About This Book

This book was written to acclimatize the pharmacy student or other healthcare student or professional to the discipline of pharmacokinetics. Typically, the pharmacokinetics curriculum in most schools of pharmacy is less well “appreciated” by students compared to other classes. This “lack of appreciation” or disinterest is likely attributable, in part, to the mathematical nature of the subject. Another contributing factor may be the fact that memorization-based learning strategies do not fare well in pharmacokinetics. As in many other disciplines, memorization of some basic principles is necessary; however, the ability to appropriately apply these basics under a variety of contexts is paramount to success. Thus, application of critical thinking and reasoning skills is the best method to learn pharmacokinetics. The goal of this book is to assist the reader in developing an appropriate level of comfort with relevant mathematical formulae and techniques in order to provide a foundation for progression to more advanced therapeutic concepts.

How to learn pharmacokinetics using this book

A complete mastery of the field of pharmacokinetics cannot be accomplished in one semester, one year, or even one lifetime. This book is intended to supplement the concepts discussed in the classroom by both providing an overview of the essential ideas and offering general guidance for dealing with clinical situations you may encounter. Simply reading about pharmacokinetics will not be sufficient to develop an understanding of the topic. This book is only one component of your pharmacokinetics education. You must spend time thinking about concepts discussed in the classroom and in this book. Ask questions of yourself, your classmates, and your instructors. Identify areas in which you have difficulty, and ask questions (preferably before exams). Merely talking about pharmacokinetics is beneficial, thus you may also benefit from forming discussion groups. Since not all students learn effectively by the same mechanisms, one aim of this book is to approach problems from a variety of angles, and to accommodate different types of learning styles. Each chapter includes learning outcomes, highlights of important concepts in the margins, and a summary of new equations, symbols and skills obtained.

Special thanks to Gary M. Pollack, PhD, Jeannie Padowski, PhD, and Kerri A. McEnroe for help in putting this book together and all editorial comments. Special thanks for all the student-pharmacists who offered input on making the book better. Finally, a special thanks to Gunther Hochhaus, PhD for daring me to write a book.
The SQ4R Method of Reading

The SQ4R method of reading is based on some well-established principles of learning from cognitive psychology. Numerous studies indicate using the SQ4R method can make a significant difference in the amount of information recalled at a later time point (like examinations). SQ4R leads to a more active learning environment and deeper processing of information. Most students use a rather passive learning strategy. Passively reading your notes may lead to the 'labor in vain' effect, where you work very hard, but remember very little.

**SURVEY**

Take a look at the material: skim the chapter headings and the boldface words, and read the learning objectives. Studies show that subjects who read a summary recalled the material better, particularly when they read the summary first. This is why this book starts with a chapter “In Brief”.

**QUESTIONS**

Make up questions about the things you found in the preview and from the learning objectives. Often you can just transform a section heading into a question. For example, the section heading might be Zero-order vs. First-order kinetics, and you could then develop questions that state “What is the difference between zero-order and first-order kinetics?” This simple technique could double the amount you can remember.

**READ**

As you read, try to answer the questions you developed. Make notes as you read. Understand the vocabulary. It is extremely important that any notes you make are in your own words and not merely duplicating the exact wording used in the text.

**RECITE**

Say the material over to yourself; put it into your own words. Answer the questions you developed. One form of recitation is to try to write your own study guide - write out the ideas in your own words, using your own organization. Another form is to try to explain the ideas to somebody else; imagine explaining perceptual maps to your mother. Or perhaps you can invent mnemonics to help remember terms. If you can't recall enough, reread sections you had trouble remembering.
**WRITE (or RECALL)**

Write down summaries in your own words. Recall information as much as possible as if you are taking a quiz or assessment. Practice recall, practice problem solving, then practice some more. Practicing recall can be more effective than simply re-reading the material.

**REVIEW**

Try to recall the material and test yourself. Study partners can help here. Making up a quiz for yourself as part of recitation and then taking it as review is a good way to study. You should review several times during your studying so you know what to concentrate on. Again, try answering the questions you made up.
# Table of Contents

About This Book........................................................................................................2
The SQ4R Method of Reading..................................................................................3
Table of Contents....................................................................................................5

1) Introduction ........................................................................................................6
2) Pharmacokinetic Tools....................................................................................11
3) Distribution Phenomenon.............................................................................25
4) Clearance Concepts ....................................................................................36
5) Intravenous Bolus .......................................................................................47
6) Extravascular Administration ........................................................................57
7) Intravenous Infusion ....................................................................................80
8) Multiple Dosing ...........................................................................................95
9) Hepatic Clearance .......................................................................................127
10) Metabolite Kinetics ....................................................................................149
11) Renal Clearance ........................................................................................154
12) Multi-Compartment Models .......................................................................175
13) Nonlinear Pharmacokinetics .......................................................................193
14) Pharmacodynamic Basics ........................................................................213
Appendix A: Math Basics ....................................................................................236
Appendix B: Common Pharmacokinetic Terms and Their Units.....................244
Appendix C: Useful Equations ..........................................................................245
Appendix D: Method of Residuals .....................................................................247
Index ......................................................................................................................251
1) Introduction

**Goal**

To develop a definition of the term “pharmacokinetics” and to understand how this field of study impacts the health care system, including the pharmaceutical industry, pharmacists, patients, and researchers.

**Objectives**

*By the end of this chapter, you should be able to:*

- Describe the differences between pharmacokinetics, biopharmaceutics and pharmacodynamics
- Describe the role of pharmacokinetics in the treatment of patients and in the pharmaceutical industry
- Explain the implications of therapeutic drug monitoring and discuss the role pharmacokinetics plays in this process

**In Brief**

This chapter defines pharmacokinetics (i.e., what the body does to the drug) and pharmacodynamics (i.e., what the drug does to the body). It discusses the importance of pharmacokinetics and dynamics for patient care and describes therapeutic drug monitoring – the monitoring of medications typically with low therapeutic indexes (the ratio between the toxic and therapeutic effects). For patient care, pharmacokinetics can help facilitate decisions for dose amount and frequency or the impact of drug interactions. Within the pharmaceutical industry, pharmacokinetics helps determine the appropriate dose and adds to labeling information. In the hospital setting, we have direct and measurable information to inform our pharmacokinetic analysis (e.g., serum creatinine, blood concentrations of drug, pharmacodynamics effects like INR). In the community setting we often do not have these direct and measurable information, but we have context clues. Understanding the patient (e.g., elderly, obese, pregnant) and their medications (e.g., which are renal cleared) are important in counseling and medication selection.

