NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

I am available to groups and individuals for pharmacology help and discussions by appointment.

lgolds01@nyit.edu

After completing the preparation materials, students should be able to:

1. Describe clearance, volume of distribution, bioavailability, elimination half-life, steady state, extraction ratio, and area under the curve using pharmacokinetic models.
2. Differentiate first-order and zero-order elimination kinetics and linear and non-linear processes in relation to drug concentration and effect.
3. Graph drug accumulation, half-life, and steady state for drugs with first-order elimination administered by continuous and intermittent dosing.
4. Calculate the loading dose and maintenance dose for an individual patient to achieve a target concentration within the therapeutic window when given specific pharmacokinetic parameters.
5. Identify pharmacokinetic variables that influence drug plasma concentrations and the criteria for therapeutic drug monitoring.

Preparation Materials (links are in the CPG and on the next slide)

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Required

- ScholarRx Bricks | Practice Questions

Highly relevant optional materials:

- Dr. Goldstein's Word handout | Lecture Videos | Guided Reading Questions
- Textbook resources with links are listed on the next slide

SUGGESTIONS:

- *Use the resources that work best for you.*
- *You do not need to study all of them.*
- *Work through the GUIDED READING QUESTIONS with pen/pencil and paper.*

Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.

- *Practice questions (not graded): Simple Recall and Case Vignettes*

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Links

Scholar Rx Bricks: (Required)

General Principles

Pharmacokinetics and Pharmacodynamics > Pharmacokinetics: Drug Concentration and Dosing
https://exchange.scholarrx.com/brick/drug-concentration-and-dosing

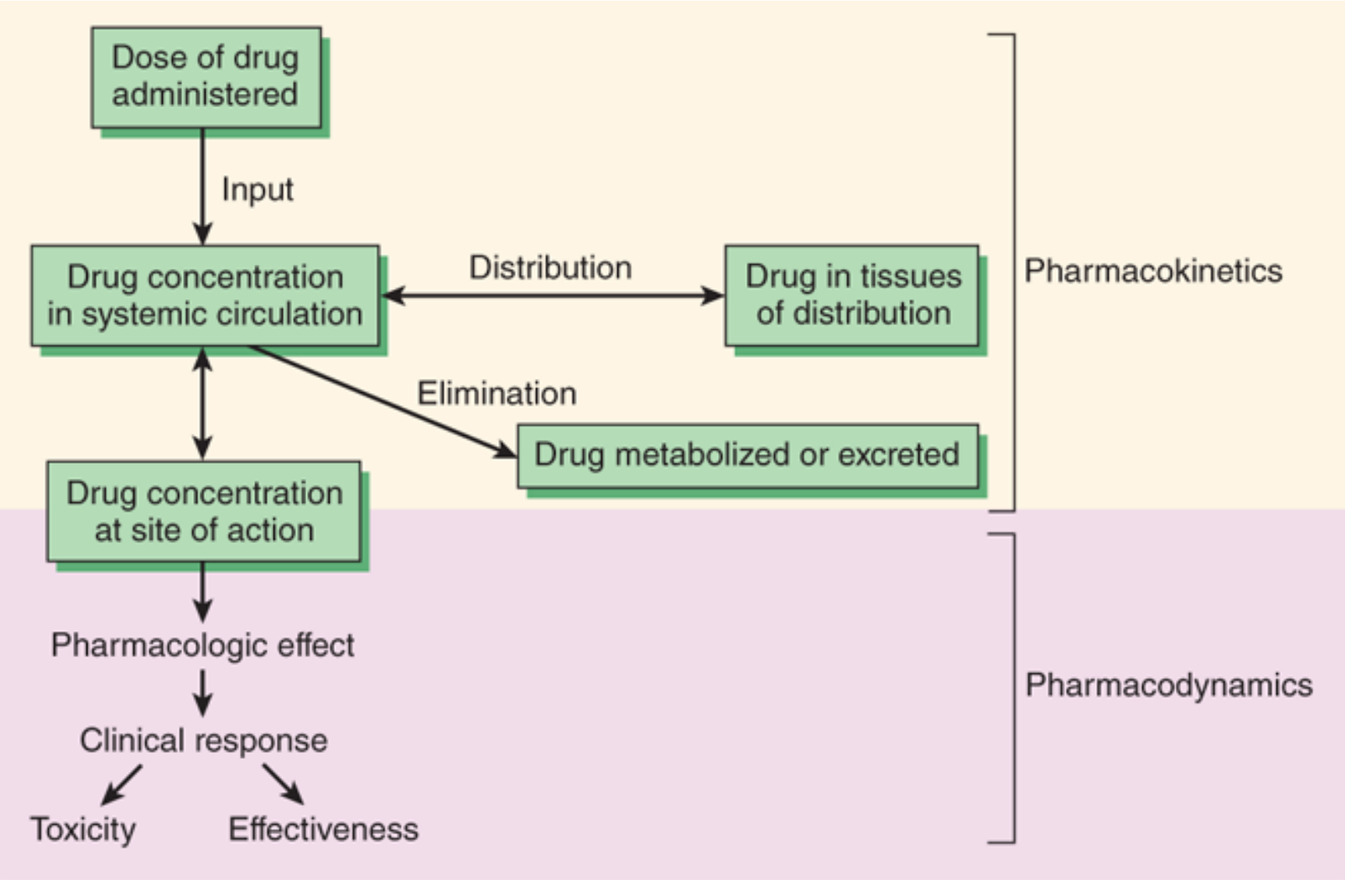
Enzymes as Drug Targets https://exchange.scholarrx.com/brick/enzymes-as-drug-targets

Katzung & Vanderah's Basic & Clinical Pharmacology, 16e, 2024; Chapter 3: Pharmacokinetics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281747069

THE REVIEW BOOKS HAVE PRACTICE QUESTIONS

Katzung & Trevor's Pharmacology: Examination and Board Review, 14e, 2024
Chapter 3: Pharmacokinetics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285589076

LWW Health Library Premium Basic Sciences; Lippincott Illustrated Reviews: Pharmacology, 8e, 2023: Chapter 1: Pharmacokinetics
https://premiumbasicsciences-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253324942&bookid=3222



A rational approach to achieving ***a desired beneficial effect with minimal adverse effects*** combines the principles of pharmacokinetics and pharmacodynamics to clarify the dose-effect relationship.

The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) components. Concentration provides the link between pharmacokinetics and pharmacodynamics and is the focus of the target concentration approach to rational dosing. The three primary processes of pharmacokinetics are input, distribution, and elimination.

Key points: What you need to know and understand Terms

Clearance (CL) CL = elimination rate / C_p Thus, Elimination rate = CL x C_p C_p: plasma concentration	The volume of blood from which the drug is removed per unit of time: it is the proportionality factor that relates the rate of elimination to drug concentration. Units: volume/time (mL/min or L/h)
Bioavailability (F)	The fraction of the administered dose of drug that reaches the systemic circulation Intravenous (IV) administration: F = 1 (100%)
Apparent Volume of distribution (V_d) V_d = Dose / C_p	The proportionality factor that relates the amount of drug in the body to the concentration of drug in the blood or plasma Units: Liters or Liters/kg body weight
Elimination half-life (t½) t½ = (0.693 x V_d) / CL Units: time	The time required for the amount of drug in the body or blood to fall by 50%. For drugs eliminated by first-order kinetics, this number is a constant regardless of the concentration.

What you need to know and understand
Terms to know

Extraction ratio $E_H = CL_H / Q$ and $F = 1 - ER$ H: hepatic; Q: blood flow	A measure of an organ's intrinsic capacity for eliminating a given drug from the systemic circulation over a single pass through the organ (usually liver or kidney)
Area under the concentration-time curve (AUC) $F = AUC_{oral} / AUC_{IV}$ $F = AUC_{formulation\ A} / AUC_{formulation\ B}$ Units: Cp x time (mg x min)/ml	The integration of the variation in plasma drug concentration over time after a single dose or during a single dosing interval AUC reflects ***the actual (total) body exposure*** to an administered dose of a drug, irrespective of the rate of absorption.
First-order elimination A constant ***fraction*** of drug is eliminated per unit of time	Drug clearance is a constant. That is, the ratio of rate of elimination to plasma concentration is the same over a broad range of plasma concentration. t½ is constant.
Zero-order elimination A constant ***amount*** (not fraction) of drug is eliminated per unit of time	Capacity-limited elimination: the drug metabolizing enzymes eventually will become saturated as the concentration of substrate increases. The rate of elimination (t½) varies depending on drug concentration.

What you need to know and understand
Terms to know

Multidose kinetics Continuous or intermittent dosing rate	Drug accumulation: The average concentration of drug will increase until a mean steady state (plateau) is reached (first-order elimination only)
Steady state	Dynamic equilibrium (first-order elimination only): the rate of drug elimination = the rate of drug administration It takes 4 half-lives to achieve 94% of steady state.
Therapeutic window	The range of safe and effective drug doses between the minimum therapeutic and minimum toxic concentrations for the drug
Peak concentration	the maximum concentration the drug achieves for a given dose
Trough concentration	the minimum concentration of the drug immediately before the next dose is given
Minimum effective concentration	the minimum concentration required to produce a therapeutic effect

What you need to know and understand: Terms to know

NEW YORK INSTITUTE OF TECHNOLOGY

Don't forget to factor in bioavailability, F.

Loading dose $LD = \frac{C_{desired} \times V_d}{F}$	The dose of drug that promptly raises the concentration of drug in plasma to the target concentration. A loading dose may be desirable when the steady state concentration needs to be achieved rapidly, e.g. life-threatening situation or a drug with a very large V_d or long t½. ➢ Switch to maintenance dose after loading dose to reduce toxicity risk.
Maintenance dose $MD = [(C_p \times CL) / F] \times \tau$ τ: dosing interval	The dose of drug required per unit time to maintain a desired steady state plasma concentration.

Simple models to describe drug distribution and elimination (first-order elimination).
The time course of drug elimination is plotted on a graph.

One-compartment model of distribution and elimination	This model assumes that the body acts like a single, uniform compartment and that a rapid intravenous injection of a dose of drug equilibrates immediately.
Two compartment model of distribution and elimination	Initial rapid changes in plasma concentration are observed because of a distribution phase – the time required for the drug to reach equilibrium distribution between the central compartment (blood) and a second compartment (tissues and fluid) followed by a slower elimination phase.

What you need to know and understand
Terms to know

Equivalence between drug products:

Pharmaceutical equivalence	Drug products that contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration
Bioequivalence	Two pharmaceutically equivalent drug products are considered to be ***bioequivalent*** when the **rates and extents of bioavailability** of the active ingredient in the two products are not significantly different under suitable test conditions.
Therapeutic equivalence	Bioequivalent drug products having similar safety and efficacy profiles.
Biosimilar	Biological (protein) product highly similar to an FDA-approved biological product and having no clinically meaningful differences in safety and effectiveness from the reference product.

Pharmacokinetic variables influencing plasma concentration and clearance.

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Factors affecting drug half-life	**Effect on t½**
Effects on volume of distribution (V_d)	
Aging: ↓ muscle mass → ↓ V_d	Decreased t½
Obesity: ↑ adipose mass → ↑ V_d of lipophilic drugs	Increased t½
Pathologic fluid: ↑ V_d of hydrophilic drugs	Increased t½
Effects on clearance	
CYP induction: ↑ rate of metabolism	Decreased t½
CYP inhibition: ↓ rate of metabolism	Increased t½
Cardiac failure: ↓ clearance	Increased t½
Hepatic failure: ↓ clearance	Increased t½
Renal failure: ↓ clearance	Increased t½

Disease states that can alter the pharmacokinetics of absorption, distribution, metabolism, excretion.

- Renal disease
- Liver disease
- Heart failure
- Shock
- Edema, ascites, pleural effusion

Therapeutic drug monitoring for optimizing the dose of a drug ***in an individual patient*** $\Rightarrow$ ***maximizing effect while minimizing toxicity***

- Only clinically meaningful when the efficacy of a drug treatment can be enhanced by achieving a certain concentration or effect range and/or the toxicity of drug therapy can be reduced by maintaining a certain concentration or effect range:

- Measuring the concentration of drug in plasma has utility when there is a(n):

1. Relationship between the concentration of drug in plasma and the clinical effect
2. Significant inter- and/or intra-patient pharmacokinetic variability
3. Established target concentration
4. Narrow therapeutic window
5. Availability of a reliable, cost-effective drug assay for clinical use

Optimization of drug therapy is based on in-depth understanding of factors that determine an individual's response to drug treatment.

Fundamental principles should guide prescribing of drugs:

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Benefits v. Risk	The benefits of drug therapy, however defined, should always outweigh the risk.
Dose	The smallest dosage necessary to produce the desired effect should be used.
Treatment regimen	The number of medications and doses per day should be minimized.
Changes in drug regimen	Prescribers should be particularly wary when adding or stopping specific drugs that are especially liable to provoke interactions and adverse reactions.
Individual variabilities	Genetics play a role in determining variability in drug response and may become a part of clinical practice
Knowledge	Keeping abreast of the literature and unbiased opinion will provide a foundation for decision-making.
Familiarity	Prescribers should use only a limited number of drugs, with which they are thoroughly familiar.

