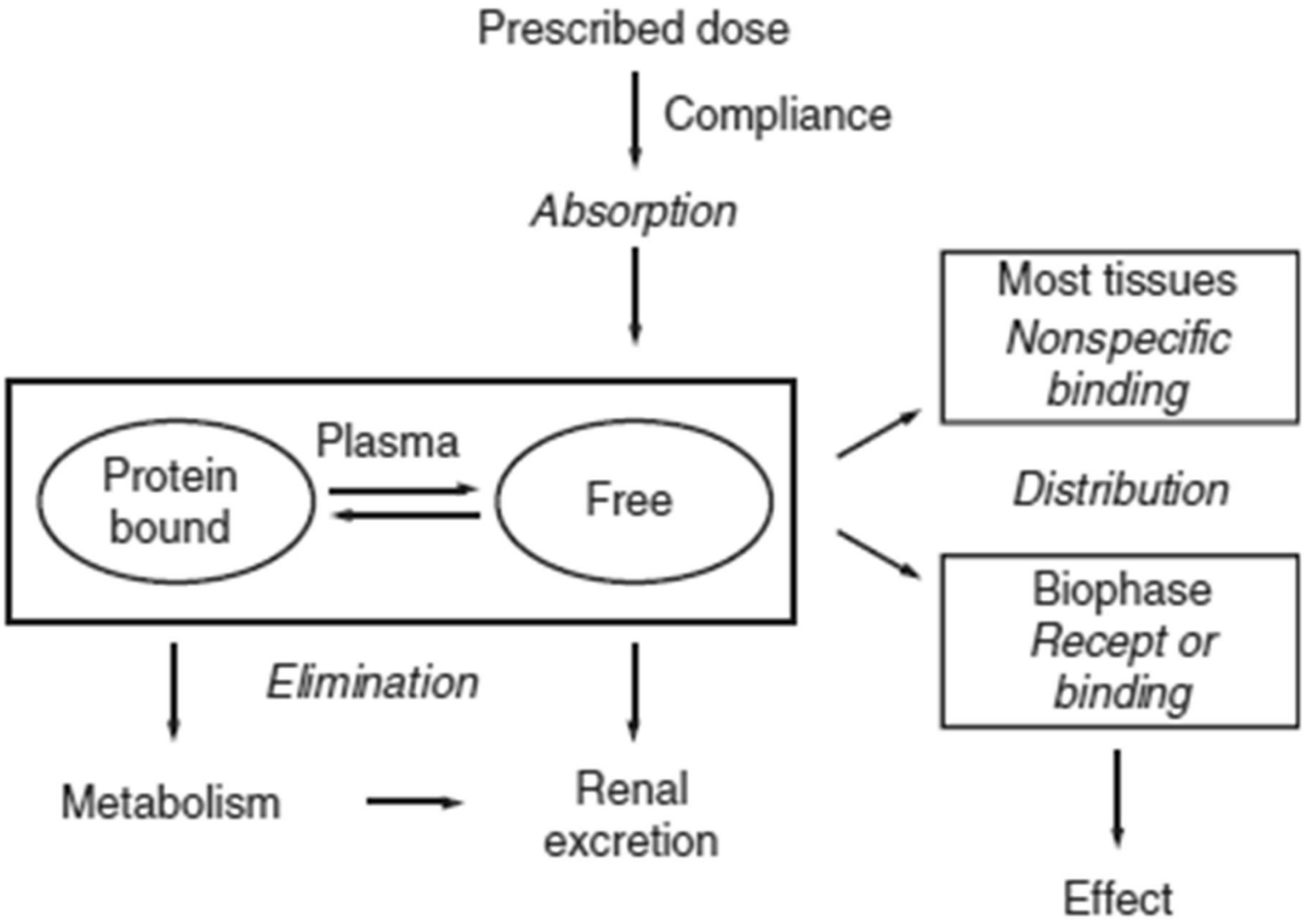
- When drugs are given **extravascularly** (e.g., orally, intramuscularly, applied to the skin via a transdermal patch, etc.), ***absorption*** must take place for the drug molecules to reach the systemic circulation.

- In order to be absorbed, the drug molecules must pass through several physiological barriers before reaching the vascular system. For example, when a medication is given orally, the drug dosage form must release drug molecules via dissolution, and the molecules must pass through the various layers of the gastrointestinal tract where they enter capillaries.

- ***Distribution*** occurs when drug molecules that have entered the vascular system pass from the bloodstream into various tissues and organs such as the muscle or heart.

- ***Metabolism*** is the chemical conversion of the drug molecule, usually by an enzymatically mediated reaction, into another chemical entity referred to as a metabolite. The metabolite may have the same, or different, pharmacological effect as the parent drug, or even cause toxic side effects.

- ***Excretion*** is the irreversible removal of drug from the body and commonly occurs via the kidney or biliary tract.


Prescribed dose
Compliance
Absorption
Most tissues
Nonspecific
binding
Plasma
Protein
bound
Free
Distribution
Biophase
Recept or
binding
Elimination
Metabolism
Renal
excretion
Effect

Pharmacokinetic principles

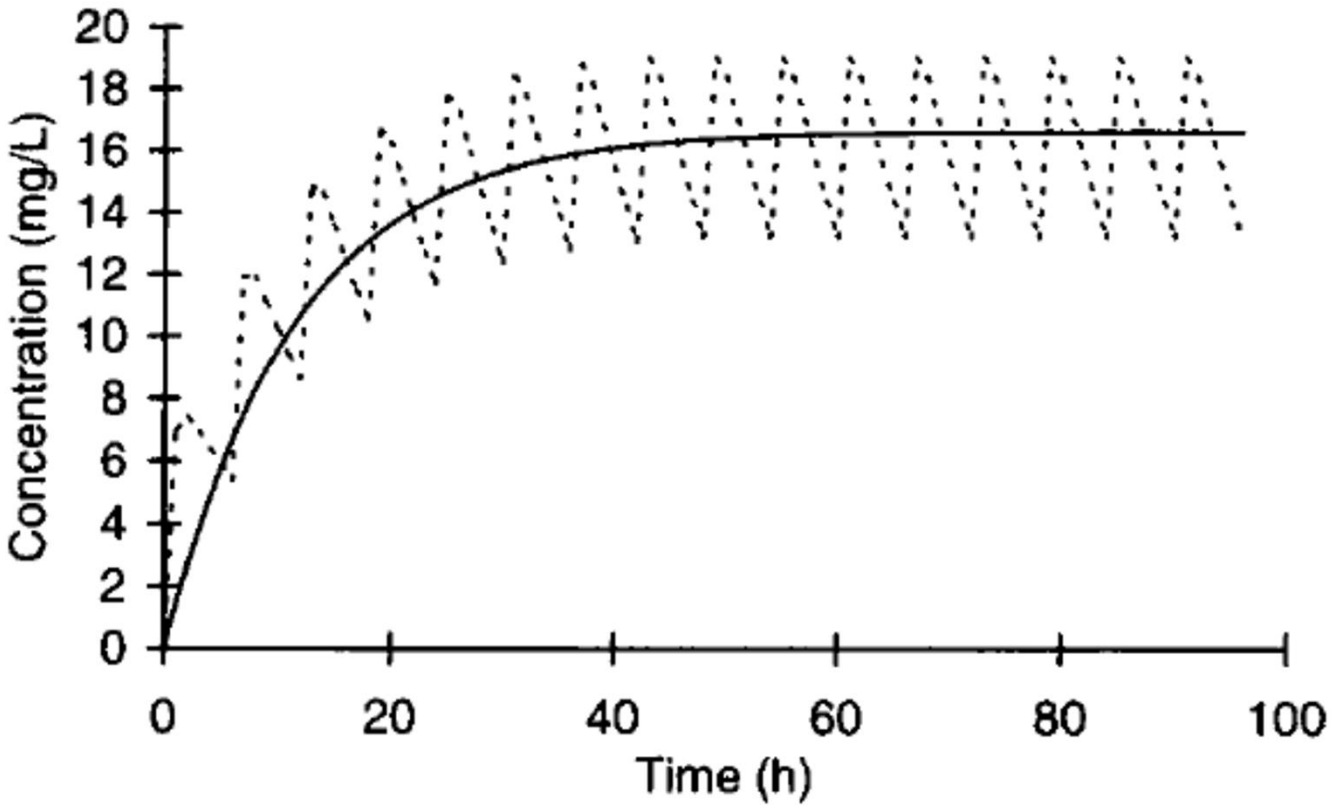
- ***steady state concentration***:

  When the rate of drug administration equals the rate of drug removal, the amount of drug contained in the body reaches a constant value.

- At Css:

  Rate of administration = Rate of the elimination rate

- Drugs with short half-life reach Css rapidly, while drugs with long half-life takes days to weeks to reach steady state.