**Introduction**

*Pharmacokinetics* (PK) is the study of how a drug behaves in the body. In other words, pharmacokinetics is the study of “what the body does to a drug”. Most textbooks use the acronym ADME to refer to four processes relevant to pharmacokinetics, with A standing for absorption (how the drug gets into the body), D for distribution (where the drug
goes once inside the body), M for metabolism (what enzymes metabolize what drugs, and how rapidly drugs are metabolized) and E for excretion (how drugs are removed from the body). Despite the commonplace use of “ADME” as a definition of “pharmacokinetics”, the two terms are not truly equivalent. Pharmacokinetics is more accurately described by the acronym “ITE”. In this case, I stands for input into the body, since some routes of administration do not have absorption components (e.g., intravenous administration), T for transfer of drug within the body, and E for elimination from the body (which includes metabolism, since metabolism is a major route of drug elimination). Each of these three pharmacokinetic processes will be emphasized throughout this book.

In summary, the term pharmacokinetics encompasses the fate of a drug after administration to the body, with respect to the drug’s (or metabolite’s) time course of input into the body, transfer within the body, and elimination from the body. Clinical pharmacokinetics pertains to the application of pharmacokinetic principles to individual patients, in order to safely and effectively manage drug therapy.

With an understanding of pharmacokinetics, pharmacists, doctors and other health-care professionals can increase the effectiveness, decrease the toxicity, or increase patient compliance with a therapeutic regimen. The majority of the adverse drug reactions seen in the clinic are dose-related, thus an understanding of pharmacokinetics can help minimize these problems. Application of pharmacokinetic principles can enhance patient compliance by 1) allowing establishment of patient-friendly dosing regimens (QD, q week, etc.) or 2) enabling formulation of controlled- or extended-release products, reducing dosing frequency. For example, depression is not well-controlled pharmaceutically when therapeutic compliance rates are low. Prozac ® (fluoxetine) was originally marketed as a once daily (QD) formulation, however introduction of a once weekly (q weekly) formulation of fluoxetine can improve patient compliance, and thus clinical outcome. The change from once a day to once a week amounts to approximately 300 tablets a patient does not have to take in a year by switching to a once weekly tablet!

As mentioned, the term pharmacokinetics refers to the behavior of drug in the body. Biopharmaceutics refers to the influence of the dosage form of a drug on its behavior in the body (e.g., blood concentrations) and its subsequent pharmacologic effect. This concept relates back to our previous discussion of improving patient compliance by designing formulations with patient-friendly dosing regimens. Switching dosage forms (e.g., once daily to once weekly) will change a drug’s concentration versus time profile, however the therapeutic effect may be maintained despite the less frequent dosing.
The goal of pharmacokinetics is to obtain the desired drug concentration in the body by optimizing the dosage regimen and dosage form. The problem with attaining this goal lies in the determination of the optimum target concentration. The solution to this problem is found in the field of pharmacodynamics (PD), or the study of the relationship between the drug concentration at the site of action and the pharmacologic response. Unfortunately, we typically do not know the drug concentration at the site of action, so we estimate it based upon plasma concentrations. Pharmacodynamics will be discussed in depth in a later chapter, but to be brief, a correlation often exists between drug concentration at the site of action and pharmacologic response. As mentioned, since we often do not know concentrations at the site of action (i.e. concentrations surrounding the receptor in a given tissue), plasma levels are frequently used as indicators of tissue concentration. Thus, blood concentrations are used to optimize the dose of the drug – that is, to maximize therapeutic effect and minimize adverse effects.

**Table 1-1: Common Terms and Definitions**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>The <em>intrinsic</em> behavior of a drug in the body</td>
</tr>
<tr>
<td>Clinical pharmacokinetics</td>
<td>Behavior of drugs in humans</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>The impact of dosage form on behavior of a drug in the body</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>The effect of the drug on the body</td>
</tr>
</tbody>
</table>

**Therapeutic Drug Monitoring**

Throughout the drug development process, researchers investigate drug disposition to understand the pharmacodynamic (concentration versus effect) and pharmacokinetic (concentration versus time) relationships. However, a growing appreciation of biological variability (the fact that not all patients behave the same, clinically) has led to the idea that the same dose may produce different concentrations in different patients based upon variability in absorption, distribution, metabolism, elimination, enzyme induction, disease state or drug interactions. For certain drugs, this biological variability can be great enough to warrant therapeutic drug monitoring (TDM) in individual patients (Figure 1-1).
TDM allows the healthcare professional to adjust the dose to achieve optimal drug concentrations in the body, based upon the assumption that there is a correlation between therapeutic effect and plasma concentrations. For example, there are certain drugs used in clinical practice that are considered to have a narrow therapeutic index (e.g., digoxin, aminoglycosides, lidocaine, lithium, phenobarbital, phenytoin, theophylline, etc.). This means that the therapeutic drug concentrations are fairly close to concentrations that are associated with toxicity (e.g., 2-fold or so). Small changes in drug concentrations for these types of drugs can cause severe adverse events. For example, lithium is prescribed in the treatment of manic-depressive disorders. The desired plasma concentrations of lithium are 0.6 to 0.8 mEq/L for long-term maintenance. If lithium concentrations reach 1.2 to 1.5 mEq/L, symptoms such as fatigue, nausea and tremor might occur. At concentrations of 1.5 to 3 mEq/L, the patient might show signs of confusion, agitation or slurred speech, while concentrations > 3 mEq/L can lead to coma or death. Again, the concentrations producing therapeutic benefit are not far apart from concentrations producing adverse effects, thus patients must be monitored to minimize adverse events from occurring. Be aware, however, that toxic or therapeutic concentration limits are not absolute; ultimately, patient response will dictate the appropriate dose.