Parameters Governing Drug Disposition

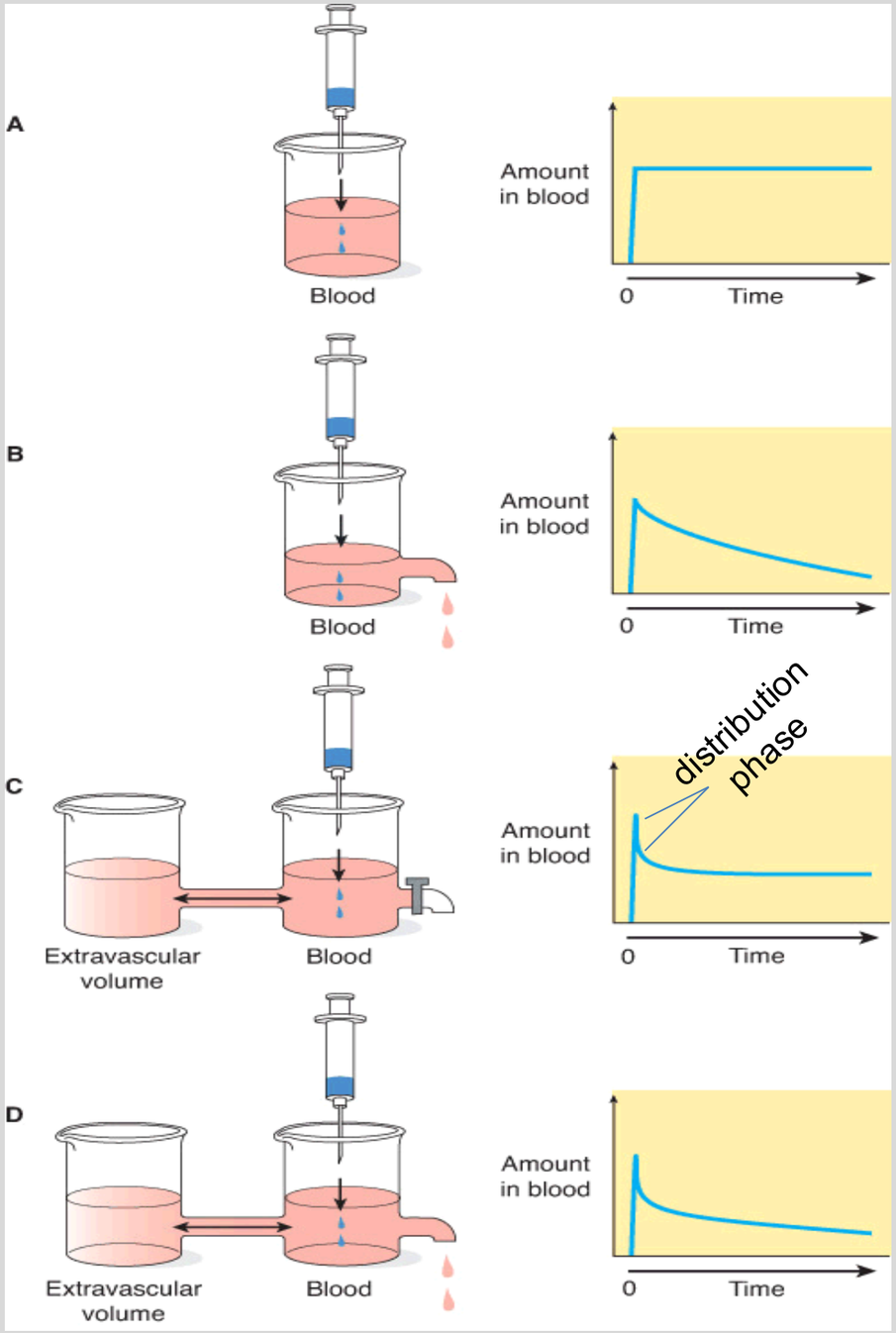
- Clearance
- Bioavailability
- Volume of distribution
- Elimination half-life

- Area under the concentration vs time curve (*AUC*)
- Steady state

dynamic equilibrium with continuous dosing

the rate of elimination = the rate of drug administration

Models of drug distribution and elimination



<u>One compartment model</u>:

no movement of drug out of the beaker ⇒ steep rise to maximum concentration followed by a plateau

route of elimination is present ⇒ a sharp rise to a maximum followed by a slow decay

<u>Two compartment model:</u>

distribution from blood to extracellular fluids and tissues (rapid equilibration)

drug in blood ⇆ drug in extravascular volume

1st compartment 2nd compartment

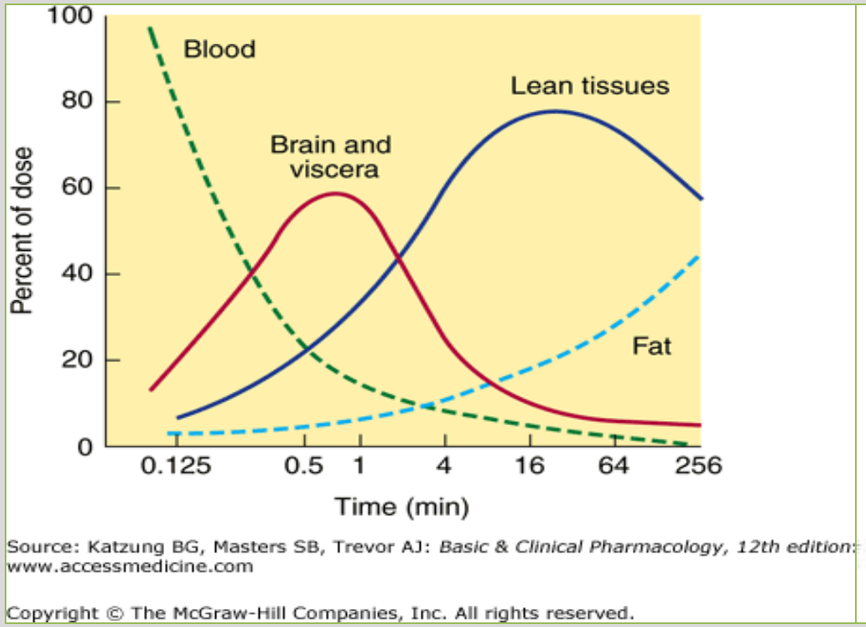
distribution phase followed by the slower elimination phase

Basic & Clinical Pharmacology **Figure 3-2.** Models of drug distribution and elimination.

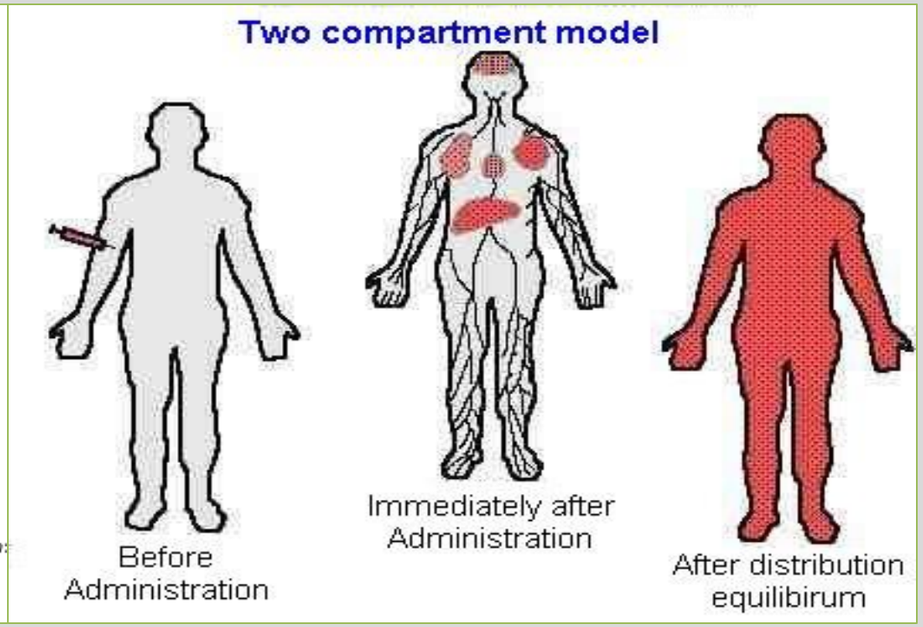
Multicompartment model (first-order kinetics)

- Central compartment: the highly perfused tissues
- Final compartment: the more slowly perfused tissues

central compartment ⇄ **peripheral compartment**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com



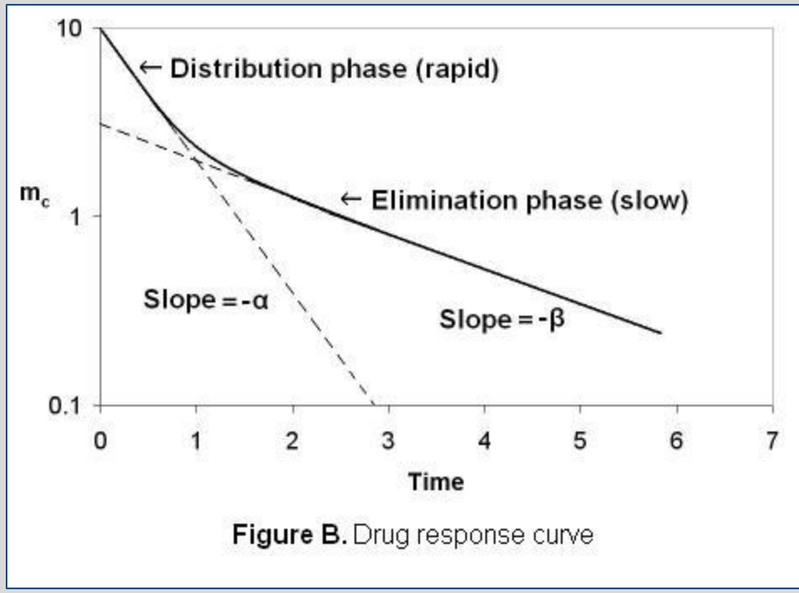


Figure B. Drug response curve

Katzung Figure 25-7

Variation in drug distribution rate

Change in blood flow to various tissues

↓

Change in rates of

drug distribution to tissues

Thus, the effect of a drug at various sites of action can vary ***depending on perfusion of these sites***.

Clearance (*CL*)

CLEARANCE

- total systemic clearance:

$$CL = CL_{renal} + CL_{hepatic} + CL_{other}$$

Excretion of drug

Biotransformation to inactive

bile, sweat, saliva, breast milk lungs (gases)

Clearance depends on:

- the drug,
- the blood flow, and
- the condition of the organs of elimination in the patient

CLEARANCE

Clearance is the proportionality factor that predicts the rate of elimination in relation to the drug concentration.

- the **rate** of drug elimination is directly proportional to drug **concentration** when clearance is constant

$$CL = \frac{\text{rate of drug elimination (mg/min)}}{\text{drug concentration in measured fluid (mg/mL/kg)}}$$

- Rearranging: Drug elimination rate = CL x C_{plasma}

At steady state

- Dosing rate_{ss} = Rate of elimination_{ss}
- Dosing rate_{ss} = CL_{ss} x C_{ss}

Extraction ratio$_{organ}$ (E_{organ}),

Bioavailability (F),and

Area under the concentration-time curve (AUC)

Extraction Ratio (*E*):

a clearance model of an organ's ***intrinsic capacity***

for eliminating a drug in a single pass through the organ at steady state

Extraction ratio compares plasma levels of free drug at steady state immediately before entering and just after exiting the organ:

$$E = \frac{(C_{in} - C_{out})}{C_{in}}$$

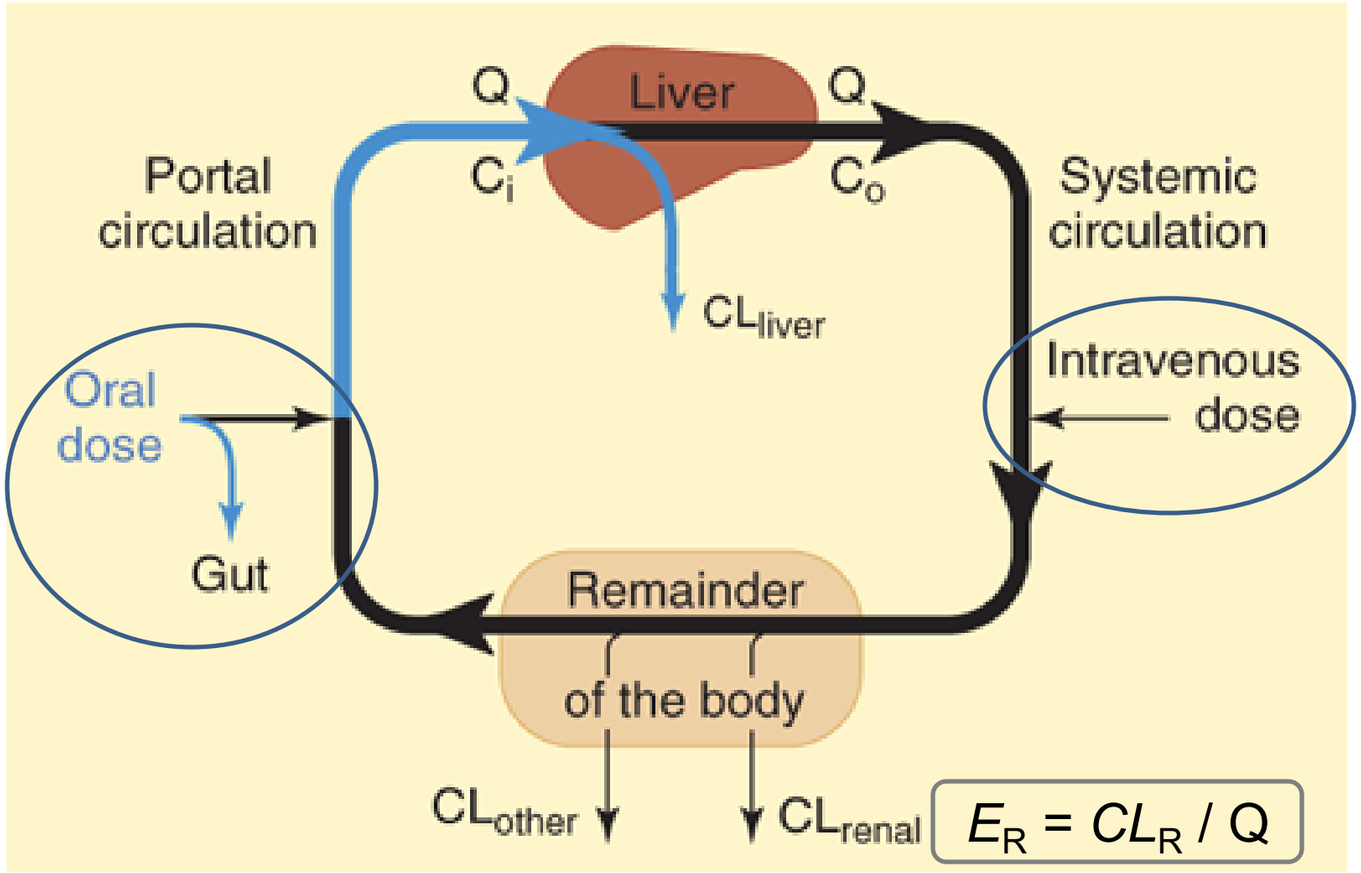
$$CL = Q \times \frac{(C_{in} - C_{out})}{C_{in}} \rightarrow CL = Q \times E$$

$$E = CL / Q$$

Drug clearance is determined by:

1. Blood flow (*Q*) through the eliminating organ
2. Free (unbound) fraction of drug in plasma
3. Intrinsic clearance – the intrinsic ability of clearance mechanisms of the organ (ie, hepatic enzymes to metabolize the particular drug or renal excretory processes)

Illustration of Hepatic and Renal Extraction (E_H and E_R) of a Drug



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

$E = (C_{in} – C_{out}) / C_{in}$

C: concentrations of unbound drug

Blood flow determines the rate of presentation of drug to the liver and the rate of exit from the liver.