Concentration (mg/L)
20
18
16
14
12
10
8
6
4
2
0
0
20
40
60
80
100
Time (h)

Half-life (t1/2):

- The time required for serum concentrations to decrease by one half (50%).
- Drug need 3-5 t1/2 to reach Css

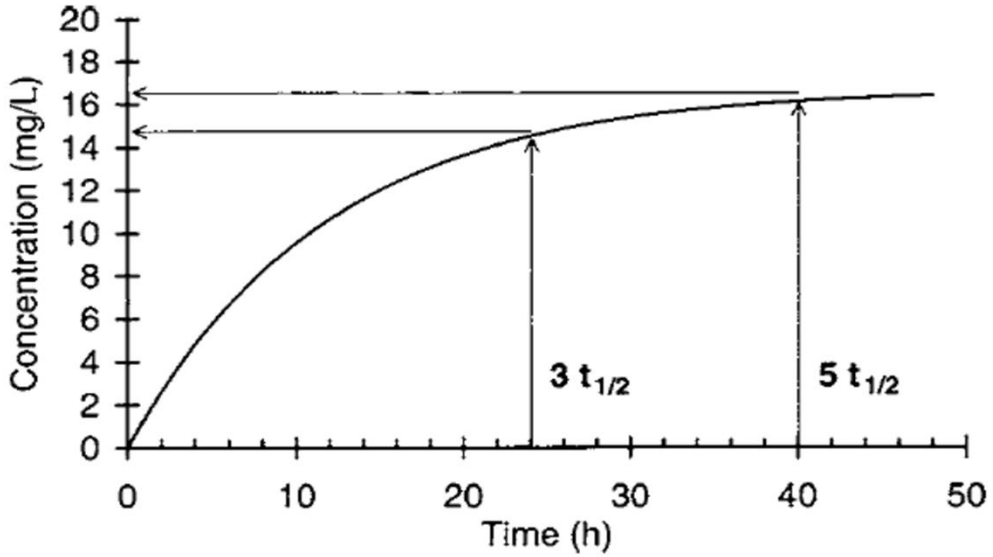
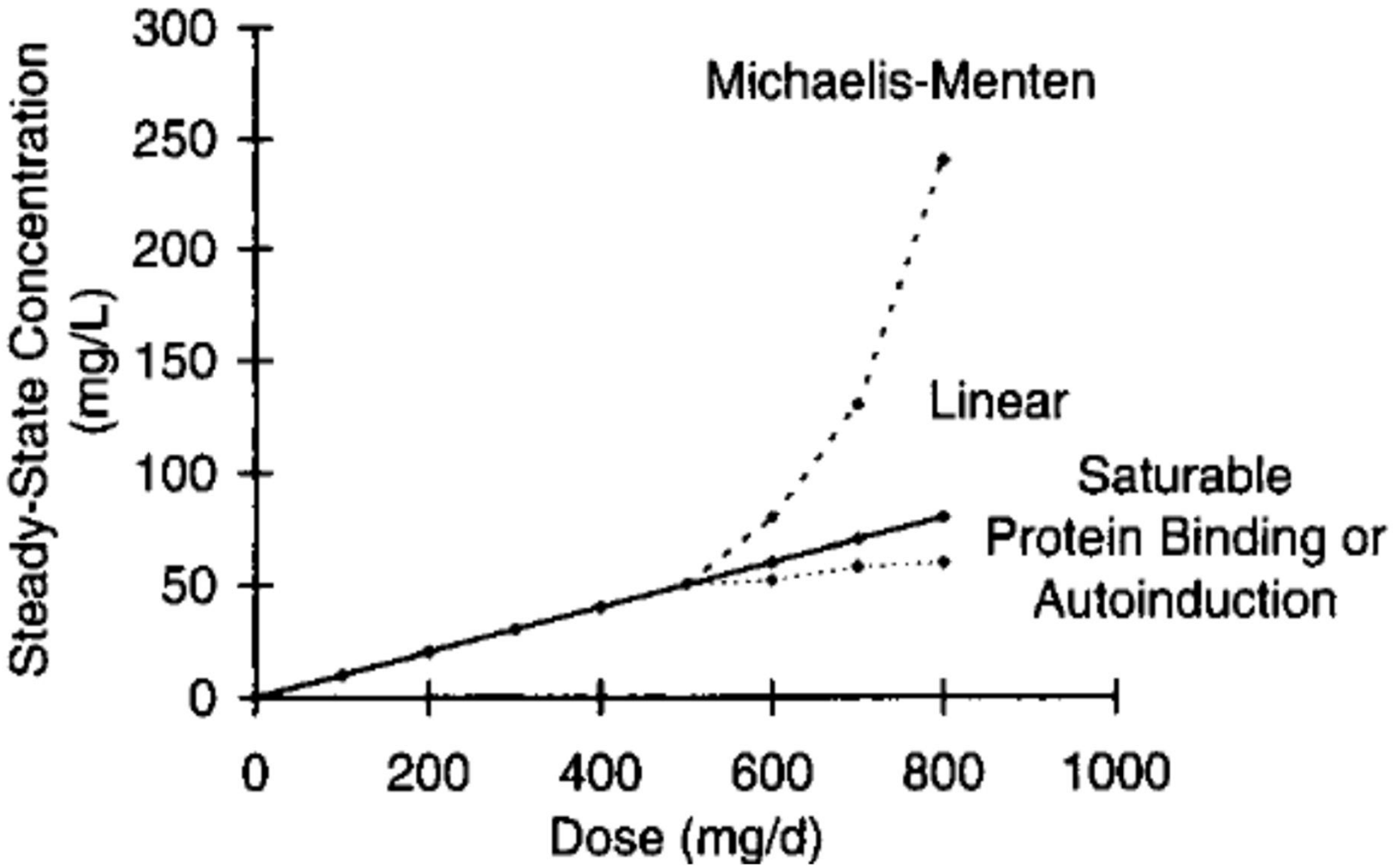


FIGURE 1-9 Serum concentration/time graph for a drug that has a half-life equal to 8 hours. The arrows indicate concentrations at 3 half-lives (24 hours, ~90% of Css) and at 5 half-lives (40 hours, ~95% of Css). Since most drug assays have 5–10% measurement error, serum concentrations obtained between 3–5 half-lives after dosing commenced can be considered to be at steady state for clinical purposes and used to adjust drug doses.

LINEAR VERSUS NONLINEAR PHARMACOKINETICS

Linear pharmacokinetics:

- If a plot of steady state concentration versus dose yields a straight line, the drug is said to follow linear pharmacokinetics. In this situation, steady-state serum concentrations increase or decrease proportionally with dose.
- For example, if theophylline is given as a continuous infusion at a rate of 50 mg/h, theophylline serum concentrations will increase until the removal of theophylline via hepatic metabolism and renal excretion equals 50 mg/h.


Steady-State Concentration (mg/L)
300
250
200
150
100
50
0
Michaelis-Menten
Linear
Saturable Protein Binding or Autoinduction
0
200
400
600
800
1000
Dose (mg/d)

LINEAR VERSUS NONLINEAR PHARMACOKINETICS

Nonlinear pharmacokinetics:

- When steady-state concentrations change in a disproportionate fashion after the dose is altered.

- A plot of **steady-state concentration** versus **dose** is **not a straight line** and the drug is said to follow nonlinear pharmacokinetics.

LINEAR VERSUS NONLINEAR PHARMACOKINETICS

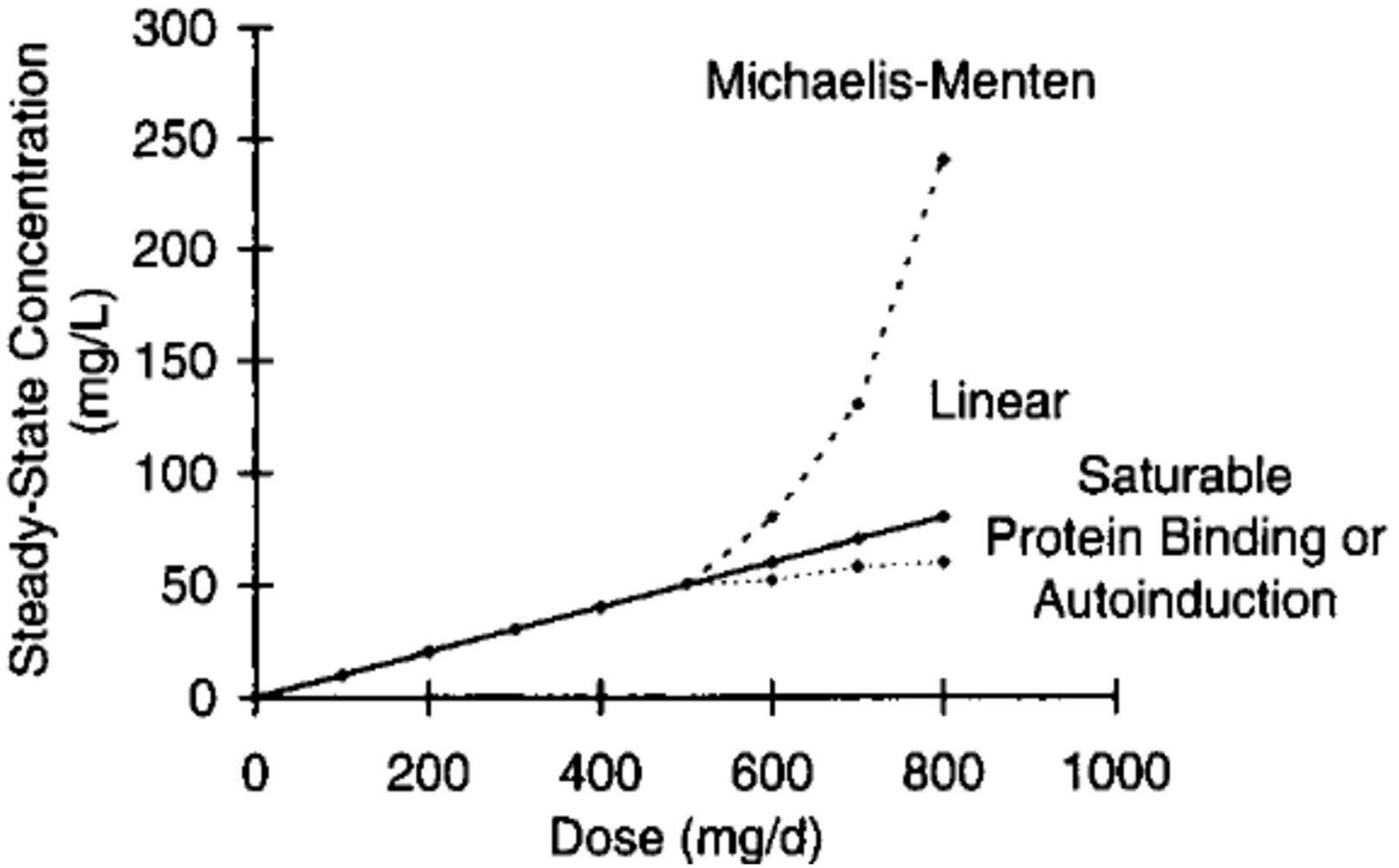
- The nonlinear pharmacokinetic is either:

1. When steady-state concentrations increase **more than expected** after a dosage increase.

   The most likely explanation is that the processes removing the drug from the body have become **saturated.**

   This phenomenon is known as saturable or **Michaelis-Menten** pharmacokinetics.