Figure 1-2 is a simple schematic of how a patient’s therapy is managed. Once the disease is diagnosed and an appropriate course of treatment is decided, therapy can be initiated using standardized regimens. For example, a patient diagnosed with mania is started on 150 mg lithium TiD. A few weeks after starting therapy, a blood sample is drawn and the concentration is lower than predicted, and more importantly, lower than the therapeutic concentrations. The dose of lithium would thus be increased, and a blood sample drawn a few weeks later to monitor the patient’s progress. This process of checks and balances ensures that the patient’s disease is being controlled.
Hopefully now you have an appreciation of what pharmacokinetics is and why we as healthcare professionals need to know about it. The ultimate goal is the patient’s response to drug therapy. Pharmacokinetics can help answer some of your patients’ questions, such as “How often do I need to take this drug?”; “What is the half-life of the drug?”; “Why can’t I take this drug with grapefruit juice?”; and “Are generic drugs really the same?”. Improvements in patient care result from effective implementation of principles of pharmacokinetics, pharmacology, pharmaceutics and pharmacotherapy. The rest of this book will guide you on how to obtain pharmacokinetic parameters from patient data and how to use these calculations to recommend appropriate changes in therapy.

**Conclusion**

Pharmacokinetics allows us to describe how a drug behaves in the body as well as how to use this information to make useful predictions. For example, pharmacokinetic principles will allow you to estimate the rate of a drug’s clearance from the body. This information will enable you to predict the drug concentrations that will result if you, for example, double the dose. If you can control the concentrations of drug in the body, you can also control the pharmacodynamic responses of the drug to optimize therapeutic effects and minimize the risk of side effects.
2) Pharmacokinetic Tools

Goal:

To introduce basic pharmacokinetic principles and data analysis techniques, and to gain proficiency in using these techniques.

Objective:

*By the end of this chapter, you should be able to:*

- Describe the components of an equation for a straight line
- Explain the differences between a zero-order and a first-order process
- Calculate the area under the concentration-time curve (AUC) using the piece-wise method (i.e., trapezoidal rule)
- Select appropriate data points and be able to calculate the terminal half-life of a drug
- Discuss why half-life is calculated for first-order but not zero-order processes

**In Brief**

Pharmacokinetics is based in math; for this course we use algebra. We often plot drug concentration versus time to calculate pharmacokinetic parameters and understand drug behavior. We use the straight line (either on a rectilinear or the semi-log coordinates) to gather information about the system (zero-order, first-order, half-life). In a zero-order system, drug concentrations change consistently in a mass per time ratio (milligrams of drug per time). This is in contrast to a first-order system, where change is measured in a fractional sense (50% lost over time). This chapter also discusses the area-under-the-curve, a measure of systemic drug exposure, and how we can calculate it by making trapezoids of the concentration-time profile. From the concentration-time profile, we can also recover patient specific parameters like half-life.

**Introduction**

Pharmacokinetics is inescapably a mathematical discipline. Most of the relevant clinical calculations involve simple algebra; however, understanding some calculus is required to grasp basic pharmacokinetic concepts. We will slowly develop a foundation of concepts and terminology that will be used throughout the book. Please note that some symbols used in this book may differ in other texts. There is no consensus on
pharmacokinetic symbols, but this text uses the most common symbols. Also please be aware that certain symbols appear very similar (e.g., the letter F is used to describe several pharmacokinetic terms). The Appendix at the end of this book lists the symbols and their meanings.

**The Straight Line**

Calculations involving straight lines are essential for solving many pharmacokinetic problems. It is of the utmost importance to understand the equation that describes a straight line.

Figure 2-1: Concentration vs. time data plotted on rectilinear coordinates

Figure 2-1 depicts a straight line and is described by the following equation

\[ y = m \cdot x + b \]

where ‘y’ is the dependent variable (drug concentration in pharmacokinetics), ‘x’ is the independent variable (time in pharmacokinetics), ‘m’ is the slope of the line and ‘b’ is the y-intercept (the point where the line crosses the y-axis). Please review this equation if it is unfamiliar to you.

The slope is a very important parameter, as it defines the rate of change. The sign value of the slope can either be positive (+), indicating the line is going up and to the right, or negative (-), indicating the line is going down and to the right. In pharmacokinetics, the slope or rate of change is usually assigned the letter ‘k’ and is usually reported as the absolute value. The slope of a line can be determined by the calculating the change in y (Δy) divided by the change in x (Δx) as seen in Table 2-1. The ability to calculate a slope is critical in pharmacokinetics.
Table 2-1: Example calculation to determine the slope of a line

<table>
<thead>
<tr>
<th>Time (h) (x-axis)</th>
<th>[Drug] (mg/L) (y-Axis)</th>
<th>Δx</th>
<th>Δy</th>
<th>Slope (k=Δy/Δx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>75</td>
<td>1 (= 1-0)</td>
<td>-25 (=75-100)</td>
<td>-25</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>1 (= 2-1)</td>
<td>-25 (=50-75)</td>
<td>-25</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>2 (= 4-2)</td>
<td>-50 (=0-50)</td>
<td>-25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Average</td>
</tr>
</tbody>
</table>

Figure 2-2: Method for calculating the slope of a straight line

Translating the basic equation for a line (y = mx+b) into pharmacokinetic terms, we get:

\[ C = -k \cdot t + C_0 \]  

Equation 2-2

where C is the concentration (dependent variable) at a specific time, t; k is the rate constant describing the change in concentration versus time (slope; note the negative symbol indicating loss of drug with time); t is time (the independent variable); and \( C_0 \) is the concentration at time zero (the y-intercept).

**Elimination Rates**

We often need to predict how a drug concentration in the plasma (or other body fluid) will change over time. Typically either zero-order or first-order processes govern the elimination of drugs. The “rate” of reaction refers to the speed at which the reaction takes pace. The “order” of the reaction refers to the influence of reactant concentrations on the rate of reaction.
Zero-Order Processes

Zero-order processes occur relatively rarely in pharmacokinetics, but may be encountered in the context of intravenous infusions (infusion is a zero-order process) as well as elimination of some drugs (e.g. ethanol). For example, a zero-order elimination process involves elimination of a constant amount of drug per unit of time, with the rate of elimination being independent of drug concentration. As depicted in the Table 2-2, a given dose of drug results in an initial concentration of 200 mg/L. Over time, these concentrations will decrease. Notice what happens to the amount of drug lost relative to the percent of drug lost.

Table 2-2: Example of a zero-order loss of drug over time.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] (mg/L)</th>
<th>Amount Lost (mg/L)</th>
<th>Percent Lost (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>200</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

Notice that the amount of drug eliminated each hour remains the same over time, however, the percent of drug lost each hour changes. Figure 2-3 shows that if you were to plot drug concentrations versus time (on rectilinear coordinates), the concentration-time relationship would be best described by a straight line (y=mx+b).