$CL = Q \times (C_{in} – C_{out}) / C_{in}$

$E_H = CL_H / Q$

Bioavailability of oral drugs can be predicted:

$F = f \times (1 – E)$

f: fraction of dose absorbed

The principles of organ extraction and first-pass effect are illustrated. Part of the administered oral dose (blue) is lost in the gut in the feces or to metabolism, and lost to metabolism in the liver before it enters the systemic circulation: This is the first-pass effect. The extraction of drug from the circulation by the liver is equal to blood flow (Q) times the difference between entering and leaving drug concentration, ie, $Q \times (C_i – C_o)$. CL, clearance. (Modified with permission from Katzung BG: Basic & Clinical Pharmacology, 8th ed. New York, NY: McGraw Hill; 2001.)

Citation: Chapter 3 Pharmacokinetics, Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. *Katzung & Trevor's Pharmacology: Examination & Board Review, 13e;* 2021, Figure 3-5. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3058&sectionid=255304212 Accessed: August 23, 2021

Slide adapted by LG

Effect of reduced hepatic blood flow on systemic drug levels

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Blood flow-dependent extraction

For drugs with high E_H (>0.7)

- **Shunting of blood past the liver will result in substantial increases in drug availability in systemic circulation.**

Hepatic clearance approximates blood flow.

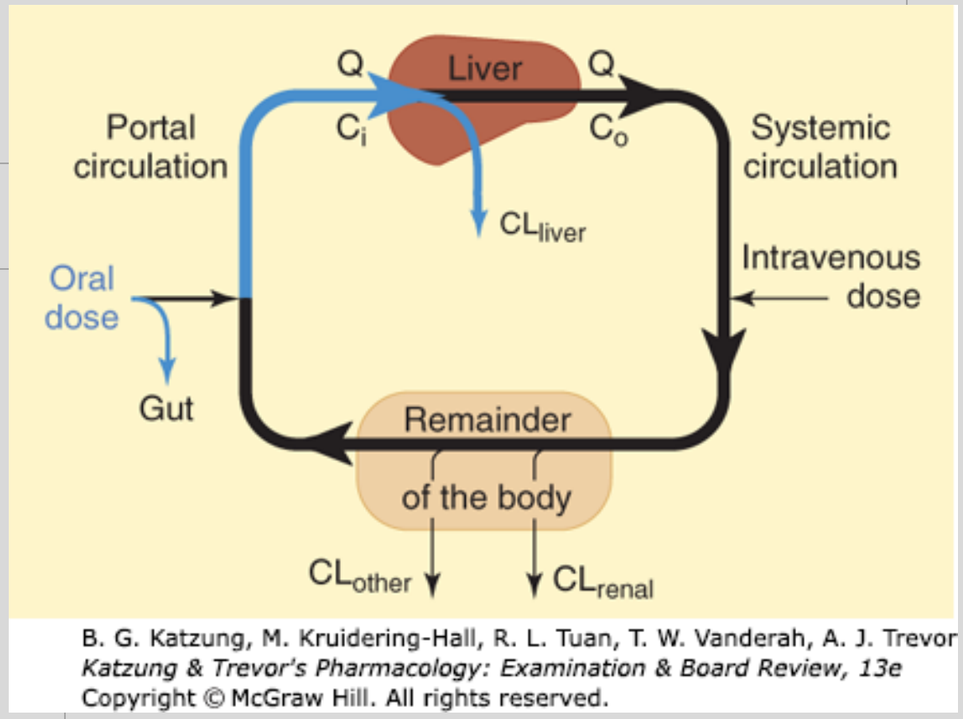
Capacity-limited extraction

For drugs with low E_H (<0.3)

- **Shunting of blood past the liver will cause little change in bioavailability.**

Clearance will be proportional to:

the unbound fraction and the drug's intrinsic clearance.



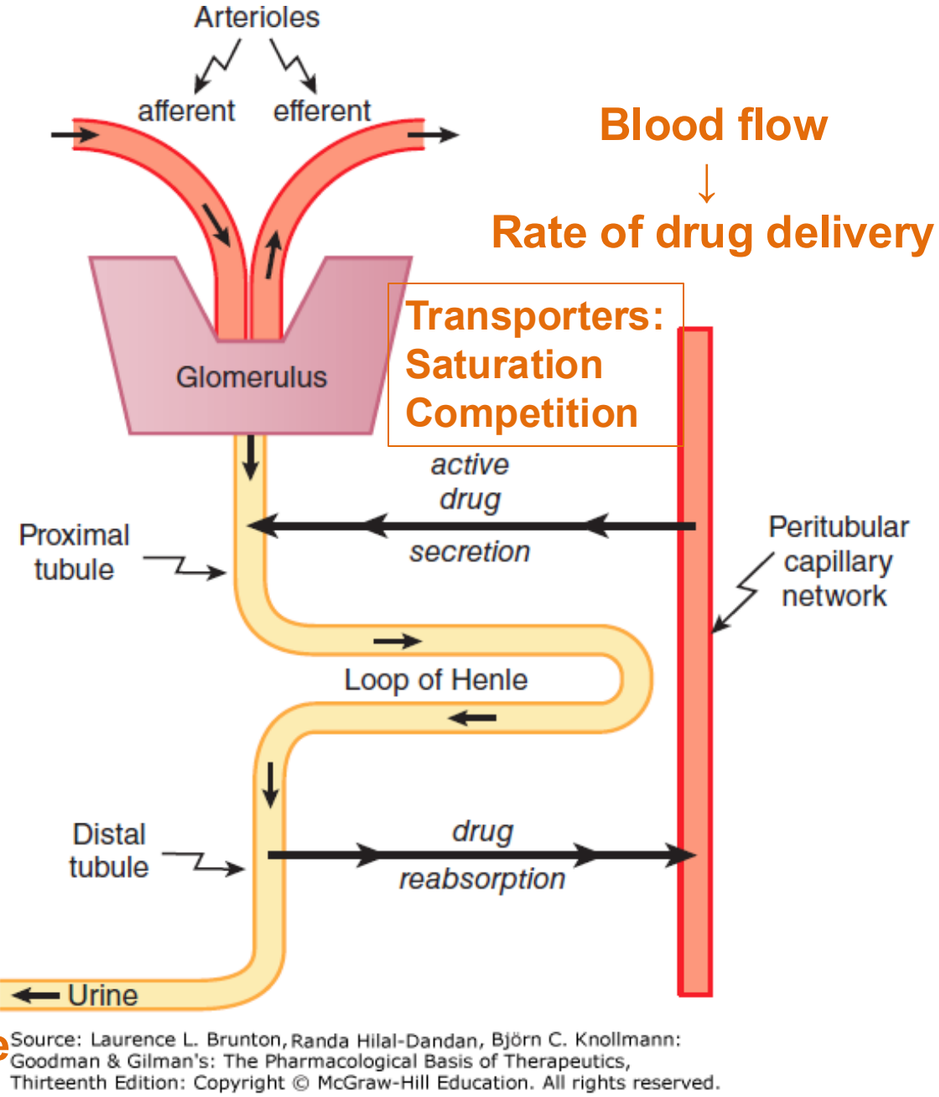
B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

Renal Extraction:

Fraction of active drug excreted in the urine

Renal clearance is affected by:

1. Renal blood flow, protein binding, function of nephrons
2. Glomerular filtration rate
3. Secretion rate from peritubular fluid into tubular fluid
4. Reabsorption from tubular fluid back into the blood stream



E_{renal}:
Fraction of drug excreted in urine

Renal drug handling. Drugs may be filtered from the blood in the renal glomerulus, secreted into the proximal tubule, reabsorbed from the distal tubular fluid back into the systemic circulation, and collected in the urine. Membrane transporters (OAT, OCT, MDR1, and MRP2, among others) mediate secretion into the proximal tubule (see Figures 5–12 and 5–13 for details). Reabsorption of compounds from the distal tubular fluid (generally acidic) is pH sensitive: Ionizable drugs are subject to ion trapping, and altering urinary pH to favor ionization can enhance excretion of charged species (see Figure 2–2).

Citation: Chapter 2 Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination, Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e;* 2017, Figure 2-5. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=166182905 Accessed: August 23, 2021

Slide adapted by LG.

Bioavailability (*F*)

the fraction of active drug that reaches the systemic circulation

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Bioavailability is determined by the:

1) **Dose** and

2) **Fraction** of the dose

that is absorbed *and* escapes first-pass elimination

$$F = f \times (1 - E)$$

f: fraction of dose absorbed

Drug absorption may be reduced due to:

- incomplete release of drug from dosage formulation
- lesser ability of drug to cross physiologic barriers
- efflux of drug by P-glycoprotein
- metabolism in the intestinal epithelium

Bioavailability is factored into oral dosing calculations.

Example

- Verapamil $E_H \approx 0.67$
- Expected oral bioavailability of verapamil

$F_{\text{verapamil}} = 1 - 0.67$

$= 0.33 \Rightarrow 33\%$

Note: Considerable interpatient variability; the actual oral bioavailability of verapamil varies from 20% to 35%

$$\text{dosing rate} = \frac{CL \times C_{ss}}{F}$$

Converting a patient from verapamil I.V. to oral form

- I.V. dose = 5 mg / hour
- = 120 mg / 24 hours
- oral dose = dose / $F_{\text{verapamil}}$

oral dose = 120 mg / 0.33

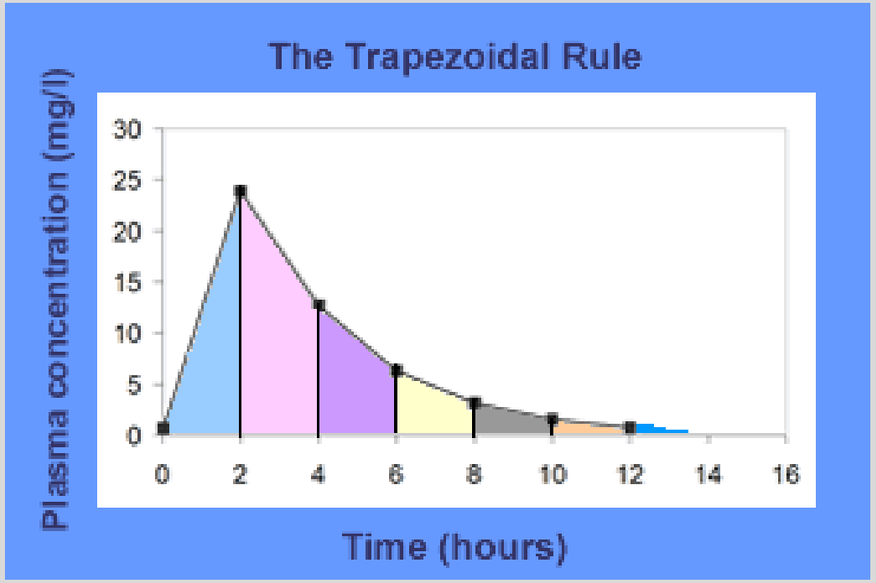
oral dose = 360 mg / 24 hrs
extended release capsule

AUC
area under the plasma concentration-time curve

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

AUC assesses the extent of ***the total body exposure*** to a dose of drug

- By integrating the concentration of drug in plasma over time
- For a single dose or during a single dosing interval at steady state.



http://sepia.unil.ch/pharmacology/index.php?id=66

- Clearance may be estimated from AUC:

  CL = dose / C_{ss} *therefore,* CL = dose / AUC

- The bioavailability of a drug determines its concentration in plasma, which, over time, determines the actual body exposure to the drug.

Equivalency between Drug Products

Bioavailability can be derived from the area under the curve.

Clinical application:

Comparing bioavailability of different formulations or different manufacturers' products of the same drug

- **Absolute bioavailability**

  comparing bioavailability of oral (or other route) to the I.V. formulation of the same drug

$$F = \frac{AUC_{\text{oral}}}{AUC_{\text{IV}}}$$

- **Relative bioavailability**

  comparing the bioavailability of:

  Different formulations of the same drug(eg, tablet, capsule, solution), or

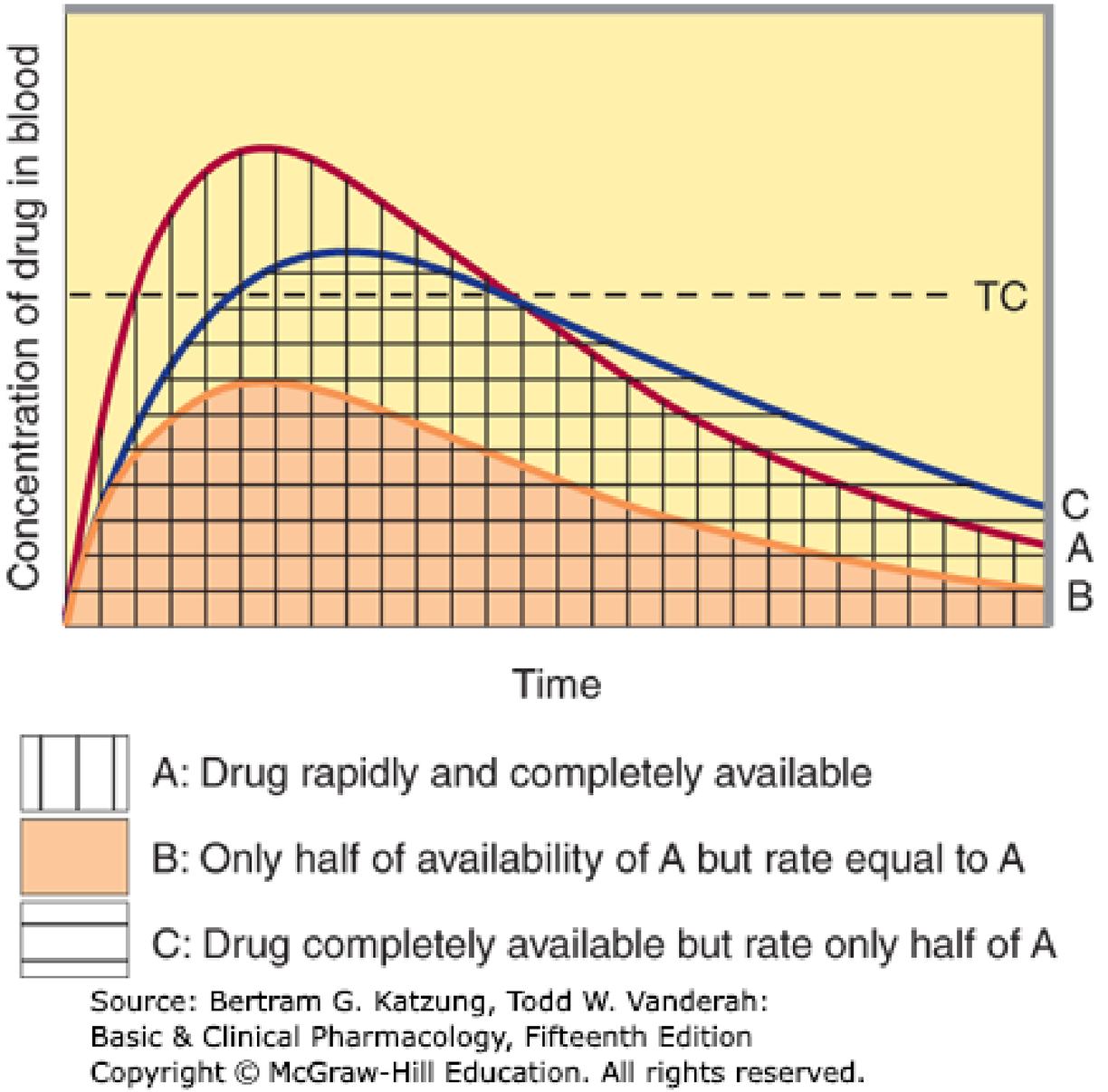
  The same formulation of the same drug made by different companies (*eg* brand and generic tablets)

$$F = \frac{AUC_{\text{version A}}}{AUC_{\text{version B}}}$$

The area under the blood concentration-time curve (AUC) is proportional to the dose and the extent of bioavailability for a drug if its elimination is first-order.