   Examples: phenytoin and salicylic acid


Steady-State Concentration (mg/L)
300
250
200
150
100
50
0
Michaelis-Menten
Linear
Saturable Protein Binding or Autoinduction
0
200
400
600
800
1000
Dose (mg/d)

LINEAR VERSUS NONLINEAR PHARMACOKINETICS

2. When steady-state concentrations **increase less than expected** after a dosage increase, there are two typical explanations.

a) Some drugs saturate plasma protein binding sites so that as the dosage is increased steady-state serum concentrations increase less than expected.

such as valproic acid.

b) Other drugs increase their own rate of metabolism from the body as dose is increased so steady-state serum concentrations increase less than anticipated. This process is known as autoinduction of drug metabolism.

such as carbamazepine

Clearance

- the volume of serum or blood completely cleared of the drug per unit time.

- Clearance (Cl) is the most important pharmacokinetic parameter because it determines the maintenance dose (MD) that is required to obtain a given steady-state serum concentration (Css):

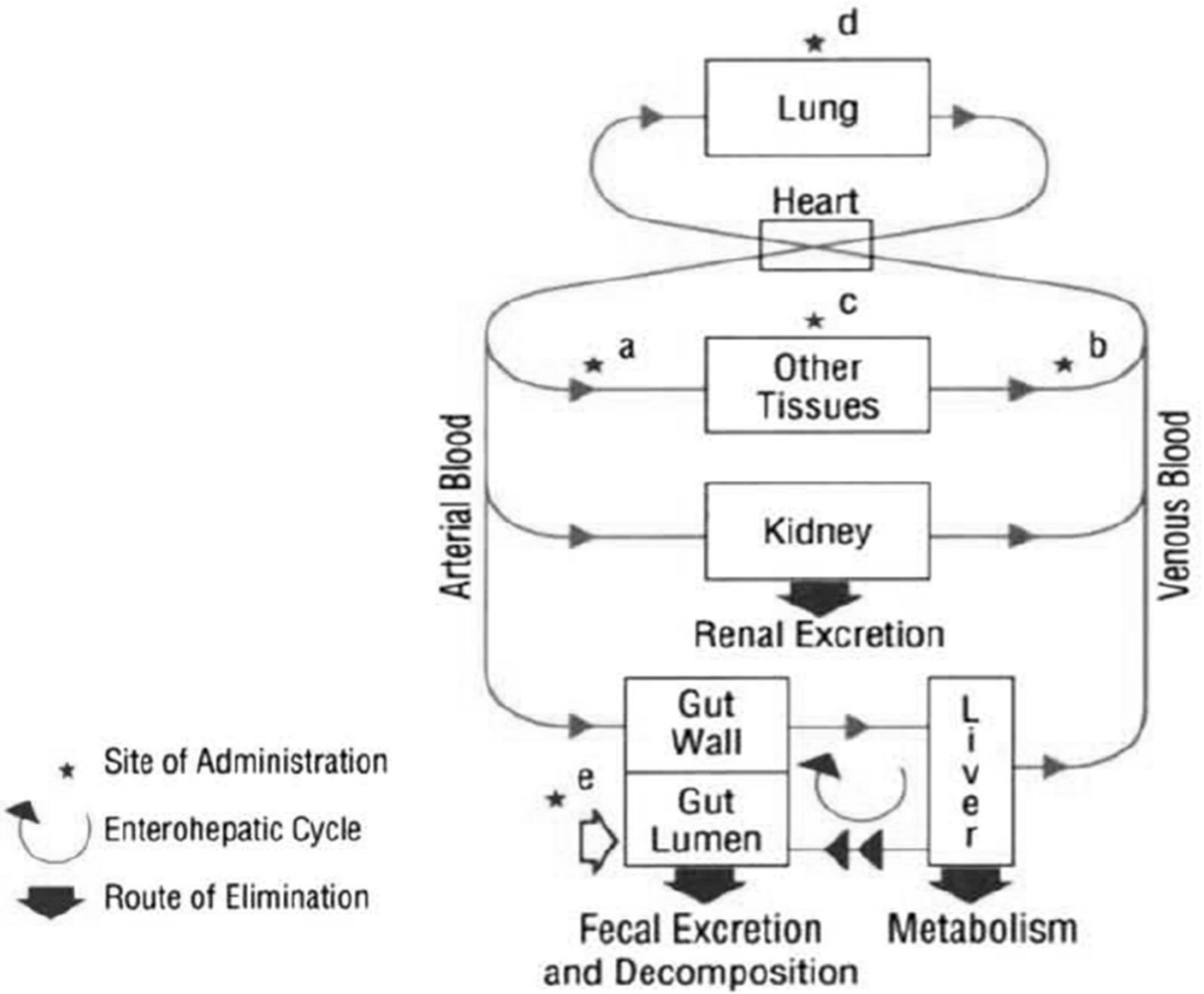
$$\mathbf{MD = Css \cdot Cl.}$$

- The dimension of clearance is volume per unit time, such as L/h or mL/min.

- The ***therapeutic range*** should be considered as an initial guideline for drug concentrations in a specific patient; drug dose and steady-state concentrations should then be titrated and individualized based on therapeutic response.

Clearance

- The **liver** is most often the organ responsible for drug metabolism while in most cases the kidney is responsible for drug elimination. The gastrointestinal wall, lung, and kidney can also metabolize some drugs, and some medications are eliminated unchanged in the bile. (examples)
- The majority of drug metabolism is catalyzed by enzymes contained in the microsomes of hepatocytes known as the **cytochrome P-450 (CYP) enzyme system**. This family of enzymes is very important to understand because specific enzymes are responsible for the metabolism of each drug entity.


d
Lung
Heart
c
a
Other Tissues
b
Arterial Blood
Venous Blood
Kidney
Renal Excretion
Gut Wall
Gut Lumen
e
Liver
Fecal Excretion and Decomposition
Metabolism
Site of Administration
Enterohepatic Cycle
Route of Elimination

CYTOCHROME P-450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	Acetaminophen Caffeine Clomipramine Imipramine Nortriptyline Ondansetron Phenacetin Tacrine	Atazanavir Cimetidine Ciprofloxacin Enoxacin Erythromycin Fluvoxamine Interferon Mexiletine	Barbiturates Carbamazepine Charcoal-broiled meat Omeprazole Phenobarbital Primidone Rifampin Tobacco/Marijuana
Smoke	Theophylline (R)-Warfarin Zileuton	Tacrine Zileuton	
CYP2B6 PM: ~4% Caucasians	Bupropion Cyclophosphamide Ifosfamide	Thiotepa Ticlopidine	Phenobarbital Rifampin
CYP2C9 PM: ~7% Caucasians	Candesartan Celecoxib Chlorpropamide Diclofenac Dronabinol Glipizide Glyburide Ibuprofen Losartan Naproxen Phenytoin Piroxicam Sulfamethoxazole Tolbutamide Torsemide Valsartan (S)-Warfarin	Amiodarone Atazanavir Clopidogrel Cotrimoxazole Delavirdine Disulfiram Efavirenz Fluconazole Fluvastatin Fluvoxamine Imatinib Isoniazid Leflunomide Metronidazole Miconazole Sulfamethoxazone Sulfinpyrazole Voriconazole Zafirlukast	Aminoglutethimide Barbiturates Carbamazepine Phenobarbital Phenytoin Primidone Rifampin
CYP2C19 PM: ~4% Caucasians ~20% Japanese & Chinese	Amitriptyline Carisoprodol Citalopram Clomipramine Desmethyldiazepam Diazepam Hexobarbital Imipramine Lansoprazole (S)-Mephenytoin Nelfinavir Omeprazole Pantoprazole Phenytoin	Chloramphenicol Cimetidine Clopidogrel Delavirdine Efavirenz Felbamate Fluconazole Felbamate Fluoxetine Fluvoxamine Isoniazid Modafinil Omeprazole Oxcarbazepine	Barbiturates Phenytoin Rifampin St. John's Wort

- ***<u>Volume of distribution</u>***
- Is an important pharmacokinetic parameter because it determines the loading dose (LD) that is required to achieve a particular steady-state drug concentration immediately after the dose is administered:

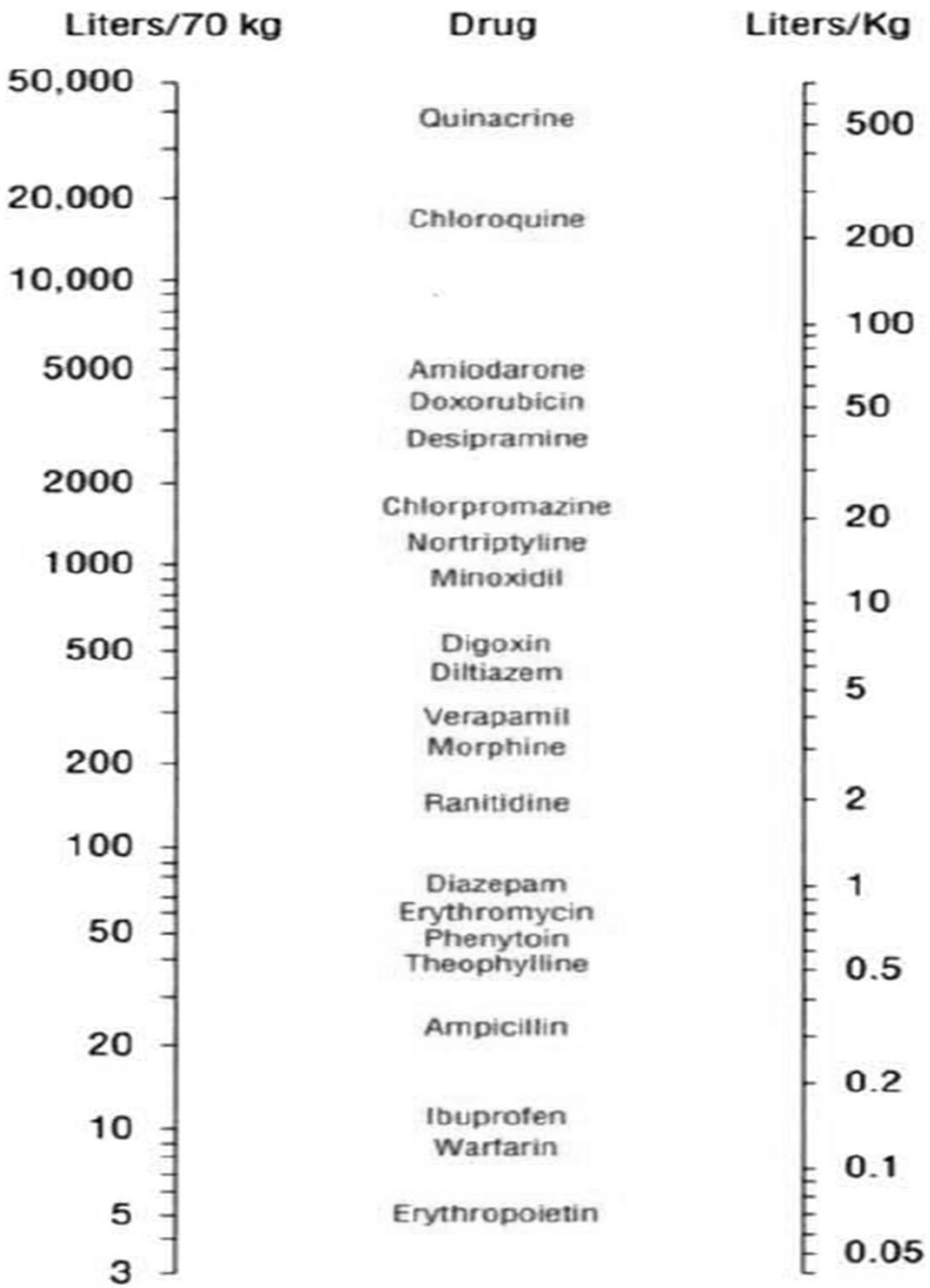
$$\mathbf{LD = Css * V}$$

- The dimension of volume of distribution is in volume units, such as L or mL.

- ***<u>Volume of distribution</u>***

- The volume of distribution can be **very small** if the drug is primarily contained in the blood (warfarin V = 5–7 L), or **very large** if the drug distributes widely in the body and is mostly bound to bodily tissues (digoxin V = 500 L).

Volume of Distribution



- ***Volume of distribution***

Factors affecting volume of distribution:

1. ***Physiological factors:***

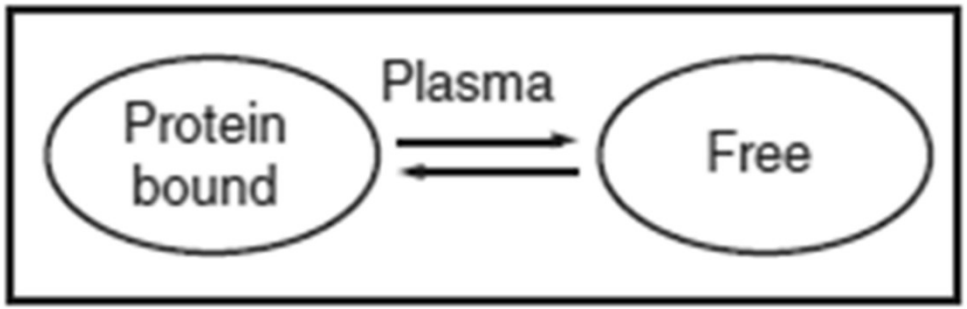
- The **actual volume of blood** (V_B) and **size** (measured as a volume) of the various tissues and organs of the body (V_T).

- Therefore, a larger person, such as a 160-kg football player, would be expected to have a larger volume of distribution for a drug than a smaller person, such as a 40-kg grandmother.

2. **How the drug binds in the blood or serum compared to the binding in tissues**

- For example, the reason warfarin has such a ***small volume of distribution*** is that it is ***highly bound to serum albumin*** so that the free fraction of drug in the blood (f_B) is very small.
- Digoxin has a very large volume of distribution because it is very highly bound to tissues (primarily muscle) so that the free fraction of drug in the tissues (f_T; f_T = unbound drug concentration in the tissue/total tissue drug concentration) is very small.

$$V = V_B + \frac{f_B}{f_T} V_T$$



- An example is how the ***volume of distribution*** changes when ***plasma protein binding*** drug interactions occur.
- If a drug that is highly bound to plasma proteins is given to a patient, and then a ***second drug*** that is also highly bound to the same plasma protein is given concurrently, the second drug will compete for plasma protein binding sites and displace the first drug from the protein. In this case, the free fraction in the serum of the first drug will increase ($\uparrow f_B$), resulting in an increased volume of distribution:

$$\uparrow V = V_B + (\uparrow f_B / f_T) V_T.$$

- ***<u>Elimination rate constant (k_e)</u>***
- Masurement used to denote how quickly drug serum concentrations decline in a patient

- The dimension for the elimination rate constant is reciprocal time ($hour^{-1}$, $minute^{-1}$, day^{-1}, etc.)

- The half-life and elimination rate constant are related to each other by the following equation, so it is easy to compute one once the other is known:

$$t_{1/2} = 0.693/k_e.$$

- The elimination rate constant can also be measured graphically by computing the slope of the log concentration versus time graph during the elimination phase: using $\log_{10}$:

$$k_e/2.303 = -(\log C_1 - \log C_2)/(t_1 - t_2)$$

- or, using natural logarithms:

$$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2).$$

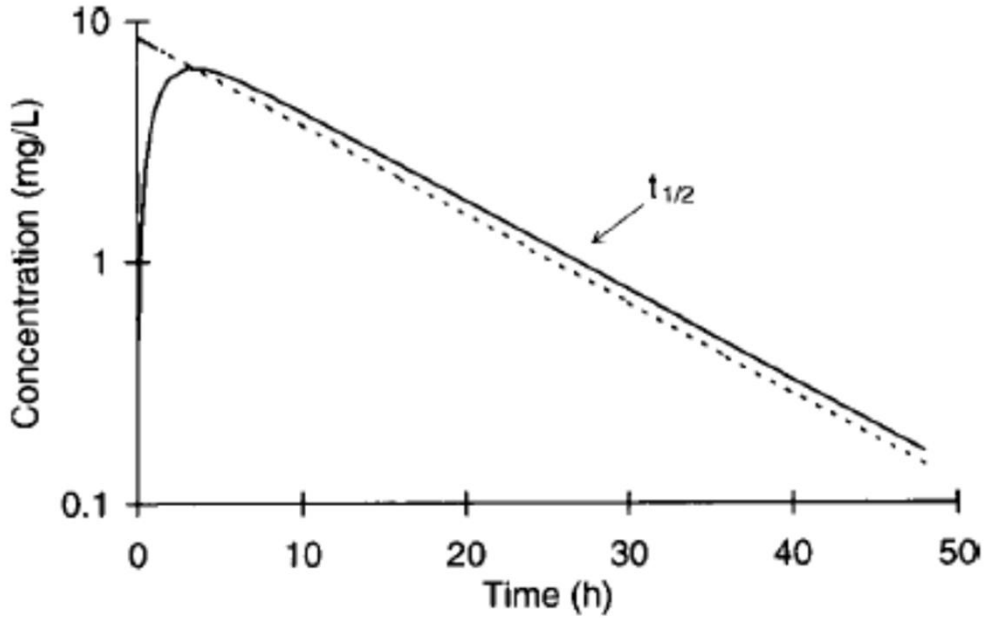


FIGURE 1-8 Serum concentration/time profile for a patient receiving 300 mg of theophylline orally (*solid line*) and by intravenous bolus (*dashed line*). If this data is plotted on semilogarithmic axes, serum concentrations decline in a straight line in both cases. When the drug is given orally, serum concentrations initially increase while the drug is being absorbed and decline after drug absorption is complete. This same data set is plotted in Figure 1-7 on rectilinear axes.

- The half-life is important because:

1. It determines the time to steady state during the continuous dosing of a drug and the dosage interval.
2. The dosage interval for a drug is also determined by the half-life of the medication. During drug development, it is very common to use the drug half-life as the initial dosage interval for the new drug compound until the pharmacodynamics of the agent can be determined.