![Graph](image.png)

Figure 2-3: Depiction of zero-order processes, plotted on rectilinear coordinates

The change in drug mass or concentration (written as dX or dC, respectively, when using differential equations) with respect to the change in time (written as dt) is equal to the product of the rate constant of change ‘k0’ (note: the subscript zero indicates that it is a zero-order rate constant and the negative sign indicates that drug concentration is decreasing.

Fun Fact: Ethanol follows zero-order elimination. One drink (12 oz beer or 1 shot = 1.5 oz) will be metabolized per hour or 1 oz ethanol/h
over time) and concentration to the zero power (hence being called a zero-order reaction, and anything to the zero power is 1). The term \( k_0 \) has units of amount per time (e.g., mg/hr).

\[
\frac{dX}{dt} = -k_0 \cdot X^0 \quad \text{Equation 2-3}
\]

Using calculus to solve this equation, you can predict a drug concentration at any given time using equation the following equation.

\[
C = -k_0 \cdot t + C_0 \quad \text{Equation 2-4}
\]

Note the similarity between this equation and the equation for a straight line. With Equation 2-4, given any 3 variables in that equation \((k_0, t, C_0, C)\), the final variable can easily be determined. For example, if \( C_0 = 100 \text{ mg/L} \) and \( k_0 = 25 \text{ mg/h} \), what will the concentration be in 2 hours? The answer is 50 mg/L.

Going back to the beginning of this discussion, we said that infusion rate and elimination of some drugs follow zero-order processes. Infusion rates have units of mass per time (e.g., mg/h), thus a constant amount of drug is administered over a given interval. For example, maybe we want to give 10 mg of drug during a half-hour infusion. The infusion rate is 10 mg / 0.5 h or 20 mg/h. Ethanol is the classic example of a drug eliminated by zero-order elimination. The reason for this, as further discussed in the chapter on nonlinear pharmacokinetics, is that at recreational doses, ethanol saturates the metabolic enzymes responsible for its metabolism, approaching the maximal velocity of the metabolic system (i.e., the \( V_{\text{MAX}} \)). \( V_{\text{MAX}} \) usually has units of mass per time (e.g., mg/h).

**First-Order Processes**

\[
A + B \underset{k}{\longrightarrow} C
\]

As discussed earlier, zero-order processes involve a *constant amount* of drug eliminated in a certain time (e.g., 50 mg per hour). First-order processes involve a *constant proportion* of drug eliminated in a certain time (e.g., 50% per hour) and are dependent on drug concentration. We generally assume that all pharmacokinetic processes are first-order. Most processes are actually not first-order, but most are well-approximated as first-order processes. As Table 2-3 shows, in a system with an initial drug concentration of 200 mg/L, concentrations decrease over time. Note what happens to the ‘amount lost’ and the ‘percent lost’.
Table 2-3: Example of a first-order loss of drug over time.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] (mg/L)</th>
<th>Amount Lost (mg/L)</th>
<th>Percent Lost (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>200</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
<td>12.5</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>6.25</td>
<td>6.25</td>
<td>50</td>
</tr>
</tbody>
</table>

Compare the above table to the table illustrating a zero-order system. Notice that in the first-order system, the amount lost changes over time but the percent lost is constant. Again, the change in drug amount (dX) over time (dt) is equal to the rate constant, K, multiplied by the amount (or concentration) of drug because, again, a first-order process is dependent on drug concentration. The term k is expressed in units of inverse time (e.g., h⁻¹).

\[
\frac{dX}{dT} = -K \cdot X
\]

Equation 2-5

Solving equation this equation will yield:

\[
C = C_0 \cdot e^{K \cdot t}
\]

Equation 2-6

In this situation, the actual amount of drug eliminated per unit time unit is changing, however the fraction of drug eliminated per unit time is constant.

The graphical relationship between drug concentration and time appears as a curved line on rectilinear coordinates. However, as depicted in Figure 2-4, plotting the data on semi-log coordinates (i.e., the Y-axis in log scale), or plotting the natural log (ln) of the drug concentration versus time on rectilinear coordinates, results in a linear relationship. Again, this linear relationship can be described by the equation for a line (y=mx+b).
Figure 2-4: Plasma concentration versus time relationship depicted on a linear (left) and log (right) scale.

\[ \ln C = \ln C_0 - K \cdot t \]  
Equation 2-7

The equations for a zero-order and a first-order process are similar to the equation of a straight line, as seen in the Table 2-4. Again, it is very important to know how to manipulate this equation; doing so will allow you to answer questions such as:

- If \( C_0 = 100 \text{ mg/L} \) and \( K = 0.10 \text{ h}^{-1} \), what is the concentration 6 hours later? (Answer \( C = 54.9 \text{ mg/L} \))

- If the concentration at 3 hours is 50 mg/L and \( k = 0.1 \text{ h}^{-1} \), what is \( C_0 \)? (Answer \( C_0 = 67.5 \text{ mg/L} \))

- If \( C_0 = 100 \text{ mg/L} \) and it takes 4 hours to reach a concentration of 10 mg/L, what is \( k \)? (Answer \( K = 0.576 \text{ h}^{-1} \))

- How long will it take for concentrations to fall from 100 mg/L to 25 mg/L if \( K = 0.2 \text{ h}^{-1} \)? (Answer \( t = 6.9 \text{ hours} \))

Table 2-4: Comparison of equations between that of a general line and for zero-order and first-order processes

<table>
<thead>
<tr>
<th></th>
<th>General Equation</th>
<th>Zero-Order</th>
<th>First-Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent Variable</td>
<td>y</td>
<td>C</td>
<td>( \ln C )</td>
</tr>
<tr>
<td>Independent Variable</td>
<td>x</td>
<td>t</td>
<td>t</td>
</tr>
<tr>
<td>Slope</td>
<td>m</td>
<td>-( k_0 )</td>
<td>-K</td>
</tr>
<tr>
<td>Y-intercept</td>
<td>b</td>
<td>( C_0 )</td>
<td>( \ln C_0 )</td>
</tr>
</tbody>
</table>

Please note that although we have discussed zero-order and first-order processes separately, they can occur simultaneously within the body. For example, during an infusion, a drug is administered at a zero-order
rate (e.g., 100 mg/hr), but it may be eliminated from the body as a first-order process (e.g., $K = 0.1 \, \text{h}^{-1}$).