The blood concentration-time curves illustrate how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations.

The dashed line indicates the target concentration (TC) of the drug in the blood.

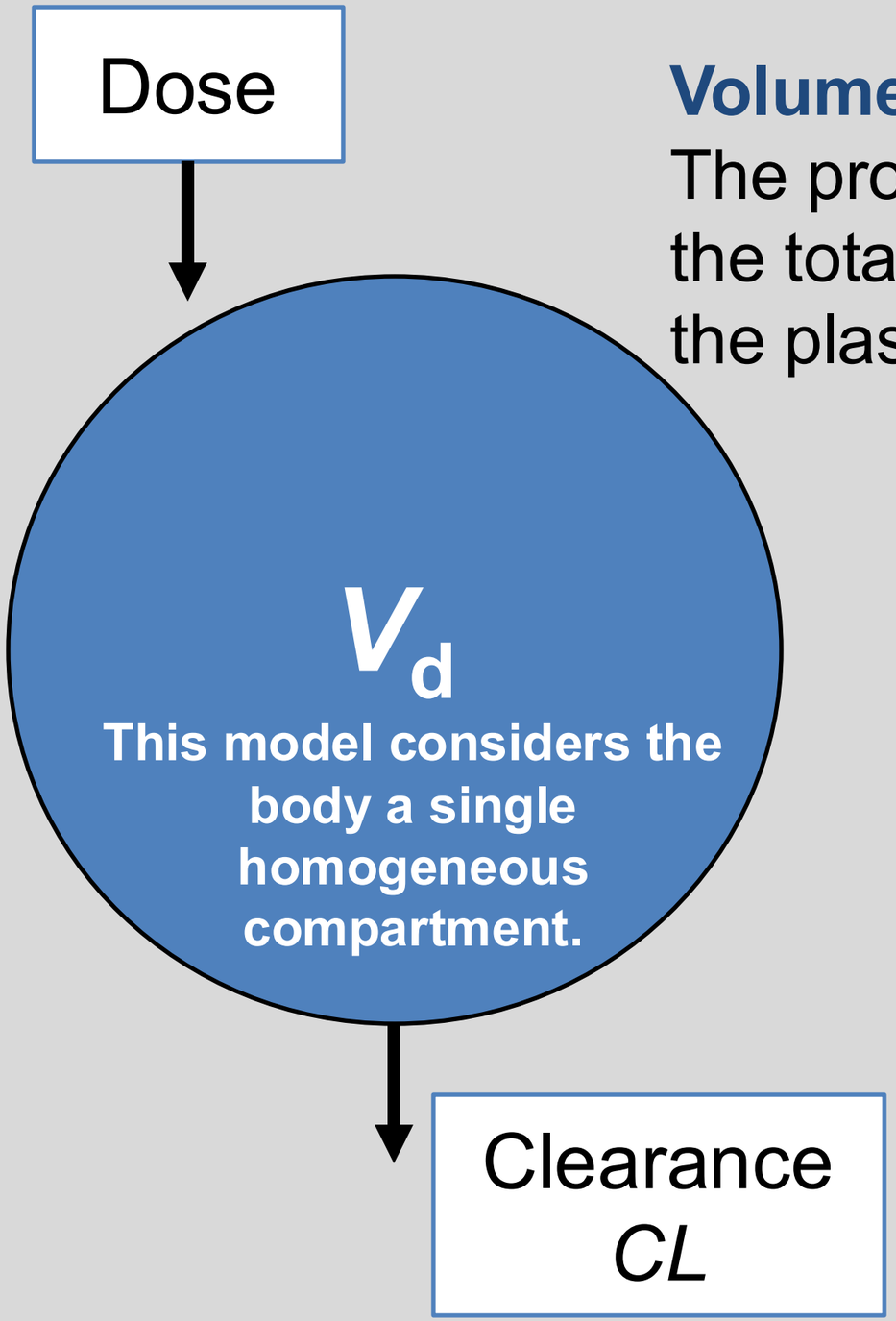


Source: Bertram G. Katzung, Todd W. Vanderah: Basic & Clinical Pharmacology, Fifteenth Edition

Citation: Chapter 3 Pharmacokinetics & Pharmacodynamics: Rational Dosing & the Time Course of Drug Action, Katzung BG, Vanderah TW. *Basic & Clinical Pharmacology, 15e;* 2021. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250594300 Accessed: August 23, 2021

Slide adapted by LG.

Apparent Volume of Distribution (V_d)



Volume of Distribution:

The proportionality constant that relates the total amount of drug in the body to the plasma concentration at a given time.

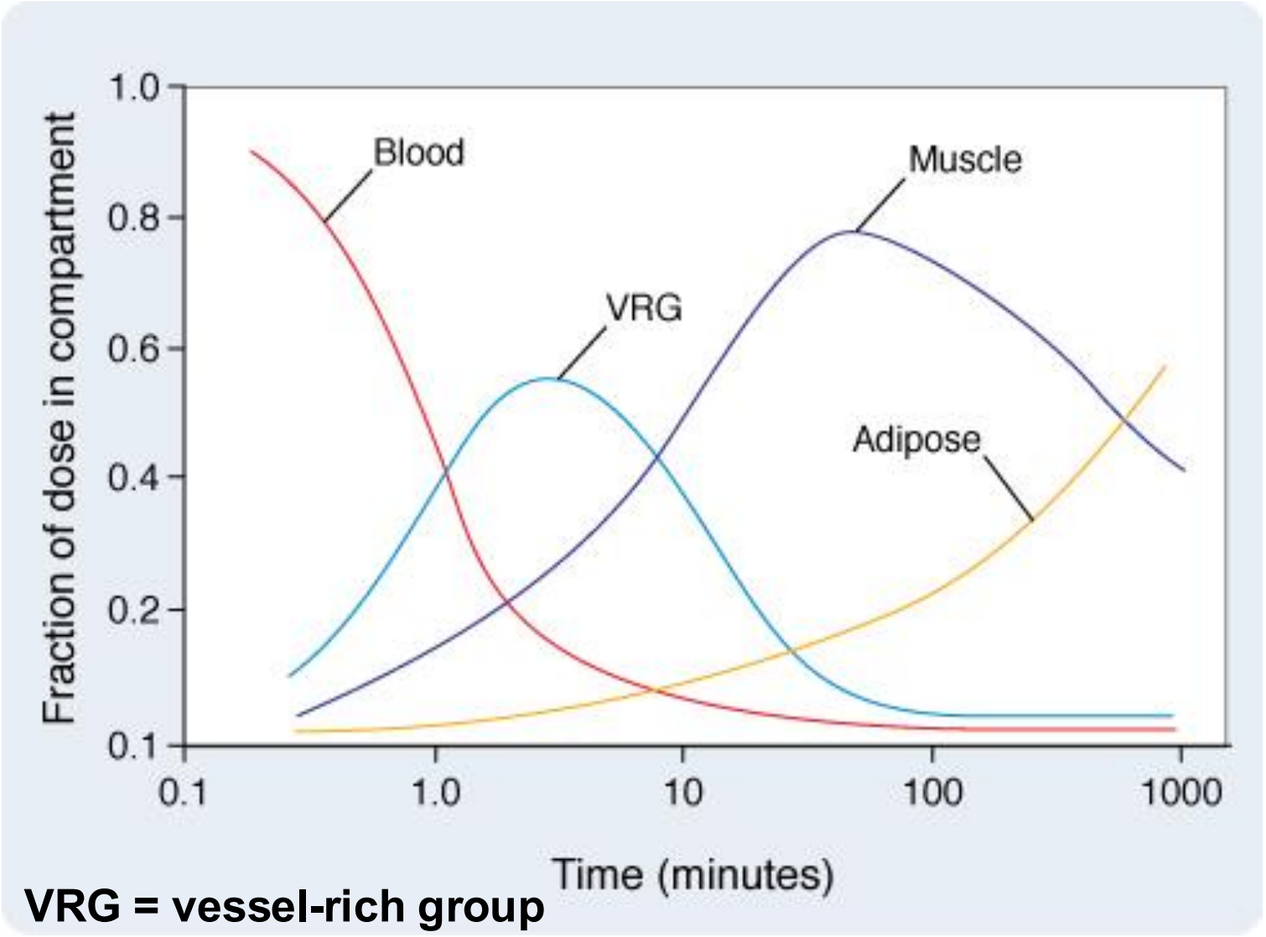
$$V_d = \frac{\text{Dose}}{C_{\text{blood or plasma}}}$$

It is an apparent (theoretical) volume that represents a drug's propensity to remain in plasma or distribute to other tissue compartments.

It is a calculated parameter.

From: **3 Pharmacokinetics**
Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy Fourth Edition, 4e, 2017

Four-compartment model of drug distribution.



VRG = vessel-rich group

Multi-compartment model:

Drug concentration in a sample varies over time as the drug distributes around the body.

The drug concentration in a sample immediately after IV bolus will produce a different V_d value than a sample taken several hours later.

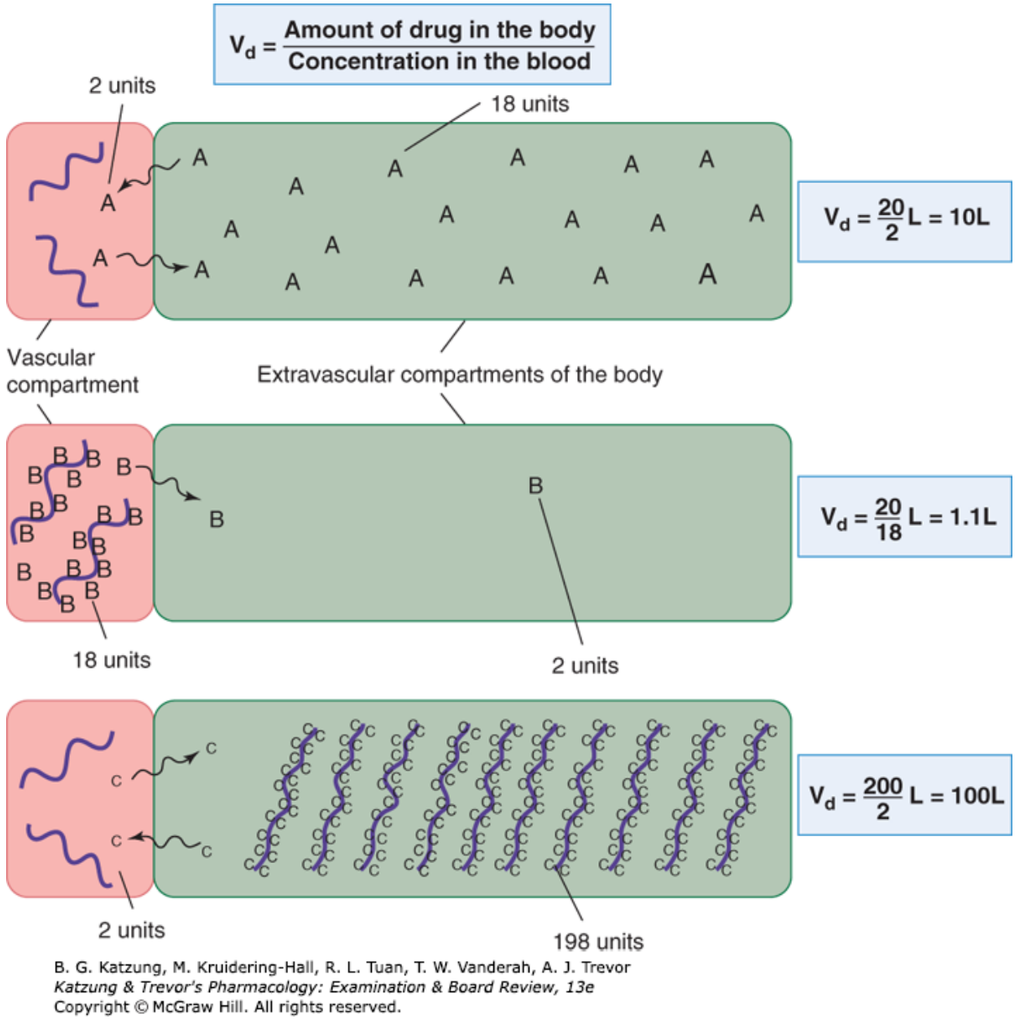
1. **Initial distribution phase**

- Highly-perfused organs – brain, kidney, liver, heart – receive most of the drug

2. **Second distribution phase**

- Delivery to muscle, most viscera, skin, and fat is slower
- May require minutes to several hours before the concentration of drug in tissue is in equilibrium with that in blood
- Involves far larger fraction of body mass relative to initial phase

Slide adapted by LG.