-

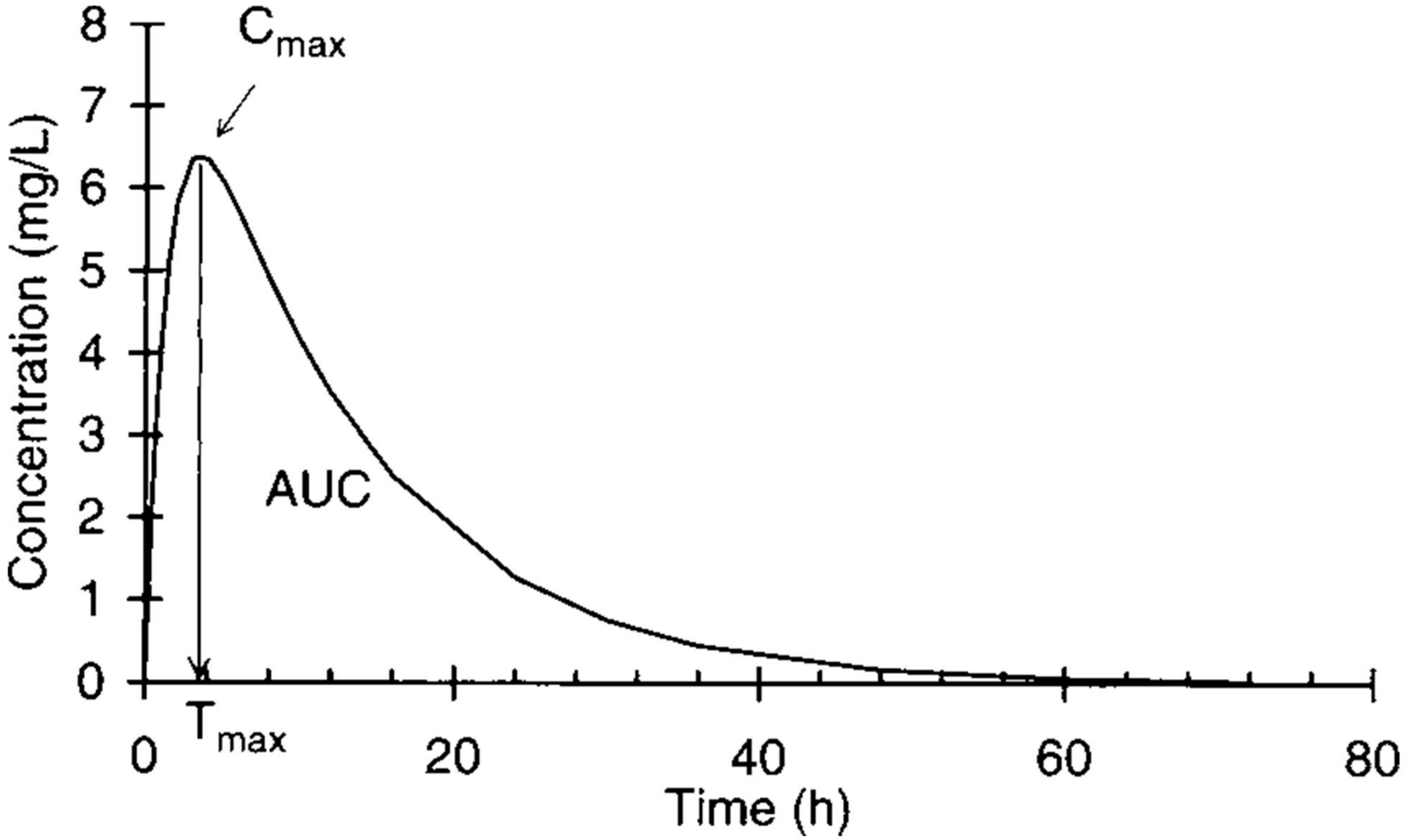
- **Note:**
- The ***half-life*** and ***elimination rate constant*** are known as ***dependent parameters*** because their values depend on the clearance (Cl) and volume of distribution (V) of the agent:

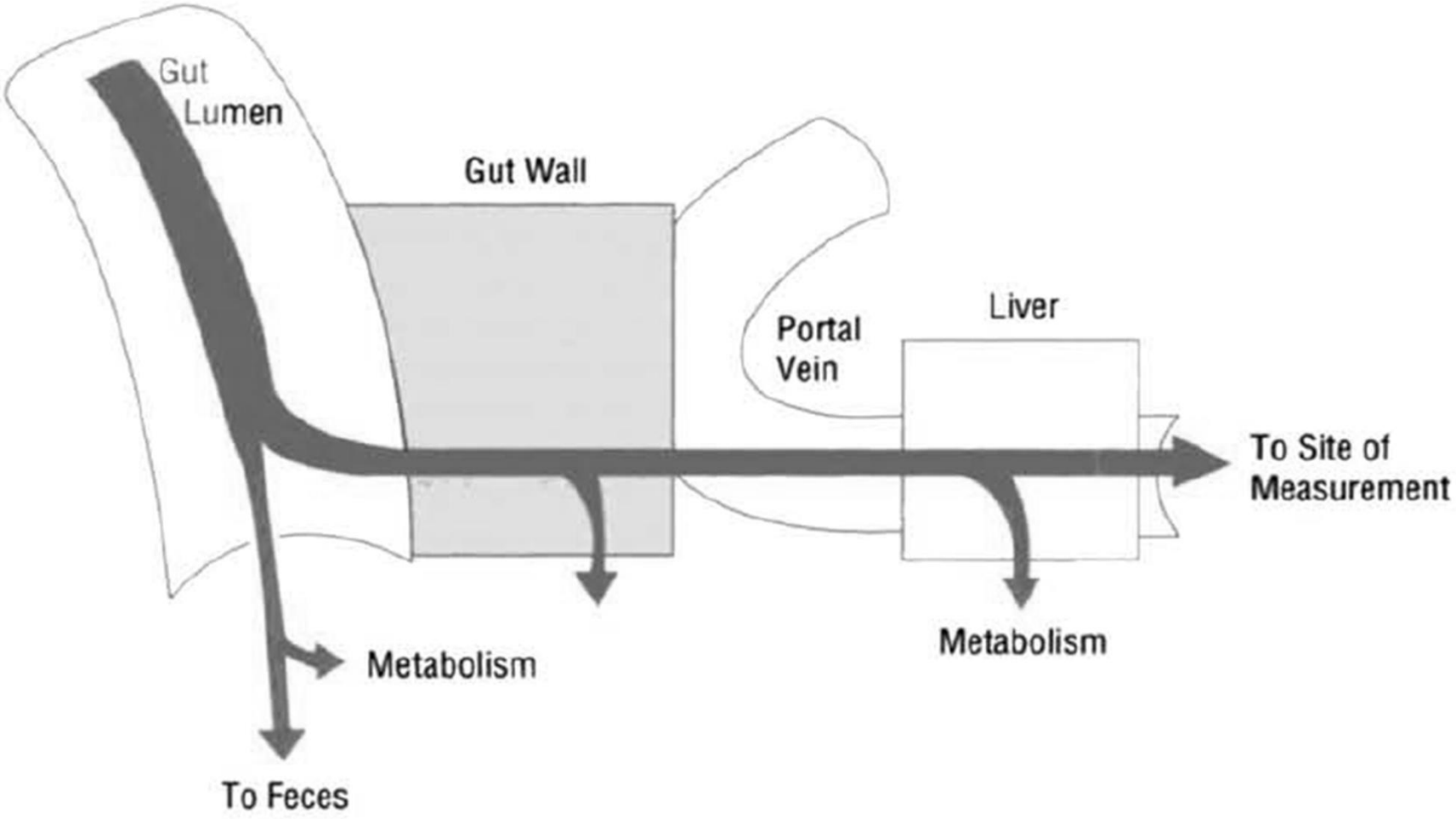
$$t_{1/2} = (0.693 \cdot V)/Cl,\ k_e = Cl/V$$

- Because the values for ***clearance*** and ***volume of distribution*** depend solely on physiological parameters and can vary independently of each other, they are known as ***independent parameters***.

- ***<u>Bioavailability (F)</u>***
- The fraction of the administered dose that is delivered to the systemic circulation.
- For drugs that follow linear pharmacokinetics, bioavailability is measured by comparing serum concentrations achieved after extravascular and intravenous doses in the same individual.

$$F = AUC_{PO}/AUC_{IV}.$$


C_{max}
AUC
T_{max}
Concentration (mg/L)
Time (h)
0
1
2
3
4
5
6
7
8
0
20
40
60
80


Gut
Lumen
Gut Wall
Portal
Vein
Liver
To Site of
Measurement
Metabolism
Metabolism
To Feces

- If it is not possible to administer the same dose intravenously and extravascularly because ***poor absorption or presystemic metabolism*** yields serum concentrations that are too low to measure, the bioavailability calculation can be corrected to allow for different size doses for the different routes of administration:

$$F = (AUC_{PO}/AUC_{IV})(D_{IV}/D_{PO})$$

- When a drug is administered extravascularly, the entire dose may not enter the systemic circulation. For example, an orally administered tablet may not completely dissolve so that part of the dose is eliminated in the stool, or a transdermal patch may not release the entire dose before it is removed from the skin.

- When medications are given orally, intramuscularly, subcutaneously, or by other extravascular routes, the drug must be absorbed across several biologic membranes before entering the vascular system.

- Drug serum concentrations rise while the drug is being absorbed into the bloodstream, reach a ***maximum concentration (Cmax)*** when the ***rate of drug absorption*** equals the ***rate of drug elimination***, and eventually decrease according to the half-life of the drug.

- If a medication is given *orally*, drug molecules must pass through several organs before entering the systemic circulation.

a) During absorption from the gastrointestinal tract, the drug molecules will encounter:

1. ***enzymes*** that may metabolize the agent (primarily CYP3A4 substrates since ~90% of cytochrome P-450 contained in the gut wall is CYP3A4) or,
2. ***pump*** the drug back into the lumen and prevent absorption from taking place (primarily P-glycoprotein substrates).

b) Once drug molecules are absorbed from the gastrointestinal tract, they enter the portal vein. If the drug is ***hepatically metabolized***, part of the drug may be metabolized by the liver even though the majority of the drug was absorbed from the gastrointestinal tract. Drugs that are substrates for CYP3A4 and CYP2D6 are particularly susceptible to presystemic metabolism by the liver.

b) Blood leaving the liver via the hepatic vein enters the inferior vena cava, and will eventually be pumped through the lung by the right side of the heart before entering the left side of the heart and being pumped into the arterial system.

b) To a lesser extent, some drugs are metabolized by the lung or irreversibly eliminated into expired air.

Note:

- The loss of drug from these combined processes is known as ***presystemic metabolism*** or the ***first-pass effect***.
- For example, the oral bioavailability of both propranolol (a substrate for CYP2D6 and CYP2C19) and verapamil (a substrate for CYP3A4 and P-glycoprotein) is about ~10% even though the oral dosage forms for each agent release 100% of the drug into the gastrointestinal tract.