**Half-Life**

The first-order process ($K$) also is used to calculate half-life, or the time it takes to eliminate half of the drug. By using the equation:

$$\ln C = \ln C_0 - k \cdot t$$

It is possible to rearrange and solve for $t$ to calculate the time it takes to lose half of the drug. This simple rearrangement can also be used to determine the amount of time it takes to go from one concentration to another. For example, how long will it take concentrations to fall from 50 mg/L to 5 mg/L with $K = 0.5 \, \text{h}^{-1}$? (Answer = 4.6 h)

Going back to the concept of half-life, if we start with 100% of the drug initially administered (e.g., $C_0=1$), at a certain time, $t$, we will have a drug concentration that is 50% less ($C=0.5$). Plugging in these values we get:

$$t = \frac{\ln(0.5) - \ln(1)}{k} = \frac{\ln(0.5)}{k} = \frac{\ln(1)}{k} = \frac{0.693}{k}$$

$$\therefore t_{1/2} = \frac{0.693}{k} \quad \text{Equation 2-9}$$

The rate constant of change for a first order process is inversely proportional to the half-life ($t_{1/2}$) and half-life has the units of time (e.g., hours). Half-life for a first-order process is constant, that is, half-life is independent of drug concentration. Now try the same procedure to calculate a half-life for a zero-order process. What do you find?

**Table 2-5: Example of trying to calculate half-life for a zero-order process**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] (mg/L)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>200</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>
What you should see is that half-life changes with concentration; hence, half-life is not an appropriate term to use to describe zero-order processes.

As you will learn later on, half-life can also be determined graphically from the concentration-time profile simply by reading from the graph the time it takes to lose half the drug concentration.

If two concentrations, and the time elapsed between those concentrations are known, it is possible to rearrange this equation:

\[ \ln C = \ln C_0 - k \cdot t \]

and solve for \( k \) to estimate half-life

\[ k = \frac{\ln \left( \frac{C_1}{C_2} \right)}{t_1 - t_2} \quad \text{or} \quad k = \frac{\ln C_1 - \ln C_2}{t_1 - t_2} \quad \text{where } C_1 > C_2 \]

The elimination rate constant and half-life are important in clinical applications. These parameters allow estimation of:

1) the time to reach steady-state
2) the time required to eliminate all or a portion of drug from the body
3) the amount of drug accumulated in the body
4) the degree of fluctuation (i.e., peaks and troughs) within a given dosing interval
5) the appropriate dosing interval.

Make sure you understand how to calculate half-life graphically and mathematically.
Before we continue, review the table below, which summarizes zero- and first-order rates.

### Table 2-6: Summary table of zero-order and first-order processes

<table>
<thead>
<tr>
<th></th>
<th>Zero-order</th>
<th>First Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential equation</td>
<td>( \frac{dX}{dt} = -k_0 )</td>
<td>( \frac{dX}{dT} = -k \cdot X )</td>
</tr>
<tr>
<td>Units on rate constant</td>
<td>( k_0 = \text{mass / time} )</td>
<td>( K = \text{time}^{-1} )</td>
</tr>
<tr>
<td>Rate dependent on concentration?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Half-life</td>
<td>Concentration Dependent</td>
<td>Concentration Independent</td>
</tr>
<tr>
<td>Concentration versus, time relationship on rectilinear coordinates</td>
<td>Linear</td>
<td>Curved</td>
</tr>
<tr>
<td>Concentration vs. time relationship on semi-log coordinates</td>
<td>Curved</td>
<td>Linear</td>
</tr>
</tbody>
</table>

### Area Under the Curve (AUC)

The area under the concentration-time curve (AUC) is one of the most important calculations in pharmacokinetics, and can be used to calculate other pharmacokinetic parameters such as clearance or bioavailability. The AUC tells us how much drug is in the body and has units of concentration*time (e.g., mg*h/L). There are several methods to calculate AUC, ranging from more complex but more accurate methods like integration of the equation that describes the pharmacokinetic profile, to an easier, but less accurate method called the trapezoidal method. This latter method is commonly used because of its ease, and is based on the idea of calculating the area of a trapezoid, as seen below.
Figure 2-6: Determining the area for various geometric shapes: area is defined as base \( \times \) height. For a square \( A = B \times H \); For a triangle which has only one side, you need to average the heights so \( A = B \times \frac{(H_1 + H_2)}{2} \) where \( H_2 = 0 \) or \( A = B \times H \times \frac{1}{2} \); for a trapezoid it is necessary to average the heights to properly use this equation of \( A = B \times \frac{(H_1 + H_2)}{2} \).

In this method, the AUC is constructed in a piece-wise fashion. As illustrated in the following figure, the curve can be broken into multiple trapezoids.

Figure 2-7: Estimation of AUC by breaking the concentration-time profile into individual trapezoids: note that AUC calculations are performed on non-transformed data (do not use log-transformed data).

The area of a trapezoid can be calculated by multiplying the base \((t_2 - t_1)\) and the average height (the average of the two sides parallel to the y-axis or \((C_1 + C_2)/2\)), as described by the equation:

\[
\text{trapezoid area (A)} = \left( \frac{C_1 + C_2}{2} \right) \cdot (t_2 - t_1) \quad \text{Equation 2-11}
\]
Sum all of the component trapezoid areas to obtain the AUC:

\[ \text{AUC} = \sum A = A_1 + A_2 + A_3 \ldots \quad \text{Equation 2-12} \]

Unfortunately, the entire AUC cannot be calculated by the trapezoidal method. Because it is impossible to measure drug concentration through infinite time, the tail portion of curve (i.e., the portion from the last measurable concentration and beyond) has to be estimated in order to calculate the AUC from time=0 to infinity. This tail portion can be calculated by the equation:

\[ \text{AUC}_{t \rightarrow \infty} = \frac{C_t}{k} \quad \text{Equation 2-13} \]

where \( C_t \) is the final known concentration, and \( k \) is the first-order elimination rate constant. This estimation of the terminal portion only works for first-order processes. To prove this equation to yourself, examine the units of each parameter. AUC has units of concentration per time (e.g., mg*h/L). \( C_t \) is a concentration and has units of mass per volume (e.g., mg/L) and \( k \) is the first order rate constant and has units of inverse time (e.g., h\(^{-1}\))

By now you will be able to 1) calculate the slope of the line and use that value to calculate a half-life and 2) calculate an AUC. It is very important to learn these basic calculations before moving further into pharmacokinetics.