- Drug A diffuses freely between the 2 compartments.
- Drug B binds avidly to plasma proteins (wavy lines).

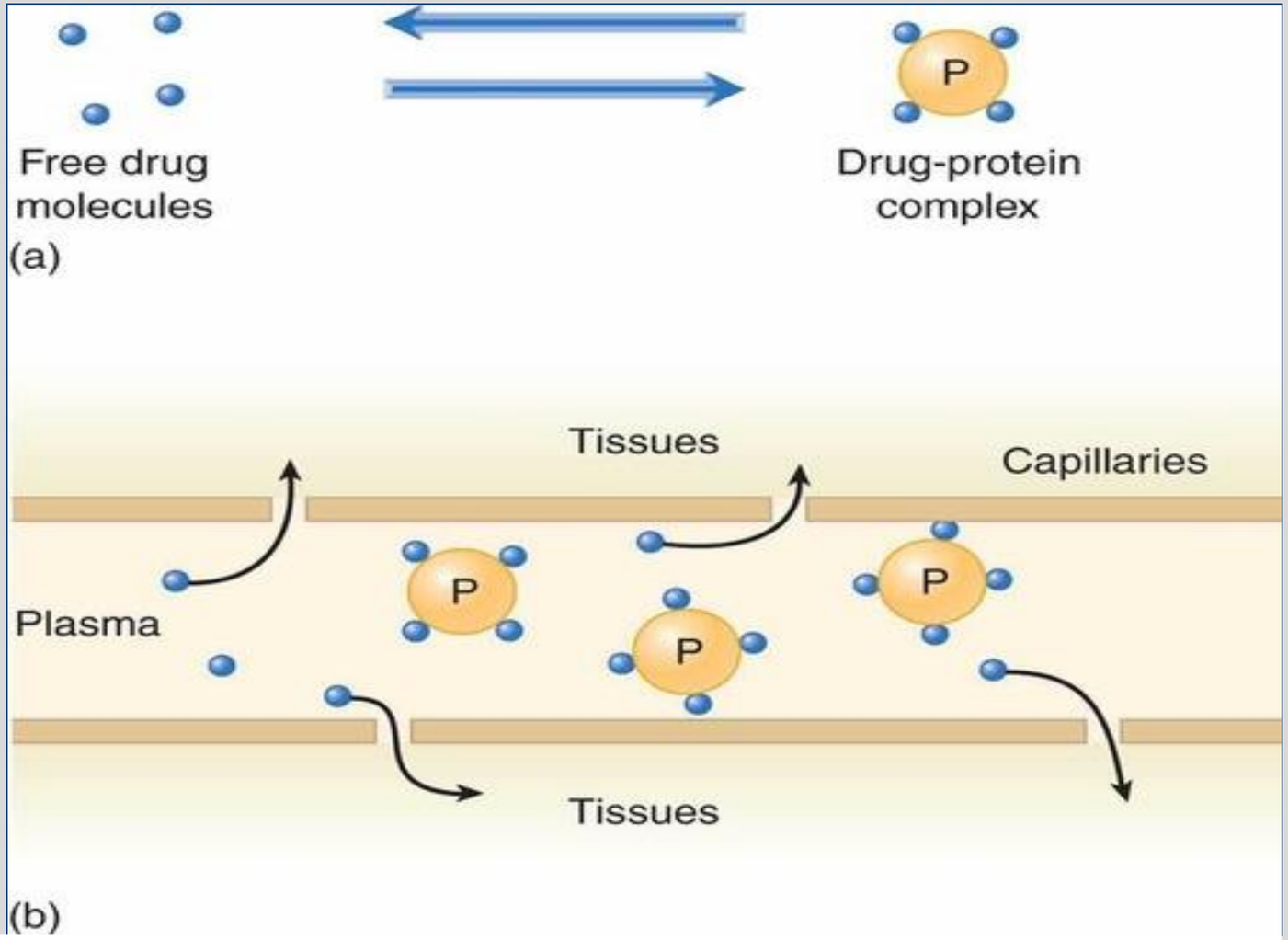
  The drug is retained in plasma compartment → low *V*d
- Drug C binds avidly to molecules in peripheral tissues.
  - Low concentration in blood
  - High *V*d
  - Larger total dose is required to achieve measurable plasma concentrations

Effect of drug binding on volume of distribution. Drug A diffuses freely between the 2 compartments and does not bind to macromolecules (heavy wavy lines) in the vascular (volume 1 L) or the extravascular compartments (volume 5 L) of the hypothetical organism in the diagram. With 20 units of the drug in the body, the steady-state distribution leaves a blood concentration of 2 units/L. Drug B, on the other hand, binds avidly to proteins in the blood. At equilibrium, only 2 units of the total are present in the extravascular volume, leaving 18 units still in the blood. In each case, the total amount of drug in the body is the same (20 units), but the apparent volumes of distribution are very different. Drug C is avidly bound to molecules in peripheral tissues, so that a larger total dose (200 units) is required to achieve measurable plasma concentrations. At equilibrium, 198 units are found in the peripheral tissues and only 2 units in the plasma, so that the calculated volume of distribution is greater than the physical volume of the system.

Slide adapted by LG.

When plasma protein binding is reversible, a chemical equilibrium exists between bound and unbound drug.

drug + protein ⇆ protein-drug complex



Processes that lower the free drug concentration lead to rapid dissociation of drug from the drug-protein complex, thereby reestablishing equilibrium between bound and free drug.

Figure: http://quizlet.com/19545630/pharmacology-4-pharmacokinetics-objectives-flash-cards/

Anticipated effect of drug displacement from plasma proteins:

Displacement of drug from plasma proteins → ***Transient*** increase in free fraction → **Rapid equilibration**

The increase in free fraction will increase the apparent clearance of the drug, thus the mean unbound plasma concentration at steady state would not change.

The ***rate*** of drug metabolism is directly proportional to the free drug concentration and the ***fraction*** of drug removed is constant.

🔑 Changes in protein binding due to disease states and drug-drug interactions are clinically relevant mainly for a small subset of drugs with a ***narrow therapeutic window and potential for significant toxicity***.

Summary: Clinical Pharmacokinetics Part 1

- The plasma concentration is a function of the rate of input of the drug (by absorption) into the plasma, the rate of distribution into other tissues, and the rate of elimination.
- If the rate of input is known, the remaining processes are well described by two primary parameters: **apparent volume of distribution (V_d)** and **clearance (CL).** These parameters are unique for a particular drug and a particular patient but have average values in large populations that can be used to predict drug concentrations.
- Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration.
- Volume of distribution is the proportionality constant that relates the total amount of drug in the body to the plasma concentration at a given time.

- Change in blood flow to various tissues change in rates of drug distribution to tissues. Thus, the effect of a drug at various sites of action can vary depending on perfusion of these sites.
- Removal of a drug by an organ can be specified as the extraction ratio – the fraction or percentage of the drug removed from the perfusing blood during one passage through the organ.
- The bioavailability of a drug is the fraction (F) of the administered dose that reaches the systemic circulation.
- The area under the concentration vs. time curve (AUC) describes the measured concentration of drug in the systemic circulation as a function of time (from zero to infinity) – the concentration of drug appearing in plasma occurs over time. It can be used to calculate bioavailability.

Matching

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Drug products that contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration	
Bioequivalent drug products having similar safety and efficacy profiles.	
Biosimilar product and meets additional standards for interchangeability	
Biological product highly similar to an FDA-approved biological product and having no clinically meaningful differences in safety and effectiveness from the reference product	
Pharmaceutically equivalent drug products show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient	

Bioequivalence

Biosimilar

Interchangeable biologic product

Pharmaceutical equivalence

Therapeutic equivalence

References

- Access Medicine Goodman & Gilman's The Pharmacological Basis of Therapeutics 14e; 2023; Chapter 2: Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination
- Access Medicine Harrison's Principles of Internal Medicine, 22e, 2025; Chapter 71: Principles of Clinical Pharmacology
- Access Medicine Katzung's Basic & Clinical Pharmacology 16e, 2024: Chapter 3: Pharmacokinetics & Pharmacodynamics: Rational Dosing & the Time Course of Drug Action, and Chapter 66: Rational Prescribing & Prescription Writing
- Access Medicine Principles and Practice of Hospital Medicine, 2e, 2017; Chapter 9: Principles of Evidence-Based Prescribing

Lecture Feedback Form:

https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R

Clinical Pharmacokinetics Part 2
Rational Dosing and the Time Course of Drug Action

Leslie Goldstein, Pharm.D.
Associate Professor
Department of Clinical Specialties
lgolds01@nyit.edu

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Do.
Make.
Heal.
Innovate.
Reinvent the Future.

After completing the preparation materials, students should be able to:

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

1. Describe clearance, volume of distribution, elimination half-life, steady state, bioavailability, extraction ratio, and area under the curve using pharmacokinetic models.
2. Differentiate first-order and zero-order elimination kinetics and linear and non-linear processes in relation to drug concentration and effect.
3. Graph drug accumulation, half-life, and steady state for drugs with first-order elimination administered by continuous and intermittent dosing.
4. Calculate the maintenance and loading doses for an individual patient to achieve a target concentration within the therapeutic window in when given specific pharmacokinetic parameters.
5. Identify pharmacokinetic variables that influence drug plasma concentrations and the criteria for therapeutic drug monitoring.

Preparation Materials (links are in the CPG and on the next slide)

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Required

- ScholarRx Bricks | Practice Questions

Highly relevant optional materials:

- Dr. Goldstein's Word handout | Video Lectures | Guided Reading Questions
- Textbook resources with links are listed on the next slide

SUGGESTIONS:

- *Use the resources that work best for you.*
- *You do not need to study all of them.*
- *Work through the GUIDED READING QUESTIONS with pen/pencil and paper.*

Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.

- *Practice questions (not graded): Simple Recall and Case Vignettes*

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Links

Scholar Rx Bricks: (Required)

General Principles

Pharmacokinetics and Pharmacodynamics > Pharmacokinetics: Drug Concentration and Dosing
https://exchange.scholarrx.com/brick/drug-concentration-and-dosing

Enzymes as Drug Targets https://exchange.scholarrx.com/brick/enzymes-as-drug-targets

Katzung & Vanderah's Basic & Clinical Pharmacology, 16e, 2024; Chapter 3: Pharmacokinetics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281747069

THE REVIEW BOOKS HAVE PRACTICE QUESTIONS

Katzung & Trevor's Pharmacology: Examination and Board Review, 14e, 2024
Chapter 3: Pharmacokinetics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285589076

LWW Health Library Premium Basic Sciences; Lippincott Illustrated Reviews: Pharmacology, 8e, 2023: Chapter 1: Pharmacokinetics
https://premiumbasicsciences-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253324942&bookid=3222

For the list of “What you need to know and understand”, please see the PowerPoint presentation for

Clinical Pharmacokinetics, Part 1

Half-life

Half-life

$t_{1/2}$ changes as a function of both clearance and volume of distribution

The time required to reduce the amount of drug in the body by one-half during elimination – that is, with each half-life the drug concentration decreases by 50% (first-order kinetics).

$$t_{1/2} = \frac{0.693 \times V_d}{CL}$$

- **t½ is an indicator of:**

1. Time required to reach steady state
2. Time required for drug to be removed from the body
3. A way to estimate dosing interval

Half-life depends on both the rate of elimination and the volume of distribution.

- t½ is prolonged in proportion to either an increase in Vd or decrease in CL.

Half-life is dependent on exponential elimination kinetics. 0.693 is the logarithm of 2 (ln2).

First-order elimination

Zero-order elimination (capacity-limited elimination)

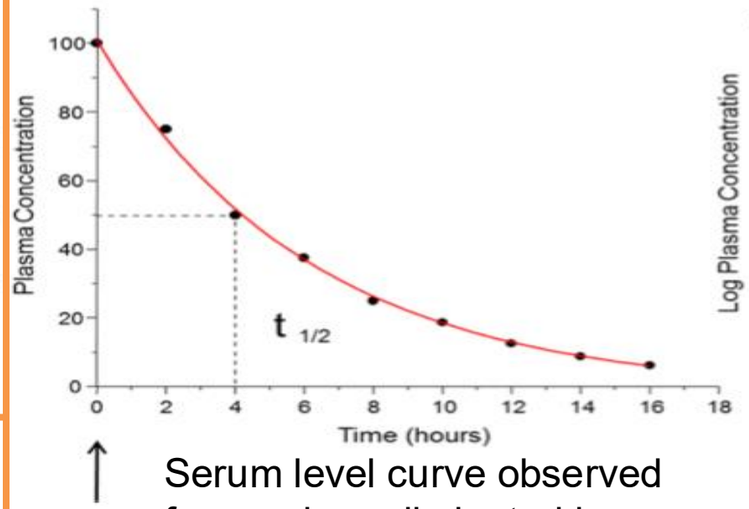
First-Order Elimination Kinetics

A constant proportion (fraction) of drug is eliminated per unit of time (linear elimination).

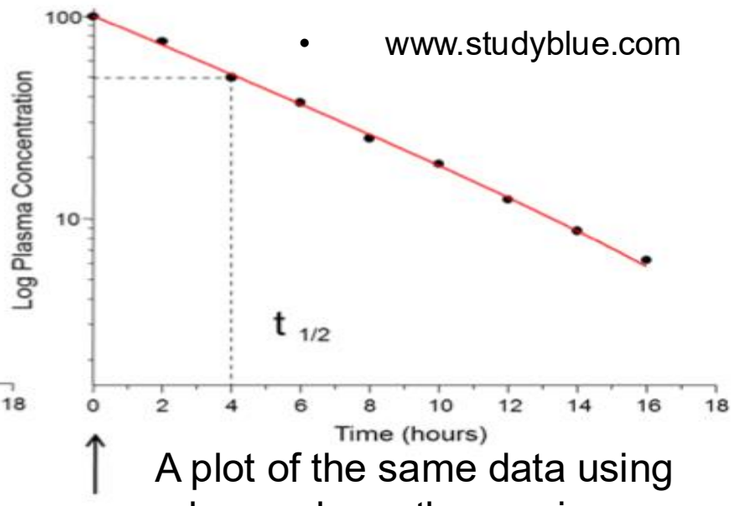
NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

The ***rate*** of drug metabolism is directly proportional to the free drug concentration and the ***fraction*** of drug removed is constant.