- ***<u>Bioequivalence</u>***
- A desirable attribute of a generic drug dosage form is that it produce the same serum concentration/time profile as its brand name counterpart. When generic drugs meet this requirement, then generic drug product is said to be bioequivalent to the brand name drug.
- In theory, it should be possible to substitute a bioequivalent generic drug dosage form for a brand name product without a change in steady-state drug serum concentrations or therapeutic efficacy.

- This is because the drug company manufacturing the generic drug ***does not have to prove that the drug is safe and effective*** since those studies were done by the pharmaceutical company producing the brand name drug.

- Bioequivalence is achieved when the serum ***concentration /time curve*** for the generic and brand name drug dosage forms are deemed indistinguishable from each other using statistical tests.

- Concentration/time curves are superimposable when the area under the total serum concentration/time curve ***(AUC)***, maximum concentration ***(Cmax)***, and time that the maximum concentration occurs ***(Tmax)*** are identical within statistical limits.

- In order to achieve the Food and Drug Administration's (FDA) definition of oral bioequivalence and be awarded an "AB" rating in the FDA publication ***Approved Drug Products with Therapeutic Equivalence Evaluations*** (also known as The ***Orange Book***):

$$F_{relative} = AUC_{generic}/AUC_{brand}.$$

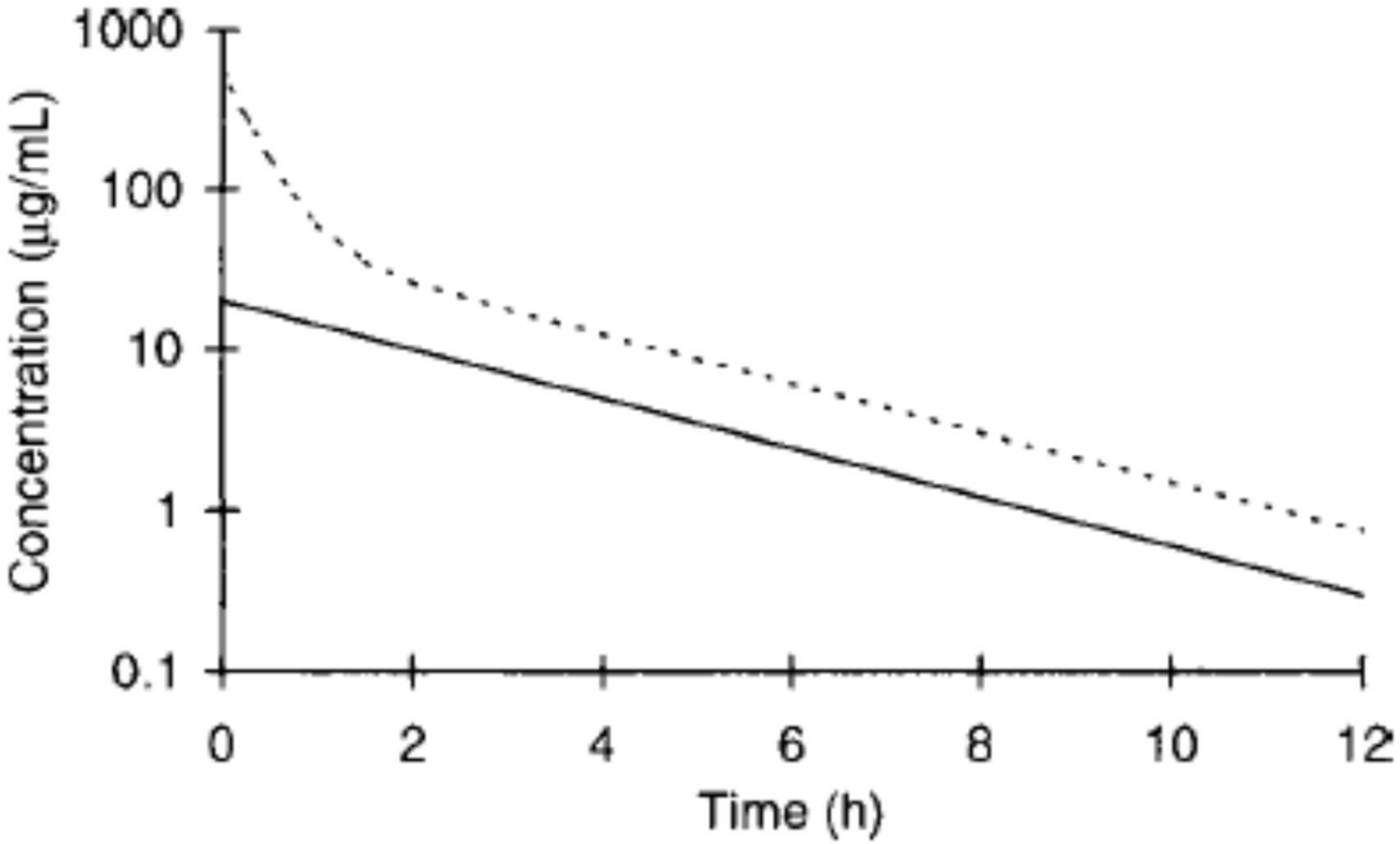
Clinical Pharmacokinetic Equations and Calculations

Clinical Pharmacokinetic Equations and Calculations

- *One-compartment model equations for linear pharmacokinetics*
- ***Intravenous Bolus Equation***
- When a drug is given as an intravenous bolus and the drug distributes from the blood into the tissues quickly, the serum concentrations often decline in a straight line when plotted on semilogarithmic axes.

$$C = (D/V)e^{-k_e t}$$

- Most drugs given intravenously cannot be given as an actual intravenous bolus because of ***side effects*** related to rapid injection.
- A short infusion of 5–30 minutes can avoid these types of adverse effects, and if the intravenous infusion time is very short compared to the half-life of the drug so that a large amount of drug is not eliminated during the infusion time, intravenous bolus equations can still be used.


1000
100
10
1
0.1
Concentration (µg/mL)
0
2
4
6
8
10
12
Time (h)

- Pharmacokinetic parameters for patients can also be computed for use in the equations. If two or more serum concentrations are obtained after an intravenous bolus dose, the ***elimination rate constant***, ***half-life*** and ***volume of distribution*** can be calculated.

- The elimination rate constant can be computed using the following equation: $k_e = 0.693/t_{1/2}$

$$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2),$$

where t1 and C1 are the first time/concentration pair and t2 and C2 are the second time/concentration pair

- The volume of distribution can be calculated by dividing the dose by the serum concentration at time = 0.

$$V = D/C_0$$

- For example, a patient is given a theophylline loading dose of 400 mg intravenously over 20 minutes. Because the patient received theophylline during previous hospitalizations, it is known that the volume of distribution is 30 L, the elimination rate constant equals 0.116 h–1, and the half-life (t1/2) is 6 hours
- (t1/2 = 0.693/ke = 0.693/0.115 h–1 = 6 h).
- compute the expected theophylline concentration 4 hours after the dose was given,
- a one-compartment model intravenous bolus equation can be used:
- $\mathbf{C = (D/V)e^{-ket}}$
- = (400 mg/30 L)e–(0.115 h–1)(4 h) = 8.4 mg/L.

- ***Continuous and Intermittent Intravenous Infusion Equations***
- Some drugs are administered using a continuous intravenous infusion, and if the infusion is discontinued the serum concentration/time profile decreases in a straight line when graphed on a semilogarithmic axes.

- one compartment model intravenous infusion equation can be used to compute concentrations (C) while the infusion is running:

$$C = (k_0/Cl)(1 - e^{-k_e t}) = [k_0/(k_e V)](1 - e^{-k_e t})$$

- where k_o is the drug infusion rate

- If the infusion is allowed to continue until steady state is achieved, the steady-state concentration (Css) can be calculated easily:

$$Css = k_0 / Cl = k_0 / (k_e V).$$

- An antibiotic has a volume of distribution of 10 L and a *k* of 0.2 hr^{-1}. A steady-state plasma concentration of 10 µg/mL is desired. What is the infusion rate needed to maintain this concentration.

$$Css = k_0 / Cl$$

$$= k_0 / (k_e V)$$

- If the infusion is stopped, postinfusion serum concentrations ($C_{postinfusion}$) can be computed by calculating the concentration when the infusion ended (C_{end}) using the appropriate equation in the preceding paragraph, and the following equation:

$$C_{postinfusion} = C_{end} e^{-k_e t_{postinfusion}},$$

$$C = (k_0/Cl)(1 - e^{-k_e t})$$

$$Css = k_0 / Cl$$

$$C_{postinfusion} = C_{end} e^{-k_e t_{postinfusion}}.$$

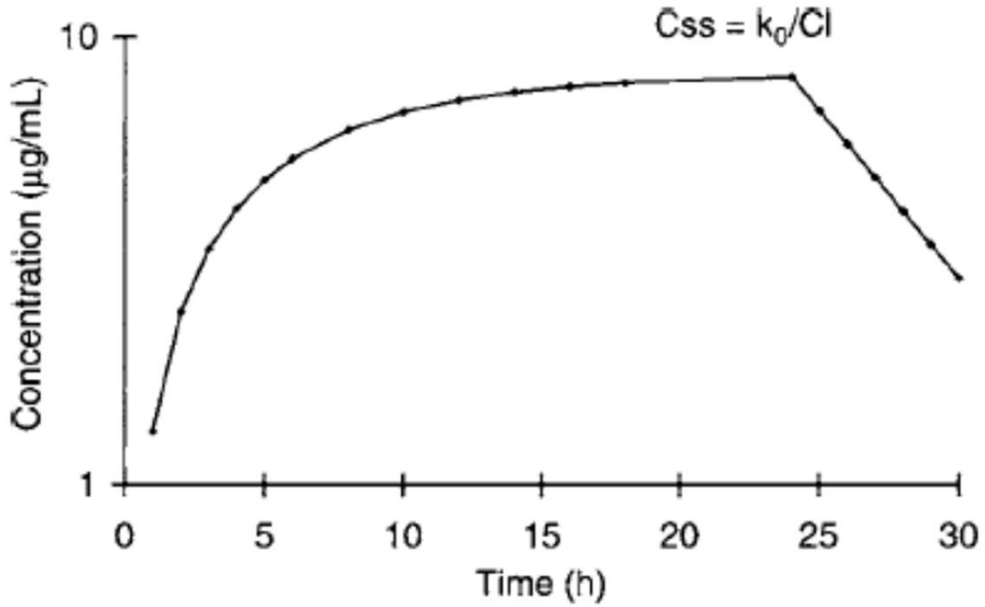


FIGURE 2-5 If a drug is given as a continuous intravenous infusion, serum concentrations increase until a steady-state concentration *(Css)* is achieved in 5–7 half-lives. The steady-state concentration is determined by the quotient of the infusion rate *(k_0)* and drug clearance *(Cl):* Css = k_0/Cl. When the infusion is discontinued, serum concentrations decline in a straight line if the graph is plotted on semilogarithmic axes. When using $\log_{10}$ graph paper, the elimination rate constant (k_e) can be computed using the following formula: slope = $-k_e/2.303$.