**Example: Calculating an AUC**

The following data were obtained after a short-term infusion. Calculate the AUC\(_t\) and AUC\(_\infty\).

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Do NOT calculate AUC on the log-transformed data!
Begin by constructing a table with the appropriate calculations, to minimize mistakes.

<table>
<thead>
<tr>
<th>Time</th>
<th>[Drug]</th>
<th>A ((t_2-t_1))</th>
<th>B ((C_1+C_2))</th>
<th>AUC ((A*B)/2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>1 (= 1-0)</td>
<td>10 (= 10+0)</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>1 (= 2-1)</td>
<td>25 (= 10+15)</td>
<td>12.5</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>1 (= 3-2)</td>
<td>33 (= 15+18)</td>
<td>16.5</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>1 (= 4-3)</td>
<td>27 (= 9+18)</td>
<td>13.5</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>1 (= 5-4)</td>
<td>13 (= 9+4)</td>
<td>6.5</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1 (= 6-5)</td>
<td>6 (= 4+2)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>SUM</strong></td>
<td><strong>57.0</strong></td>
<td><strong>57.0</strong></td>
</tr>
</tbody>
</table>

\[ \text{AUC}_t = 57.0 \text{ mg}^*\text{h}/\text{L} \]

In this table, we have estimated the area for each trapezoid and then summed them. These calculations describe the area associated with all the data collected (from time =0 through 6 hours).

To calculate through infinite time (AUC\(\infty\)) we need to extrapolate the terminal portion from t=6 h to infinity using the equation

\[ \text{AUC}_{t \rightarrow \infty} = \frac{C_t}{k} \]

where \(C_t=2 \text{ mg}/\text{L}\) and \(k=0.693\). The value of \(k\) is obtained based upon half-life (drug concentrations drop from 4 to 2 mg/L in 1 hour, thus \(t_{1/2} = 1\text{h}; \) again, this is an instance where graphing the data is helpful for determining parameter values). Therefore AUC\(t \rightarrow \infty\)=2.89 mg*h/L and AUC\(\infty\)= 60.89 mg*h/L.

**Skills Obtained**

- Graphing concentration-time data on rectilinear and semi-log coordinates
- Differentiating between a zero-order and first-order process
- Estimating half-life graphically
- Calculating half-life from the first order rate constant, \(k\)
- Calculating AUC using the trapezoidal rule
**Summary Equations**

The general equation of the line:

\[ y = m \cdot x + b \]

Linear form of the equation to describe first-order loss of drug:

\[ \ln(C) = -k \cdot t + \ln(C_0) \]

To determine the first-order loss of drug:

\[ C = C_0 \cdot e^{-k t} \]

To determine half-life, given a first-order rate constant:

\[ t_{1/2} = \frac{0.693}{k} \]

To determine AUC using the trapezoidal rule:

\[ \text{trapezoid area } (A) = \left( \frac{C_1 + C_2}{2} \right) \cdot (t_2 - t_1) \]

To determine the terminal AUC:

\[ \text{AUC}_{t \to \infty} = \frac{C_t}{k} \]

**New Symbols**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_0 )</td>
<td>Zero-order rate constant</td>
<td>The zero-order rate constant for a process</td>
<td>Mass per time (e.g., mg/h)</td>
</tr>
<tr>
<td>( K )</td>
<td>First order rate constant</td>
<td>The first order rate constant for a process</td>
<td>Inverse time (e.g., 1/h)</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
<td>The area under the concentration-time curve; a measure of systemic exposure of a drug to the body</td>
<td>Mass-time per volume (e.g., mg*h/L)</td>
</tr>
<tr>
<td>( t )</td>
<td>Time</td>
<td>Time</td>
<td>Time (e.g., h)</td>
</tr>
</tbody>
</table>
3) Distribution Phenomenon

**Goals**

To understand how and why a drug distributes throughout the body

**Objectives**

*By the end of this chapter you should be able to:*

- Define the term “apparent volume of distribution”
- Explain the relationship between plasma protein binding and tissue protein binding in determining volume of drug distribution
- Explain the importance of unbound drug in distribution processes
- Summarize important physicochemical properties of a drug that will affect its distribution
- Differentiate between permeability-limited distribution and perfusion-limited distribution

**In Brief**

The apparent volume of distribution is a measure of where drug is located – predominately in the blood, extracellular space, or out in the tissues. This measure is determined by the drug's lipophilicity, charge at physiologic pH and how strongly it binds to proteins in the blood or tissue space. This latter is important because only unbound drug (drug not bound to proteins) are free to move throughout the body. We categorize drugs into two categories with respect to their distribution, permeability-limited – drugs where the rate limiting step is the ability to cross biologic membranes, and perfusion-limited – drugs where the rate limiting step is access to the tissue or the blood flow to that tissue.

**Introduction**

Suppose 1 g of drug is placed into a beaker of water. A sample of the water has a drug concentration of 100 mg/L. How much liquid is in the beaker? The answer is 10 L. It is this premise of “dilution” that describes a drug’s volume of distribution (V).

The volume of distribution is the volume which would account for the concentration of that drug in the compartment from which it is sampled (i.e., the blood), given that a known mass of drug was administered. Therefore, the volume of drug distribution does not have a true physiological meaning, thus, it is more correctly referred to as the *apparent volume of distribution*. In most cases, the apparent volume of distribution...
does not refer to the volume of a specific body compartment (e.g., fluid, tissue, organ); it is the volume necessary to account for the total amount of drug in the body if that drug was present throughout the body at the same concentration as in the plasma. The volume of distribution (V) is one of the primary pharmacokinetic parameters; the other primary pharmacokinetic parameter, clearance (CL), is described in a later chapter. ‘Primary pharmacokinetic parameter’ essentially means that other pharmacokinetic parameters (e.g., AUC, half-life) are calculated from these parameters; parameters like half-life and AUC could be considered secondary pharmacokinetic parameters because they are determined from other variables.