The vast majority of drugs follow first-order elimination kinetics at therapeutic doses.



Serum level curve observed from a drug eliminated by a first-order process.

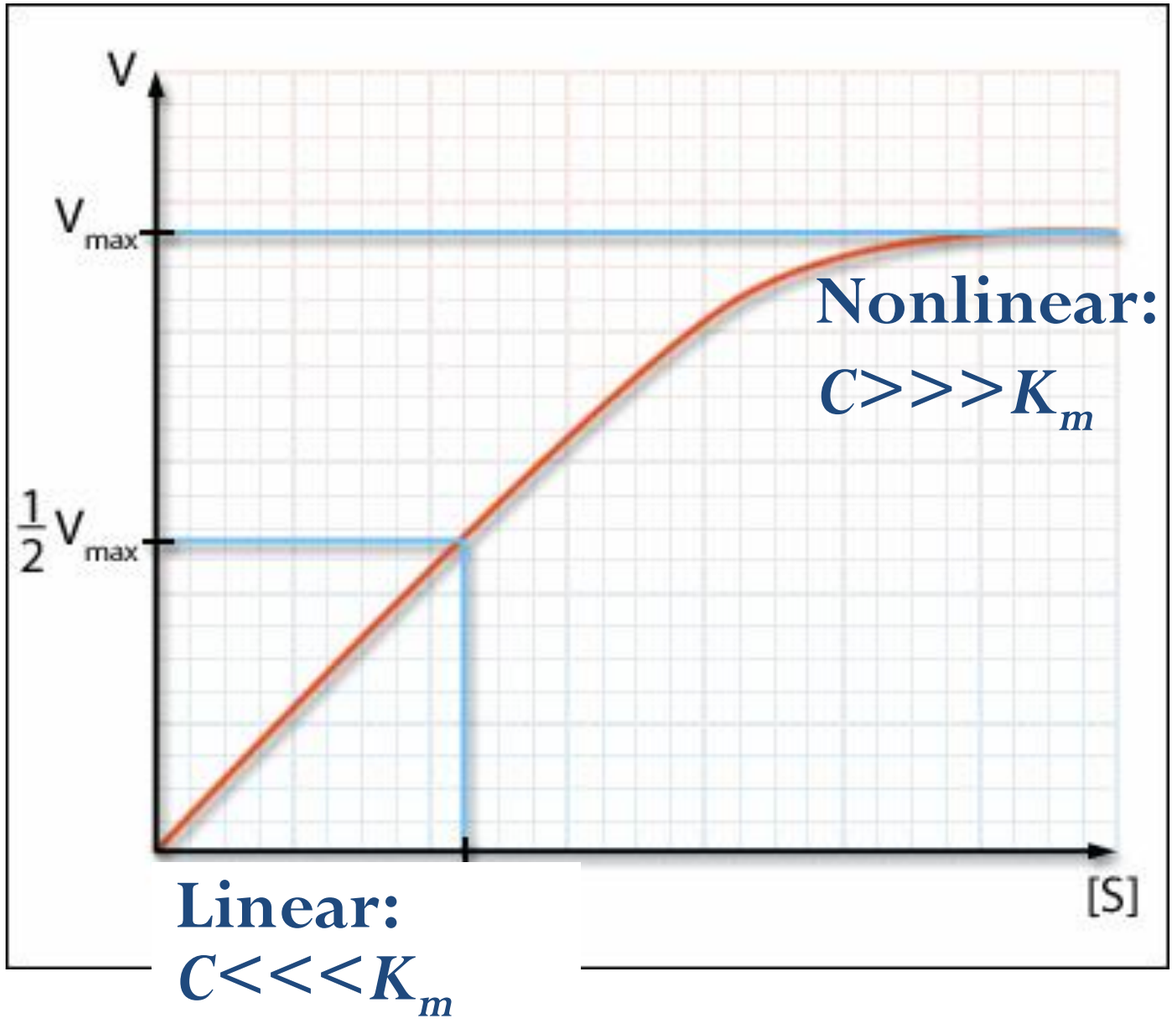


A plot of the same data using a log scale on the y-axis results in a straight line.

- www.studyblue.com

t½ = 4 hours in this illustration

Zero-order kinetics: Clearance mechanisms become saturated – the rate of metabolism remains constant – a constant amount (not fraction) of drug is metabolized per unit of time. Dangerously elevated drug concentration can result.



$$\text{Rate of Elimination} = \frac{V_{max} \times C}{K_m + C}$$

$$Css = \frac{\text{Dosing rate} \times K_m}{V_{max} - \text{Dosing rate}}$$

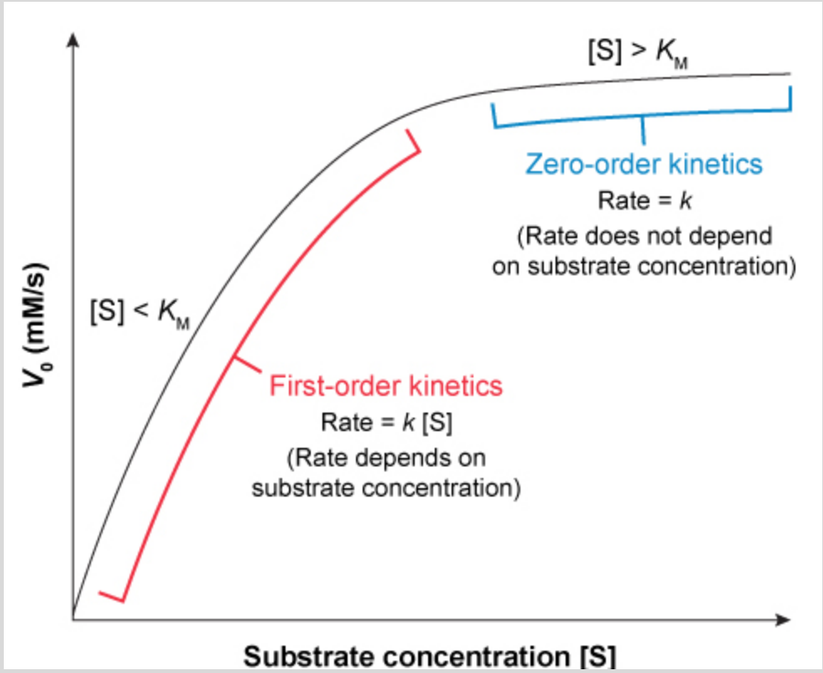
As dosing rate approaches V_{max},

V_{max} – dosing rate approaches zero → disproportionate increase in concentration.

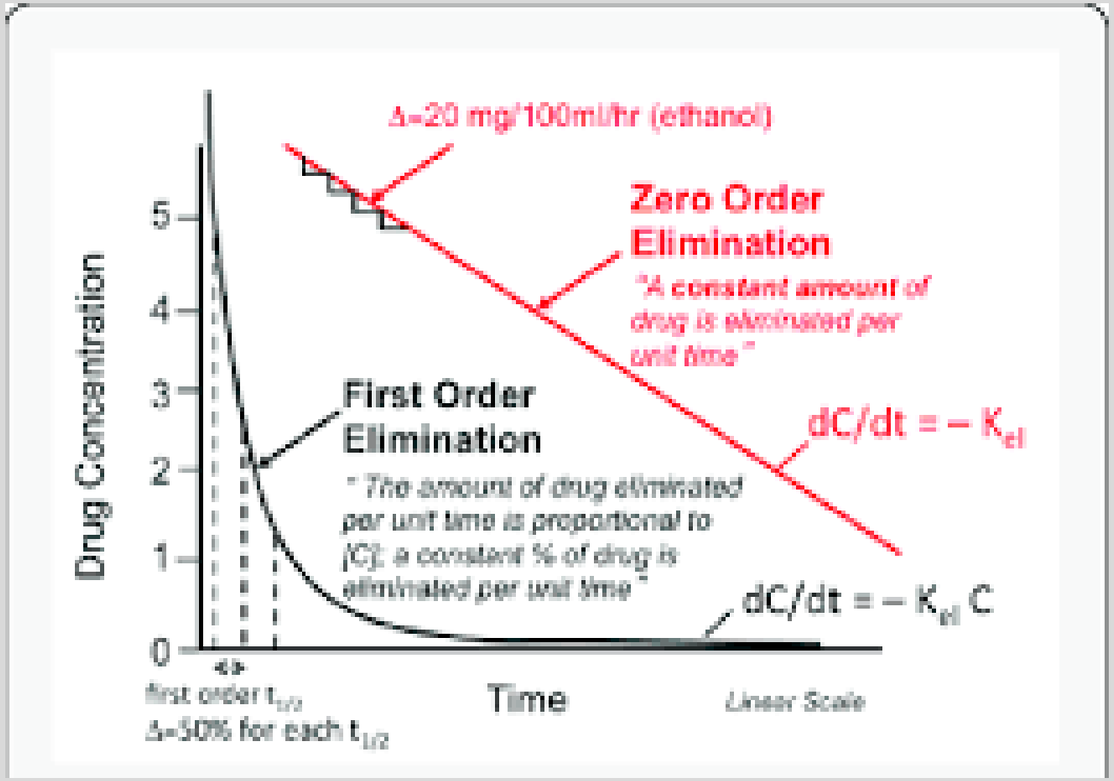
At C >> K_m elimination rate is almost independent of concentration.

K_m is the concentration of substrate at which enzyme activity is at half maximal – ½ Vmax.

Enzyme Kinetics Curve comparing zero-order and first-order kinetics.



Linear Plot of Cp Versus Time Showing High Cp and Low Cp Zero Order and First Order Elimination



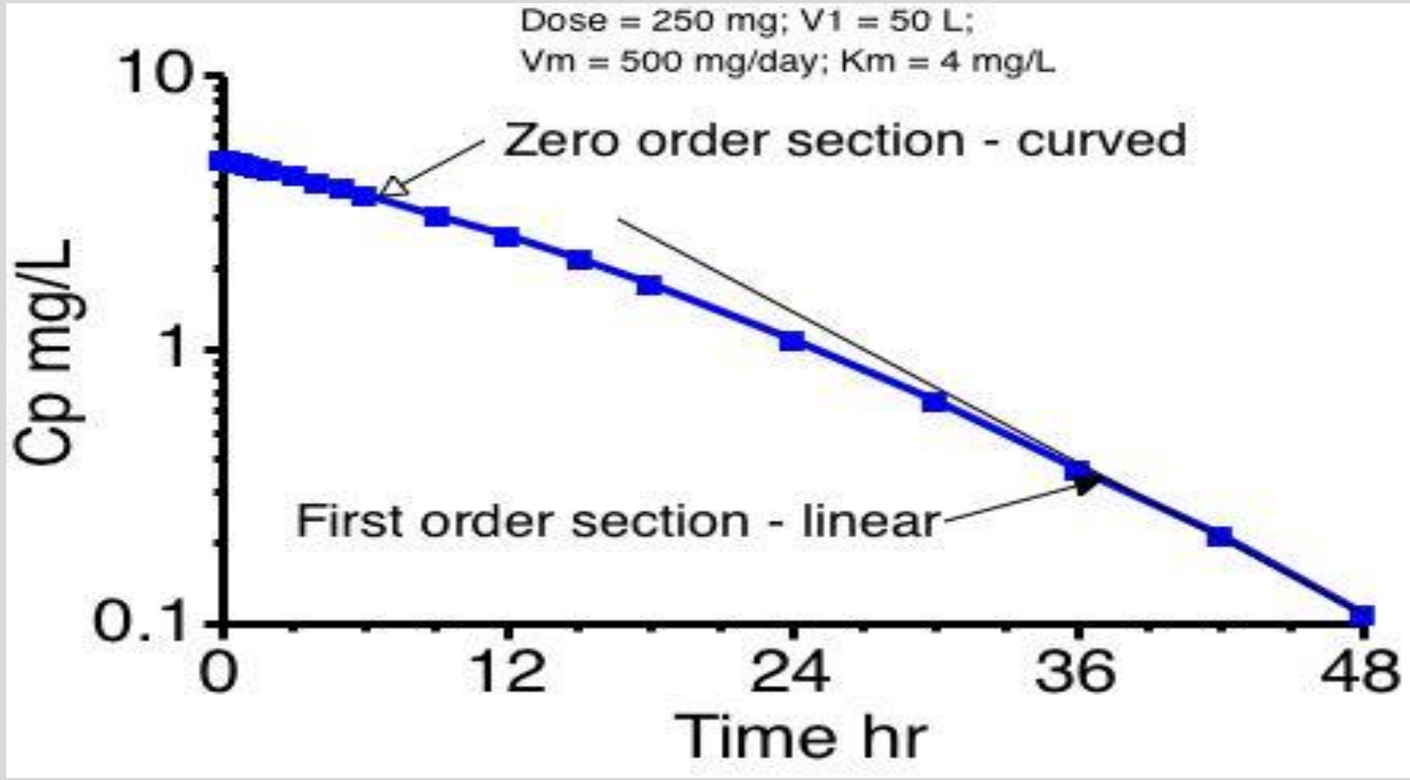


Figure 21.3.2 http://www.boomer.org/c/p4/c21/c2103.html

Saturable elimination: Clinical correlates

If dosing rate exceeds elimination capacity, steady state cannot be achieved …the concentration will keep rising as long as dosing continues.

Changing the dosing rate for a drug with nonlinear kinetics is difficult and unpredictable.

Three drugs exhibit zero-order kinetics at therapeutic *concentrations*:

Ethanol, **aspirin** (anti-inflammatory doses), and **phenytoin**.