- Pharmacokinetic parameters for patients can also be computed for use in the equations. If two or more serum concentrations are obtained after an intravenous bolus dose, the ***elimination rate constant***, ***half-life*** and ***volume of distribution*** can be calculated.

- The volume of distribution (V) can be computed using the following equation:
-

$$V = \frac{k_0(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{predose} e^{-k_e t'})]}$$

- t' = infusion time

- **Extravascular Equation**
- When a drug is administered extravascularly (e.g., orally, intramuscularly, subcutaneously, transdermally, etc.), absorption into the systemic vascular system must take place .

- one compartment model extravascular equation can be used to describe the serum concentration/time curve:

$$C = \frac{Fk_aD}{V(k_a - k_e)}(e^{-k_et} - e^{-k_at})$$

- **ka** is the absorption rate constant,

- Since the absorption rate constant is hard to measure in patients, it is also desirable to avoid drawing drug serum concentrations during the absorption phase in clinical situations. When only postabsorption, postdistribution serum concentrations are obtained for a drug that is administered extravascularly, the equation simplifies to:

$$C = [(FD)/V]e^{-k_e t}$$

- This approach works very well when the extravascular dose is rapidly absorbed and not a sustained- or extended-release dosage form.

The hybrid volume of distribution/bioavailability (V/F) parameter:

$$V/F = D/C_0 ;$$

The extrapolated serum concentration at time = zero (C0) is calculated using a variation of the intravenous bolus equation:

$$C_0 = C/e^{-k_e t},$$

- ***<u>For example,</u>*** a patient is given an oral dose of valproic acid 750 mg as capsules. Six and twenty-four hours after the dose, the valproic acid serum concentrations are 51.9 mg/L and 21.3 mg/L, respectively. Calculate the The hybrid volume of distribution/bioavailability constant (V/F).
-

$$V/F = D/C_0 :$$

$$C_0 = C/e^{-k_e t},$$

$$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$$

- ***Multiple-Dose and Steady-State Equations:***
- In most cases, medications are administered to patients as ***multiple doses***, and drug serum concentrations for therapeutic drug monitoring are not obtained until steady state is achieved.

- For these reasons, multiple dose equations that reflect steady-state conditions are usually more useful in clinical settings than single dose equations.

- it is simple to convert single dose compartment model equations to their multiple dose and steady-state counterparts.

- ***For intravenous bolus equation is:***

$$C = (D/V)e^{-k_e t}$$

- the multiple dosing factor at steady state is:

$$C = (D/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$$

- ***For extravascular administered drugs:***

$$C = [(FD)/V]e^{-k_e t}$$

- the multiple dosing factor at steady state is:

$$C = (FD/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$$

- ***Intermittent Intravenous Infusion Equations***

$$C = [k_0/(k_e V)][(1 - e^{-k_e t'})/(1 - e^{-k_e \tau})]$$

- ***Average Steady-State Concentration Equation***
- A very useful and easy equation can be used to compute the average steady-state concentration (Css) of a drug:

$$Css = [F(D/\tau)]/Cl$$

- **Example:** A patient is administered **250 µg** of digoxin tablets daily for heart failure until steady state. The pharmacokinetic constants for digoxin in the patient are: F = 0.7, Cl = 120 L/d.
- Calculate the Css?

$$Css = [F(D/\tau)]/Cl$$

- ***Designing individualized dosage regimens using one compartment model equations:***
- The goal of therapeutic drug monitoring is to customize medication doses that provide the optimal drug efficacy without adverse reactions.
- One compartment model equations can be used to compute initial drug doses employing population pharmacokinetic parameters that estimate the constants for a patient.
- The patient's own, unique pharmacokinetic parameters can be computed once doses have been administered and drug serum concentrations measured. At that time, individualized dosage regimens at steady state can be designed for a patient.

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR k_0), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$ $D = Css_{max}\, V(1 - e^{-k_e\tau})$ $LD = Css_{max}\, V$
Continuous intravenous infusion	$k_0 = Css\, Cl = Css\, k_e V$ $LD = CssV$
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t'$ $k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau})/(1 - e^{-k_e t'})]$ $LD = k_0/(1 - e^{-k_e\tau})$
Extravascular (postabsorption, postdistribution)	$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max}$ $D = [(Css_{max} V)/F][(1 - e^{-k_e\tau})/e^{-k_e T_{max}}]$ $LD = (Css_{max} V)/F$
Average steady-state concentration (any route of administration)	$D = (Css\, Cl\, \tau)/F = (Css\, k_e V\tau)/F$ $LD = (CssV)/F$

Symbol key: Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k_e is the elimination rate constant, V is the volume of distribution, Css is the steady-state concentration, k_0 is the continuous infusion rate, t' is the infusion time, T_{max} is the time that Css_{max} occurs, F is the bioavailability fraction.

- ***Design an individualized dosage regimens using one compartment model equations for the following:***

- ***<u>Example 1:</u>*** a patient that needs to be treated for complex partial seizures with intravenous phenobarbital. An initial dosage regimen is designed using population pharmacokinetic parameters (ke = 0.139 d–1, V = 50 L) to achieve maximum (Cssmax) and minimum (Cssmin) steady-state concentrations equal to 30 mg/L and 25 mg/L, respectively.

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$$

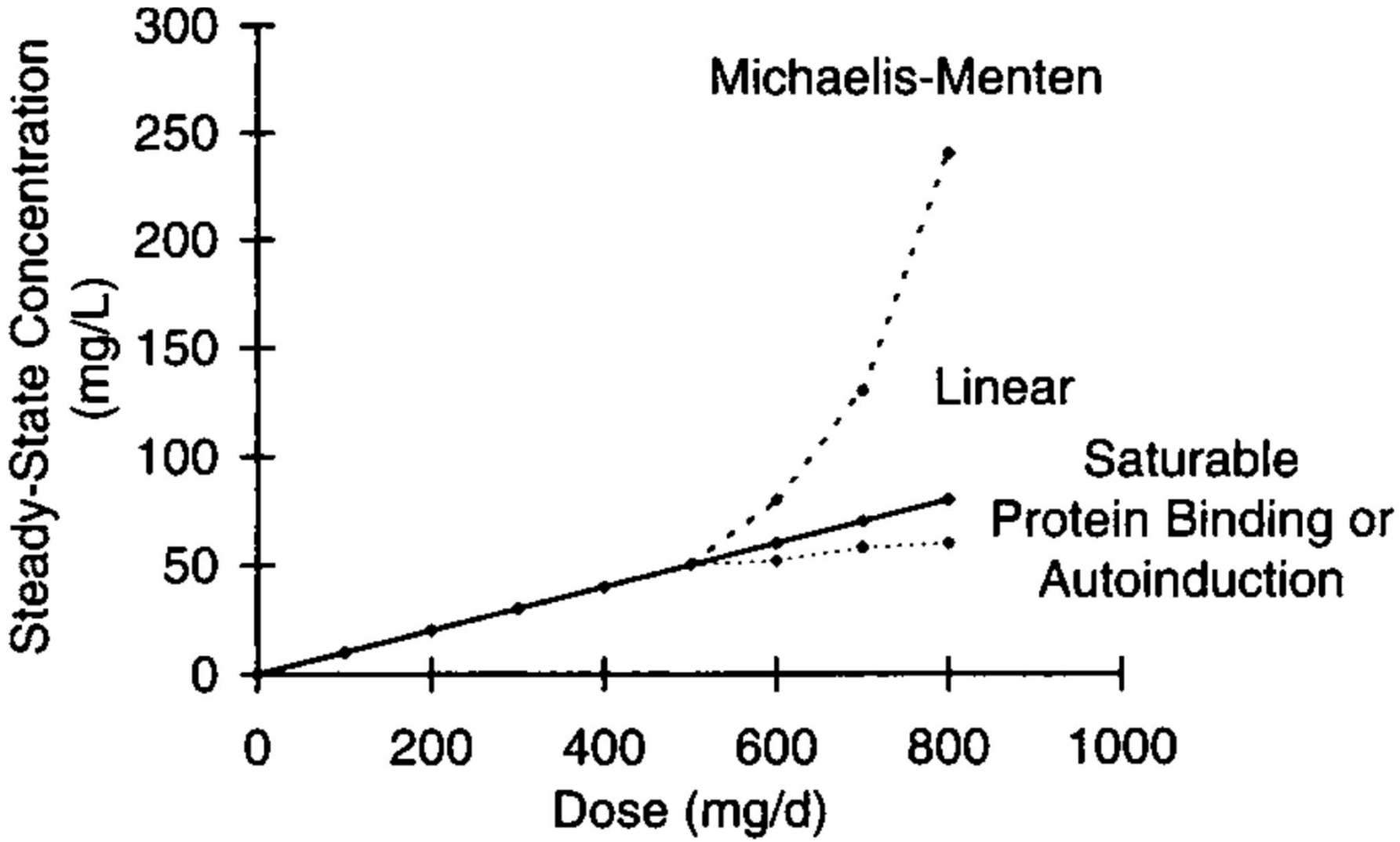
$$D = Css_{max}\, V(1 - e^{-k_e \tau})$$

- **Michaelis-Menten(or saturable)pharmacokinetics:**

- Drugs that are metabolized by the cytochrome P-450 enzymes and other enzyme systems may undergo Michaelis-Menten or saturable pharmacokinetics.