![Figure 3-1: A dose (X₀) enters a beaker of water of volume V: the resulting concentration is a function of the dose and volume of the beaker](image)

\[ V = \frac{X_0}{[\text{Drug}]} \]

In general, after a drug is administered, it will equilibrate rapidly in the body. However, various tissues may contain different drug concentrations due to the affinity of the drug for that particular tissue. The affinity of a drug for a tissue is determined by physicochemical properties of the drug molecule, blood flow, the extent of protein binding in the plasma and tissue, and the presence of transporter proteins that may move drug across membranes. For example, digoxin has a high affinity for skeletal and cardiac muscle, whereas tetracycline has a high affinity for bone. Endogenous compounds like creatine, neurotransmitters and vitamins are fairly hydrophilic, and can enter the brain via specific uptake transporters but cannot diffuse into the brain passively.

Most hydrophilic drugs have difficulty passing through biological membranes, but are able to distribute within the extracellular fluid unless they are too large to pass through fenestrations in capillaries (e.g., heparin). Lipophilic substances, on the other hand, are able to distribute throughout the body because they can pass through biological membranes more easily than hydrophilic drugs can. Remember the saying “like dissolves like”: hydrophilic molecules will partition into aqueous substances (e.g., water) but lipophilic molecules tend to partition into lipid substances (e.g., fat).

**Fun Fact:** THC, the active ingredient in marijuana, is very lipophilic and will reside in fat stores for long periods of time, hence giving the ability to detect marijuana use weeks after discontinuation of the drug.
When a drug is administered, it first distributes in the plasma, extracellular fluid and "easily accessible tissues", because these are the most accessible compartments. Drug will then either move into less accessible areas like tissues, or will be eliminated, although these may be simultaneous processes. The questions that arise are 1) To what degree does the drug penetrate into tissues? and 2) How fast does the drug penetrate into tissue? During our future discussions of one-compartment models, we will assume that drug instantaneously distributes throughout the body, but in reality some drugs do not distribute instantaneously in the body. This phenomenon will lead to our discussion of multiple-compartment models.

While the distribution of a drug into blood and highly-perfused organs (e.g., kidneys, liver) is typically very fast, it takes time to enter tissues that are less well-perfused (e.g., fat) or tissues that have protective barriers (e.g., the brain). The overall contribution of these slowly-equilibrating tissues, called peripheral tissues, to the total apparent volume of distribution dictates the appropriate compartmental model for describing the drug’s pharmacokinetic behavior, as you will see in other sections. The figure below illustrates a central compartment that quickly equilibrates with plasma drug concentrations and a peripheral compartment that slowly equilibrates with plasma drug concentrations. Please note that the specific organs comprising the central and peripheral compartments will vary for individual drugs, since the volume of distribution is drug-specific, (e.g., muscle may be a rapidly-equilibrating tissue for one drug, but not for another).

![Figure 3-2: Drug distribution could be dependent on blood flow, with highly-perfused organs equilibrating faster than poorly-perfused organs](image_url)

**Determinants of the Volume of Distribution**

Physicochemical properties are a major determinant of the volume into which a given drug will distribute. Hydrophilic drugs (i.e., drugs with a small or negative logP value) or highly charged drugs (which may depend on pKa) have difficulty partitioning into lipid membranes and fatty tissue, and therefore would have a volume of distribution close to the
total volume of water in the body (41 L). For example, aminoglycosides are fairly hydrophilic and exhibit a V of ~25% body weight (or around 17 L).

Lipophilic drugs or drugs with no charge can enter lipid membranes and fatty tissue more easily, and therefore can have volumes of distribution larger than total body volume. Tricyclic antidepressants are very lipophilic and often have volumes > 1000 L (15 times greater than body weight). This may seem like a very large volume, but what this tells us is that tricyclic antidepressants tend to distribute into tissues rather than remaining confined to the blood. Again, for this reason the term *apparent volume of distribution* is used, because the volume is not a true physiological parameter.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Apparent Volume of Distribution (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>10</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>17</td>
</tr>
<tr>
<td>Theophylline</td>
<td>35</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>42</td>
</tr>
<tr>
<td>Lithium</td>
<td>46</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>98</td>
</tr>
<tr>
<td>Codeine</td>
<td>182</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>280</td>
</tr>
<tr>
<td>Digoxin</td>
<td>660</td>
</tr>
<tr>
<td>Desipramine</td>
<td>1400</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>8050</td>
</tr>
</tbody>
</table>

We mentioned that the charge of a drug can affect the ability of the drug to pass through membranes. Please review the concept of pKa and the Henderson-Hasselbach equation (at right) to remind yourself of the relationship between pH, the pKa of a drug, and the resulting overall charge of the drug molecule. In general, ionized drugs have difficulty passing through membranes and thus cannot distribute into tissue passively. You will see an example of this when we discuss renal clearance and how urine pH will affect whether certain ionizable drugs (such as amphetamines) will undergo reabsorption in the renal tubule.

\[ pK_a = pH - \log \left( \frac{[\text{salt}]}{[\text{acid}]} \right) \]
Another important basic principle that governs distribution is Fick’s law of diffusion, which describes the change in flux or movement of a molecule (dQ) with respect to changes in time (dT):

\[
\frac{dQ}{dT} = \frac{D \cdot K \cdot (C_{\text{plasma}} - C_{\text{tissue}})}{h}
\]

Equation 3-1

where D is the diffusion coefficient, K is the partition coefficient, C is the concentration and h is the thickness of the membrane. In this equation, the rate of diffusion (dQ/dT) is directly proportional to the difference in drug concentrations between the tissue and plasma - the greater the concentration difference, the greater the mass of drug that will diffuse. Consider what would happen if you opened a bottle of perfume in the classroom. Initially, the bottle contains a high concentration of perfume and the room contains a low (or zero) concentration. Eventually that perfume will diffuse throughout the room until there is equilibrium between amount of perfume in the bottle and in the room.

**Membranes**

We now need to address the question of whether membranes can affect distribution processes. The answer is yes! The first situation we will discuss, called *perfusion-limited distribution* concerns a membrane situated between blood and tissue, with very high permeability for a given drug (i.e., lipophilic drugs, or cell membranes which are loosely-knitted like muscle). Essentially, the membrane provides *no barrier* for the drug and results in fast uptake of drug into tissues until unbound drug levels in blood and tissues are in equilibrium. In this case, the faster the blood flow through that organ, the faster the distribution into tissue. For example, imagine trying to get into a football game with no gate at the entrance. Essentially, you could walk in at will because there is no barrier...
to impede your entry. The more flow (or traffic) coming into the game, the more people will be able to enter the game.