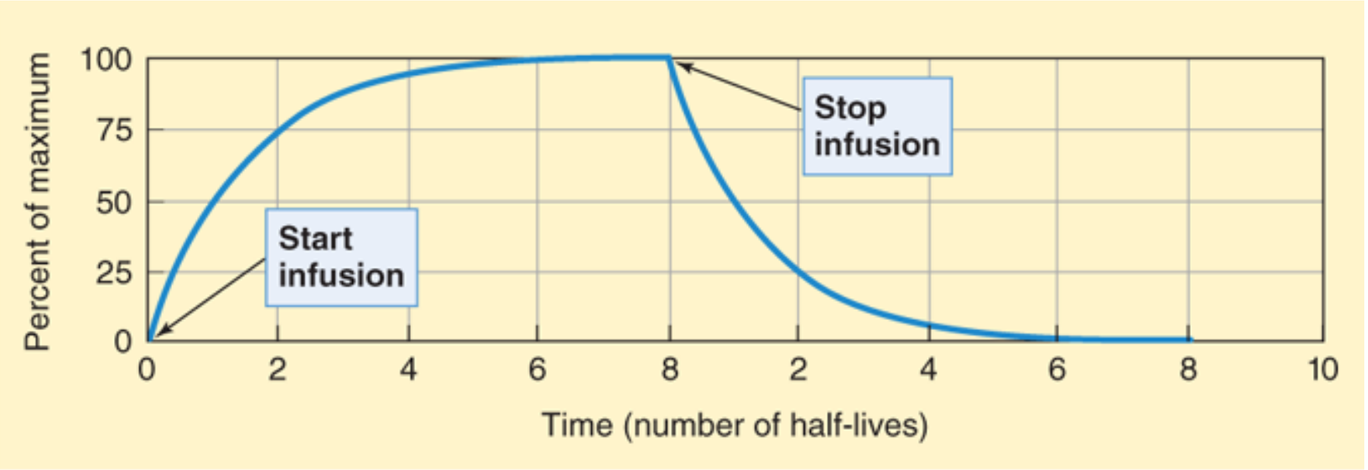
Most drug elimination pathways will become saturated if the dose is high enough→…→ toxicity.

Multidose kinetics: Drug Accumulation and Steady State for drugs that exhibit first-order elimination

Continuous administration results in drug accumulation until the rate of drug going in = rate going out.

After that point, no additional accumulation occurs.

Dynamic equilibrium – steady state – is reached.



4 half-lives is the time required …

- to approach steady state and full effects to be seen, and
- for drug to be removed from the body by elimination

1 t½ → 50%
2 t½ → 75%
3 t½ → 87.5%
4 t½ → ~94%

Plasma concentration (plotted as percentage of maximum) of a drug given by constant intravenous infusion for 8 half-lives and then stopped. The concentration rises smoothly with time and always reaches 50% of steady state after 1 half-life, 75% after 2 half-lives, 87.5% after 3 half-lives, and so on. The decline in concentration after stopping drug administration follows the same type of curve: 50% is left after 1 half-life, 25% after 2 half-lives, and so on. The asymptotic approach to steady state on both increasing and decreasing limbs of the curve is characteristic of drugs that have first-order kinetics.

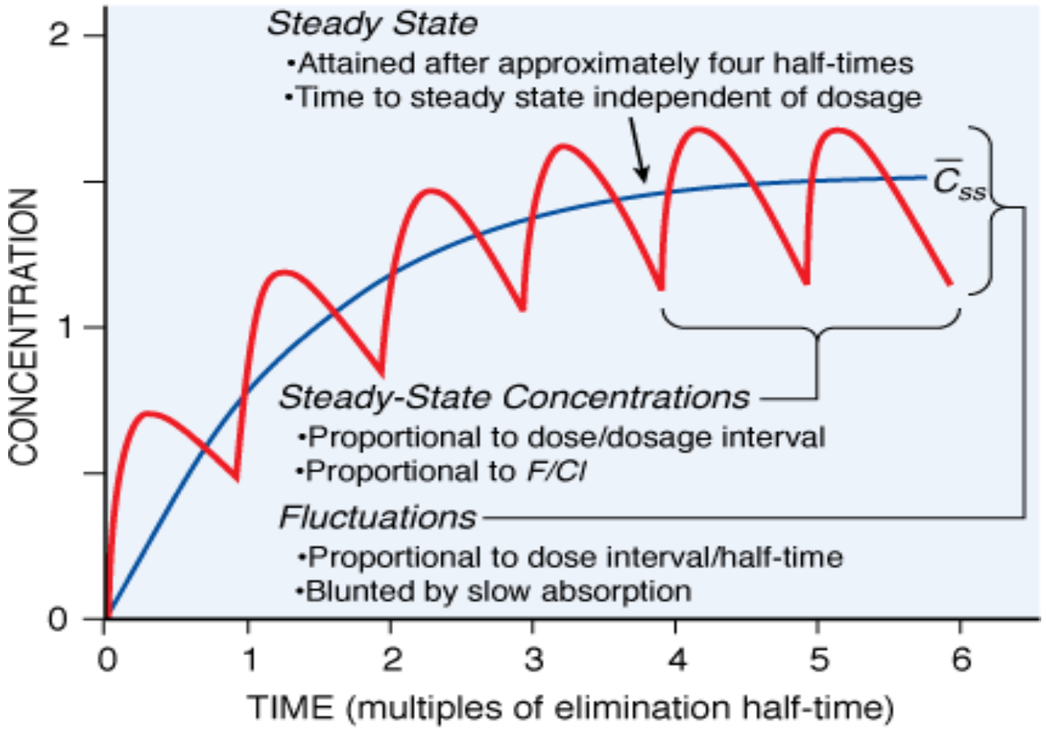
Slide adapted by LG

Drug accumulation with a continuous or intermittent dosing rate is based on the fundamental principle of clearance:

- Clearance = the volume of blood from which a drug is removed per unit of time (in mL/min or L/h)
- Clearance relates the rate of elimination to the plasma concentration (in μg/mL or mg/L)

$$\text{dosing rate} \times F = CL \times C_p$$

- Clearance of a particular drug remains constant although the actual amount of drug in the clearance volume varies with the plasma drug concentration.



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

The legend for this figure is in the notes section of the PowerPoint slide.

Steady state:

Rate of drug elimination = Rate of drug administration

when drug is administered at a constant rate.

Citation: Chapter 2 Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination, Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e;* 2017, Figure 2-7. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=166182905 Accessed: August 23, 2021

Optimizing Dosing Regimens
Therapeutic Concentration Strategy

Target concentration strategy: Application of pharmacokinetics and pharmacodynamics for individualizing dose.

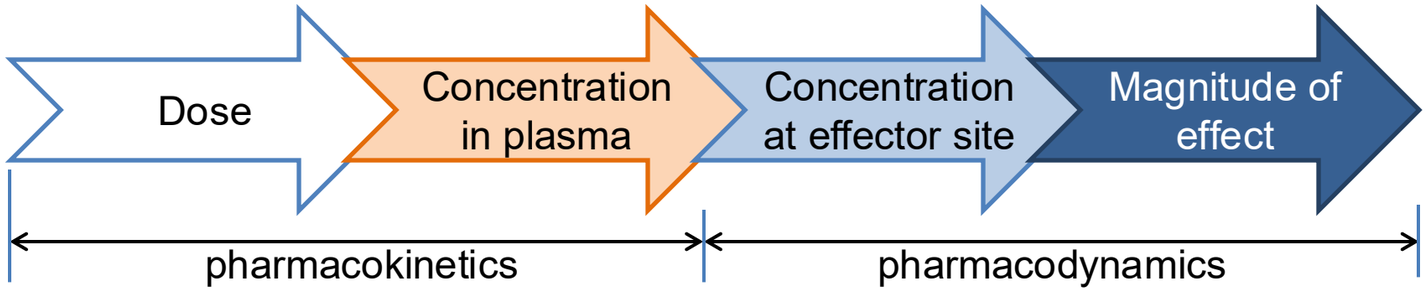
NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Basis: The assumption that the target concentration will produce the therapeutic effect.

Therapeutic Goal: To maintain steady state drug levels within the therapeutic range to provide therapeutic efficacy and minimum toxicity

Target concentration strategy: Desired steady state concentration (C_{ss}) is selected and a dose is calculated that is predicted to achieve this value.

Dosage adjustments: The standard dose based on heathy individuals is not suitable for all patients. Physiologic and pathologic processes may be applied for dose adjustment in the individual patient. Drug concentrations may guide dose changes. Information is in the drug monographs.



Therapeutic Window:

The range associated with therapeutic efficacy and a minimum of toxicity for a given agent

Peak concentration:

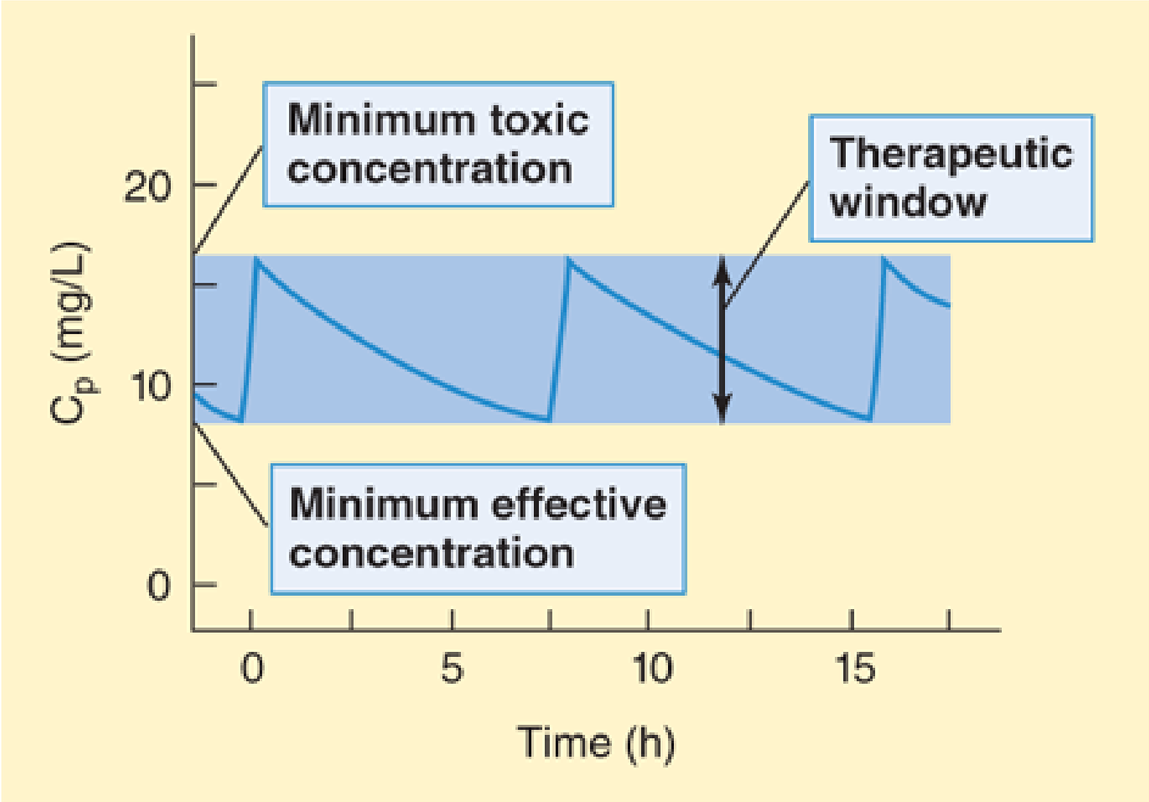
The maximum concentration (C_{max}) achieved during repeated dosing cycles.

Trough concentration:

The minimum drug concentrations achieved during repeated dosing cycles.

Minimum effective concentration:

the minimum concentration required to produce a therapeutic effect



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

The therapeutic window for theophylline in a typical patient. The minimum effective concentration in this patient was found to be 8 mg/L; the minimum toxic concentration was found to be 16 mg/L. The therapeutic window is indicated by the blue area. To maintain the plasma concentration (C_p) within the window, this drug must be given at least once every half-life (7.5 h in this patient) because the minimum effective concentration is half the minimum toxic concentration and C_p will decay by 50% in 1 half-life. (Note: This concept applies to drugs given in the ordinary, prompt-release form. Slow-release formulations can often be given at longer intervals.)

Citation: Chapter 3 Pharmacokinetics, Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. *Katzung & Trevor's Pharmacology: Examination & Board Review, 13e;* 2021, Figure 3-6. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3058&sectionid=255304212 Accessed: August 18, 2021

Target Calculation Approach to Rational Dosing

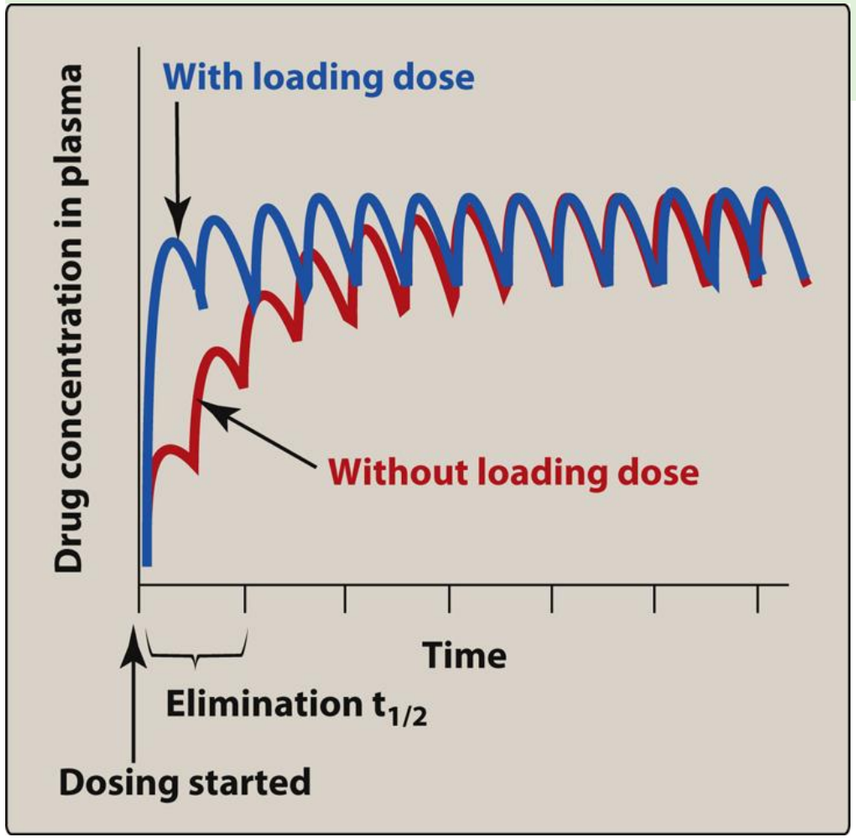
$$\text{Loading Dose} = \frac{V_d \times C_{ss\ \text{desired}}}{F}$$

relates amount of drug in the body to drug concentration in plasma

$$\text{Maintenance dosing rate} = \frac{C_{ss\ \text{desired}}}{F} \times CL$$

relates the dosing rate to the rate of elimination at steady state

From: **1 Pharmacokinetics**
Lippincott® Illustrated Reviews: Pharmacology, 8e, 2023



Legend:

Accumulation of drug administered orally without a loading dose and with a single oral loading dose administered at t = 0.