- This is the type of nonlinear pharmacokinetics that occurs when the number of drug molecules or saturates the enzyme's ability to metabolize the drug.

- When this occurs, steady-state drug serum concentrations increase in a disproportionate manner after a dosage increase.


Steady-State Concentration (mg/L)
300
250
200
150
100
50
0
Michaelis-Menten
Linear
Saturable Protein Binding or Autoinduction
0
200
400
600
800
1000
Dose (mg/d)

- In this case the **rate of drug removal** is described by the classic Michaelis-Menten relationship that is used for all enzyme systems:

$$\text{rate of metabolism} = (V_{max} \cdot C)/(Km + C)$$

Where:

Vmax is the maximum rate of metabolism,

C is the substrate concentration,

Km is the substrate concentration where the rate of metabolism = Vmax/2.

- The clinical implication of Michaelis-Menten pharmacokinetics is that the **clearance** of a drug is not a constant as it is with linear pharmacokinetics, but is concentration- or dose-dependent.

- As the dose or concentration increases, the clearance rate (Cl) decreases as the enzyme approaches saturable conditions:

$$Cl = V_{max}/(Km + C)$$

- Also, **half-life** (t1/2) is still related to clearance and volume of distribution using the same equation as for linear pharmacokinetics:

$$t_{1/2} = (0.693 \cdot V)/Cl.$$

- As doses or concentrations increase for a drug that follows Michaelis-Menten pharmacokinetics, clearance decreases and half-life becomes longer for the drug:

$$\uparrow t_{1/2} = (0.693 \cdot V)/\downarrow Cl.$$

- The clinical implication of this finding is that the time to steady state (3–5 t1/2) is longer as the dose or concentration is increased for a drug that follows saturable pharmacokinetics.
-

- The **volume of distribution** (V) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (V_B) and tissues (V_T) as well as the unbound concentration of drug in the blood (f_B) and tissues (f_T):

$$V = V_B + \frac{f_B}{f_T} V_T$$

- **Under steady-state conditions the rate of drug administration equals the rate of drug removal.**

- Therefore, for a drug that is solely **removed** by metabolism via **one enzyme system**, the Michaelis-Menten equation can be used to compute the maintenance dose (MD) required to achieve a target steady-state serum concentration (Css):

$$MD = \frac{V_{max} \cdot Css}{Km + Css}$$

- **Clearance**
- The clearance for an organ, such as the liver or kidney, that metabolizes or eliminates drugs is **determined by :**

1. the blood flow to the organ
2. the ability of the organ to metabolize or eliminate the drug.

- **Extraction ratio** (ER), The ability of an organ to remove or extract the drug from the blood or serum, ER is computed by measuring the concentrations of the drug entering (Cin) and leaving (Cout) the organ:

$$ER = (C_{in} - C_{out})/C_{in}.$$

- The drug clearance for an organ is equal to the **blood flow to the organ** and **the extraction ratio** of the drug.

- Therefore, hepatic clearance (Cl_H) for a drug would be determined by taking the product of liver blood flow (Q_H) and the hepatic extraction ratio (ER_H) for the drug.

$$Cl_H = Q \cdot ER_H$$

- The ***total clearance*** for a drug is the sum of the individual clearances for each organ that extracts the medication.
- For example, the total clearance (Cl) for a drug that is metabolized by the liver and eliminated by the kidney is the sum of hepatic and renal clearance for the agent:

$$Cl = Cl_H + Cl_R$$

- **Hepatic Clearance:**
- There are three main factors affecting the hepatic clearance :

1. Intrinsic ability of the enzyme to metabolize a drug (intrinsic clearance)
2. The fraction of drug present in the bloodstream that is not bound to cells or proteins, such as albumin, α1-acid glycoprotein, or lipoproteins, but is present in the unbound, or “free,” state (unbound fraction of drug);
3. Liver blood flow

$$(Cl_H = \quad Q \cdot ER_H)$$

$$ER = \frac{f_u CL_{int}}{Q + f_u CL_{int}}$$

- Therefore:

$$CL_H = Q\left[\frac{f_u CL_{int}}{Q + f_u CL_{int}}\right]$$

- Two limiting cases arise

1. ***<u>when fuCLint << Q:</u>***

- For drugs with a **low** hepatic extraction ratio (extraction ratios <0.3), hepatic clearance is mainly a product of the free fraction of the drug in the blood or serum and intrinsic clearance.

$$CL_H = \cancel{Q}\left[\frac{f_u CL_{int}}{\cancel{Q} + \cancel{f_u CL_{int}}}\right]$$

- The equation can be simplified to:

$$CL_H = f_u CL_{int}$$

- In this case, **drug interactions** that displace drug molecules bound to proteins will increase the fraction of unbound drug in the blood (↑**fu**); more unbound drug molecules will be able to leave the vascular system (drug-protein complexes are far too big to exit the vascular system) and **enter hepatocytes** where the additional unbound drug will be metabolized and hepatic drug clearance will increase.

$$\uparrow CL_H = \uparrow f_u CL_{int}$$

- Additionally, drug interactions that **inhibit** or **induce** the cytochrome P-450 enzyme system (decreasing or increasing Cl′int, respectively) will change the hepatic clearance of the medication accordingly.

$$CL_H = f_u CL_{int}$$

- The hepatic clearance of drugs with low extraction ratios does not change much when liver blood flow decreases secondary to liver or cardiac disease.

- Examples of drugs with low hepatic extraction ratios are valproic acid, phenytoin, and warfarin.

2. ***When fuCLint >> Q***

- For drugs with **high** hepatic extraction ratios (extraction ratios >0.7), hepatic clearance is mainly a function of liver blood flow:

$$CL_H = Q\left[\frac{f_u CL_{int}}{Q + f_u CL_{int}}\right]$$

- the equation can be reduced to:

$$CL_H = Q$$

- The rate limiting step for drug metabolism in this case is **how much drug can be delivered to the liver** because the capacity to metabolize drug is very large.

- In this case, hepatic clearance is very **sensitive to changes in liver blood flow** due to congestive heart failure or liver disease.

- However, the hepatic clearance of drugs with high extraction ratios does not change much when **protein binding** displacement or **enzyme induction or inhibition** occurs due to drug interactions.
- Examples of drugs with high hepatic extraction ratios are lidocaine, morphine, and most tricyclic antidepressants

- **Renal Clearance**

The physiological determinants of renal clearance are :

1. Glomerular filtration rate (GFR)
2. The free fraction of drug in the blood or serum (f*u*)
3. The clearance of drug via renal tubular secretion (Clsec)
4. The fraction of drug reabsorbed in the kidney (FR)

$$Cl_R = [(f_u \cdot GFR) + Cl_{sec}](1 - FR)$$

Also:

$$CI_{R_{sec}} = Q\left[\frac{f_u CL_{int}}{Q + f_u CL_{int}}\right]$$

Therefore:

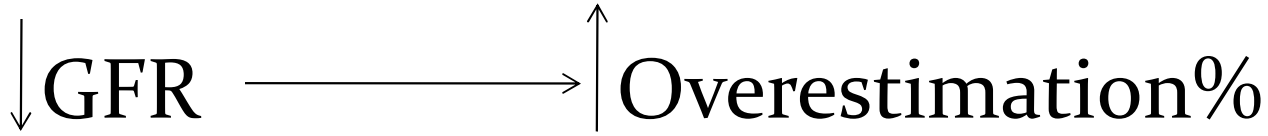
$$Cl_R = \left[(f_u \cdot GFR) + \frac{Q_R \cdot (f_u Cl'_{sec})}{Q_R + (f_u Cl'_{sec})}\right](1 - FR)$$

- **Clinical Assessment of Renal Function**
- In routine clinical practice, it is not practical to collect the urine samples that are needed to measure creatinine clearance directly. However, creatinine clearance in adult patients can be estimated either from a standard nomogram or from equations such as that proposed by Cockcroft and Gault:
- For men

$$CL_{CR}\,(\text{mL/min}) = \frac{(140 - \text{age})(\text{weight in kg})}{72(\text{serum creatinine in mg/dL})}$$

- For women multiply the equation by 85% (0.85).

- Creatinine clearance overestimates true glomerular filtration rate (GFR) as measured by inulin clearance because creatinine is secreted by the renal tubule in addition to being filtered at the glomerulus.
- The overestimation increases as GFR declines from 120 to 10 mL/min/1.73 m^2, ranging from a 10–15% overestimation with normal GFR to a 140% overestimation when GFR falls below 10 mL/min.



- Serum creatinine does not start to rise until GFR falls to 50 mL/min because increasing tubular secretion of creatinine offsets the decline in its glomerular filtration.

- The Cockcroft and Gault equation also overestimates glomerular filtration rate in patients with **low creatinine production** due to **cirrhosis** or **cachexia** and may be misleading in patients with rapidly changing renal function. In these situations, accurate estimates of creatinine clearance can only be obtained by actually **measuring urine creatinine excretion rate** in a carefully timed urine specimen.

- The Cockcroft and Gault equation cannot be used to estimate creatinine clearance in **pediatric** patients because muscle mass has not reached the adult proportion of body weight. Therefore, **Schwartz** and colleagues developed the following equation to predict creatinine clearance in these patients:

$$CL_{CR}\,(\text{mL/min/1.73 m}^2) = \frac{k \cdot L\ (\text{in cm})}{\text{plasma creatinine in mg/dL}}$$

- where L is body length and k varies by age and sex as follows:
- Neonates to children 1 year of age: $k = 0.45$
- Children 1–13 years of age: $k = 0.55$
- Females 13–20 years of age: $k = 0.57$
- Males 13–20 years of age: $k = 0.70$