A loading dose promptly raises the concentration of drug in plasma to the target plasma concentration ($C_{desired}$ or C_{ss})

- V_d is the proportionality factor that relates total amount of drug in the body to the concentration in plasma.
- V_d at steady state V_{ss} is clinically relevant and used to determine the loading dose.

$$V_d = \text{dose} / C_{ss} \rightarrow$$

$$\text{Loading dose} = \frac{V_d \times C_{ss}}{F}$$

Loading doses are larger than maintenance doses.

Loading dose may be desirable when steady state concentration should rapidly be reached (emergent situations) or for drugs with long $t_{½}$, when considerable time is required to reach steady state.

Loading dose example:
Theophylline intravenously for relief of acute asthma attack

- Theophylline V_d is 35 L for a 70 kg person
- $C_{p\ desired}$ is 10 mg/L (adult)
- F = 1 for intravenously administered drugs

$$LD = (V_d \times C_p) / F$$

$$LD = (35\ L \times 10\ mg/L) / 1 = 350\ mg\ I.V.\ for\ a\ 70\ kg\ person.$$

PK parameters are listed on Katzung & Vanderah's Basic & Clinical Pharmacology Table 3–1

Risk of toxicity when using loading dose

Sensitive individuals may be exposed abruptly to a toxic concentration of a drug.

Excessive concentration may take a long time to fall if drug involved has a long t½.

Toxic effects may result from actions at undesirable sites.

- loading doses tend to be large, based on calculation using V_{ss}
- rapid administration – LD is often administered by rapid intravenous injection.

Example: Maintenance dose calculation

Maintenance dose is administered after the loading dose is given to maintain plasma level within the therapeutic window.

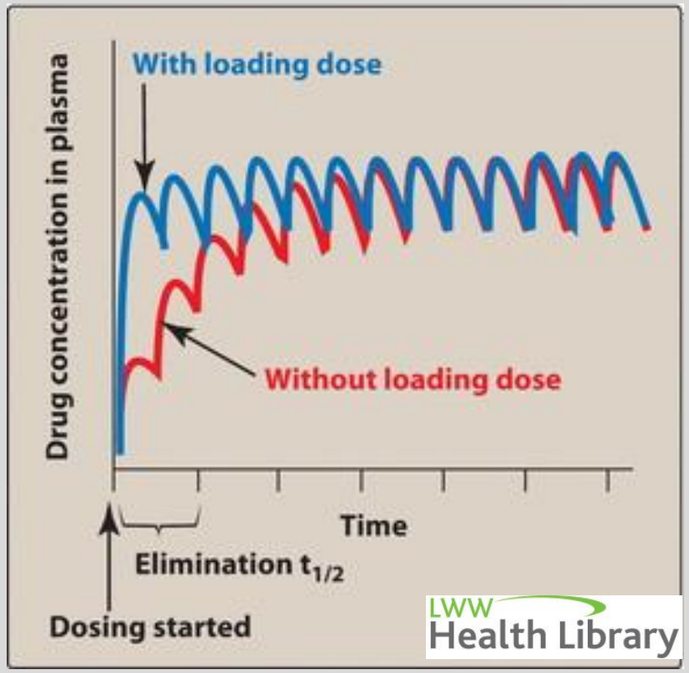
For theophylline, the maintenance dose by continuous IV infusion:

PK parameters:

- $C_{p\ desired}$ = 10 mg/L
- *CL* = 2.8 L/h/70 kg
- *F* = 1 (I.V.)
- **Dosing rate = (*CL* x $C_{p\ desired}$) / 1**

  = (2.8 L/h x 10 mg /L) / 1

  = 28 mg/h for 70 kg person



PK parameters are listed on Katzung's Basic & Clinical Pharmacology Table 3–1

Switch to oral maintenance dose when asthma attack is relieved and the patient is stable.

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

$$MD = \frac{CL \times Css_{desired} \times \tau}{F}$$

- Theophylline $F_{oral} = 0.96$
- τ (tau) dosing frequency = every 12 hours

MD = (2.8 L/h x 10 mg /L) / 0.96 x 12

= (28 mg/h / 0.96) x12h = 26.88 mg/h x12 = 322.56 mg per dose

Commercially available:

= 350 mg extended release tabs every 12 hours for a 70 kg patients

➢ Practice point:
F=0.96 is nearly 100% bioavailability.
In practice, *F*=1 would be used.
When *F*=1, it is omitted from the calculations.

Optimizing theophylline therapy:

Theophylline has a narrow therapeutic window and considerable interpatient variability → Monitor theophylline serum levels.

Pharmacokinetic and Pharmacodynamic Variables influencing plasma concentration and response

Disease states may modify a patient's response to drug therapy.

Factors that potentially affect Drug Absorption, *CL* and V_d

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Absorption from GI tract	• Solubility in enteral fluid • Acid-base characteristics • Lipid solubility • Food (presence/absence)	• Coadministration with other drugs that complex with it in gut (such as antacids, cholestyramine) • Blood flow to gut • GI transit time	
Clearance, impaired organ function	Hepatic: Unpredictable (related to intrinsic hepatic clearance)	Renal: ↓*CL* for drugs excreted in urine	Heart failure or shock: Decreased perfusion of liver, kidneys → ↓*CL*
Volume of distribution	Edema, ascites, pleural effusion: ↑total body water →↑V_d for hydrophilic drugs that distribute in body water	• ↑Plasma protein binding → ↓V_d as more drug molecules remain in plasma • ↑Tissue binding →↑V_d	• ↓Skeletal muscle mass → ↓V_d • Obesity → ↑V_d for lipophilic drugs

Factors influencing pharmacokinetic parameters

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Effects on volume of distribution	**Effect on t½**
Aging: ↓ muscle mass → ↓ distribution	↓ t½
Obesity: ↑ adipose mass → ↑ distribution	↑ t½
Pathologic fluid: ↑ distribution	↑ t½
Effects on clearance	
Cytochrome P450 induction: ↑ metabolic rate → ↑ elimination rate, ↑ CL	↓ t½ and reduction of therapeutic effect
Cytochrome P450 inhibition: ↓ metabolic rate → ↓ rate of elimination, ↓ CL	↑ t½, drug accumulation and increased risk of toxicity
Cardiac failure: ↓ clearance	↑ t½
Hepatic failure: ↓ clearance	↑ t½
Renal failure: ↓ clearance	↑ t½

Pharmacodynamic variables influencing response

- Maximum effect attainable in the target tissue (E_{max})
- Sensitivity of the tissue to the drug

Individualizing Drug Therapy

Fundamental principles to guide prescribing

The **benefits** of drug therapy should always outweigh the risk.	Select a **therapeutic objective** (goal of therapy).
Simplify the dosing per day and minimize the number of drugs as appropriate.	**Choose a drug therapy** on the patient characteristics and clinical presentation.
Genetics play a role in interpatient variability to drug response.	**Determine** the appropriate dose and dosing schedule.
Prescribers should use only a limited number of drugs with which they are **thoroughly familiar**.	**Electronic medical records** and pharmacy systems increasingly incorporate prescribing information, such as unindicated medications being prescribed, potential dosing errors, drug interactions, and genetically determined drug responses
Provide **patient education** on the disease and treatment. Repeat, extend, and reinforce the information to the patient as often as necessary.	

Therapeutic monitoring of drug plasma concentration in the individual patient: *maximizing effect while minimizing toxicity*

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Measuring the concentration of drug in plasma has utility when there is a/an:

Relationship between the concentration of drug in plasma and the clinical effect	Significant inter- / intra-patient pharmacokinetic variability
Established target concentration	Narrow therapeutic window

Availability of a reliable, cost-effective drug assay for clinical use

Measuring drug concentrations in plasma or serum establishes the **individual** patient's pharmacokinetics.

One well-done drug concentration is more valuable than any algorithm that seeks to predict concentration or effect using patient characteristics, comorbidities, or other factors.	Poorly-done therapeutic monitoring may produce results that are misleading, and in this way are worse than having no testing at all.
The duration of an infusion and the correct timing of the sample after the infusion are critical to having results that can be assessed in light of published data and guidelines.	
The major use of measured concentrations of drugs (at steady state) is to **refine the estimate of *CL/F*** (oral clearance) for the patient being treated. *CL/F* (patient) = dosing rate / C_{ss} (measured)	

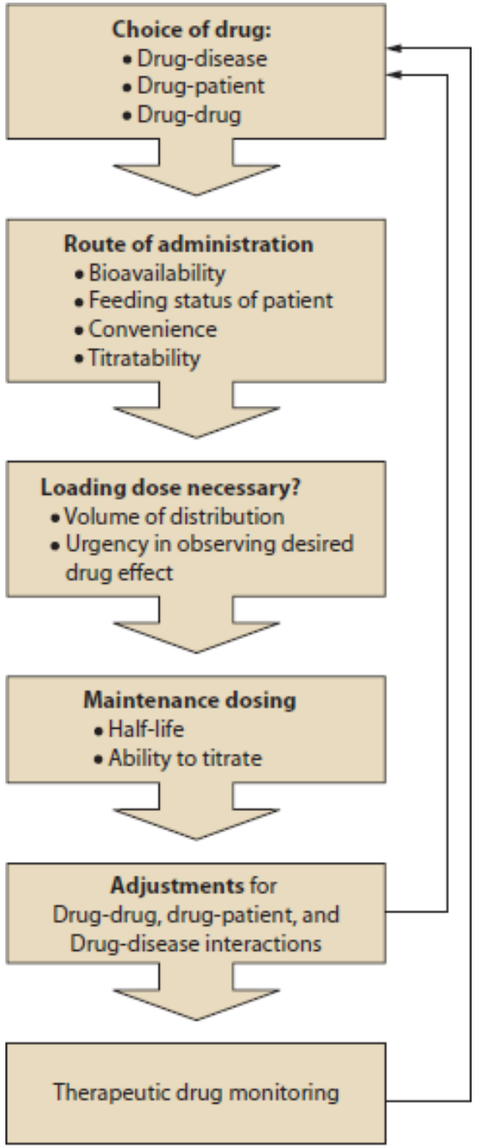
Summary of Clinical Pharmacokinetics, Part 2

- The elimination half-life is a measure of the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%. Half-life is a function of volume of distribution and clearance. Half-life elimination curves track the amount of drug in the body over time.
- In first-order elimination kinetics, the drug elimination rate is directly proportional to plasma free drug concentration. Most clinically relevant drugs follow first-order kinetics.
- In zero-order elimination kinetics, the metabolic enzymes eventually will become saturated as the concentration of substrate increases. The rate of drug elimination is constant (a constant amount) and independent of plasma drug concentration. A few drugs follow zero-order kinetics at therapeutic concentrations.

- When a drug that exhibits first-order pharmacokinetics is administered to a patient continuously or intermittently, the drug will accumulate until it reaches a plateau – a dynamic equilibrium = steady-state plasma drug concentration.
- The time to reach the steady state is a function of the elimination half-life of the drug. Four half-lives is 94% of steady state concentration and provides full therapeutic effect. If the half-life or the dosing rate changes, it will again take 4 half-lives to approach the new steady state plasma concentration.
- The therapeutic goal of the target concentration strategy is to maintain steady state drug levels within the therapeutic range to provide therapeutic efficacy and minimum toxicity. This approach links pharmacokinetics and pharmacodynamics.

- A loading dose rapidly raises the plasma drug concentration to the target concentration. The volume of distribution relates the total amount of drug in the body to plasma drug concentration: LD = (V_d x $C_{desired}$)/F
- The maintenance dose is administered after the loading dose to maintain the desired steady state concentration: MD = (CL x $C_{desired}$)/F.
- Disease states may modify pharmacokinetic parameters and pharmacodynamic actions and response to drug therapy.
- Optimization is based on in-depth understanding of factors that determine an individual's response to drug treatment.
- *Fundamental principles should guide prescribing of drugs.*

Flowchart for a suggested method of design for a rational drug dosing regimen.



- Individualization of drug therapy involves careful consideration of the patient's unique clinical status for each step along the path of drug prescription and dosing.
- The initial choice of drug, route of administration, loading dose, and maintenance dose calculations involve consideration of desired drug effects, titratability, and convenience.
- Modifications of the dosing regimen may be required to accommodate the individual characteristics of the patient, including allergies, age, sex, and race; potential drug-drug interactions; and potentially confounding disease states.
- Once a drug regimen is designed and implemented, therapeutic drug monitoring is indicated to ensure adequate drug effect and to minimize potential adverse events.
- The results of therapeutic drug monitoring may indicate the need for further modification of the drug regimen.

Legend: Flowchart for a suggested method of design for a rational drug dosing regimen. This illustration serves to depict the process of drug prescription and dosing as a perpetual cycle of actions. Individualization of drug therapy involves careful consideration of the patient's unique clinical status for each step along the path of drug prescription and dosing. The initial choice of drug, route of administration, loading dose, and maintenance dose calculations involve consideration of desired drug effects, titratability, and convenience. Modifications of the dosing regimen may be required to accommodate the individual characteristics of the patient, including allergies, age, sex, and race; potential drug-drug interactions; and potentially confounding disease states. Once a drug regimen is designed and implemented, therapeutic drug monitoring is indicated to ensure adequate drug effect and to minimize potential adverse events. The results of therapeutic drug monitoring may indicate the need for further modification of the drug regimen.

Citation: CHAPTER 125 Critical Care Pharmacology, Hall JB, Schmidt GA, Kress JP. *Principles of Critical Care, 4e;* 2015, Figure 125-5. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=1340&sectionid=80028183 Accessed: August 25, 2021

References

- Access Medicine Goodman & Gilman's The Pharmacological Basis of Therapeutics 14e; 2023; Chapter 2: Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination
- Access Medicine Harrison's Principles of Internal Medicine, 21e, 2022; Chapter 67: Principles of Clinical Pharmacology
- Access Medicine Katzung's Basic & Clinical Pharmacology 16e, 2024: Chapter 3: Pharmacokinetics & Pharmacodynamics: Rational Dosing & the Time Course of Drug Action, and Chapter 66: Rational Prescribing & Prescription Writing
- Access Medicine Principles and Practice of Hospital Medicine, 2e, 2017; Chapter 9: Principles of Evidence-Based Prescribing

NEW YORK INSTITUTE OF TECHNOLOGY

College of Osteopathic Medicine

Lecture Feedback Form:

https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R