The second situation is called *permeability-limited distribution*. In this case, the membrane is not very permeable to drug (e.g., the blood brain barrier), functioning as a barrier between blood and tissue. Drug will enter permeability-limited tissue very slowly, and blood flow is not important for rate of uptake (unlike in our first situation). Uptake of drug in this case is determined by Fick’s law of diffusion (a function of the surface area of a membrane, membrane thickness, concentration gradient, partition coefficient and ionization). Returning to the football game analogy, imagine a very slow ticket collector at the football game; the ticket collector is now limiting your ability to enter and no matter how much flow (or traffic) there is, access to the game will instead depend primarily upon the rate of ticket collection.

These concepts as you may recognize go back to the idea of rate-limiting steps – that is, in any process the slowest step determines the overall rate. In situations described here, the rate limiting step can be flow to the tissue or the ability of the drug to permeate into the tissue. In later chapters we will again talk about rate limiting steps with absorption kinetics (absorption rate versus elimination rate), hepatic clearance (blood flow versus enzyme activity) or metabolite kinetics (metabolite formation versus metabolite elimination).

**Protein Binding**

At the molecular level, the ability of a drug to penetrate outside of plasma is determined by how strongly it binds to plasma proteins versus tissue proteins—a tug of war *per se*. Whoever can pull harder (i.e., the bigger people on the right), will determine the volume of distribution. If tissue pulls harder (in terms of drug-binding affinity) than blood, then V will be larger but if plasma pulls harder than tissue, V will be smaller. Essentially, the volume (in part) can indicate whether the drug primarily resides in plasma or tissue.

Unbound drug is free to diffuse through membrane and interact with receptors. Drugs bound to proteins cannot.
When a drug interacts with plasma proteins, only a portion of the drug in the plasma is bound to protein at a given time, while the remainder of the drug is unbound, thus, there are always two pools of drug: unbound drug and bound drug. It is only the unbound drug in the plasma that is in equilibrium with unbound drug in tissue. As in the blood, there are two pools of drug in the tissue, unbound drug and bound drug. The fraction of unbound drug ($f_U$) is the ratio of the unbound concentration and the total drug concentration. In most clinical scenarios, when drug concentrations are requested, total concentrations are reported. In a few instances, however, unbound concentrations can be requested. This unbound concentration is important, as you will learn later, because it is the unbound concentration that drives pharmacologic effect.

Albumin, lipoproteins, immunoglobulins (e.g., IgG), erythrocytes and $\alpha_1$-acid glycoprotein can and will bind various drugs. Albumin is distributed in plasma and extracellular water, and will transport various endogenous compounds (e.g., free-fatty acids, bilirubin, aldosterone) and exogenous compounds, especially weak acids (e.g., salicylic acid, penicillin). Albumin levels will change with certain diseases (e.g., acute renal failure). Levels of $\alpha_1$-acid glycoprotein, which predominantly binds weak bases (e.g., propranolol, imipramine), are known to be altered in various pathologic states (e.g., myocardial infarction, surgery).

**Table 3-1: Summary of relevant binding proteins**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Weight (kDa)</th>
<th>Normal Range (in plasma)</th>
<th>Normal Range (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>65</td>
<td>35-50</td>
<td>0.5-7.5</td>
</tr>
<tr>
<td>$\alpha_1$-acid glycoprotein</td>
<td>44</td>
<td>0.4-1.0</td>
<td>0.01-0.022</td>
</tr>
<tr>
<td>Lipoproteins</td>
<td>200-3400</td>
<td>variable</td>
<td></td>
</tr>
</tbody>
</table>
Drugs also bind to tissue components (e.g., proteins, DNA, bone, fat) and thus, a portion of the drug in the tissue is bound while the remainder of the drug is unbound. Unfortunately, tissue binding cannot easily be measured directly, but binding to plasma protein can be measured easily. One very important reason to focus on unbound drug levels is the fact that only unbound drug is able to interact with receptors, therefore, unbound drug concentrations dictate pharmacologic effect. The process of protein binding is a dynamic process where drug bound to protein is in equilibrium with unbound drug. This is an important concept to understand, especially when discussing hepatic clearance.

![Diagram showing drug binding to proteins](Image)

**Figure 3-5: Equilibrium exists between drug bound to proteins in the blood, unbound drug in and out of the cell and drug bound to tissue**

Below is an equation to describe how tissue binding and plasma protein binding determine the volume of distribution

\[
V = V_p + V_T \cdot \frac{f_u}{f_{ut}} \quad \text{Equation 3-2}
\]

where \(V\) is the volume of distribution, \(V_p\) is the volume of plasma (typically 3-5 L), \(V_T\) is the accessible tissue volume (15-38 L depending if the drug is hydrophilic or lipophilic – lipophilic drugs are ‘accessible’ to fat whereas hydrophilic drugs are typically not accessible to fat), \(f_u\) is the fraction of unbound drug in plasma and \(f_{ut}\) is the unbound fraction in tissue. This equation can be used to calculate volume, but it is presented here as a summary of all the major factors that impact the volume of distribution. If the unbound fraction in blood increases (\(f_u\) increases from 0.1 to 0.2), the volume of distribution increases – there is more ‘free’ drug to distribute into tissue. If the unbound fraction in tissue decreases (\(f_{ut}\) decreases from 0.01 to 0.05), volume will increase because tissue is ‘pulling harder’, thus drawing more drug into the tissue. If plasma vol-
ume expands ($V_p$ increases from 3 to 5 L), then volume will increase. If fat mass increases ($V_T$ increases from 38 L to 43 L), this will increase overall volume.

Based equation 3-2, the following scenarios are true. Please make sure that you understand why.

If a drug has a V of <3 L, drug is mostly in the plasma.

**Explanation:** Plasma water is approximately 3 L. If a drug’s volume of distribution is below 3L, you can assume it is mainly confined to the plasma.

If a drug has V of ~40 L, drug is evenly distributed throughout the body.

**Explanation:** Total body water is approximately 40 L. If a drug’s volume of distribution is close to this value, it means that the drug can partition into cells, but is also hydrophilic enough to partition into aqueous space.

If tissue binding exceeds plasma protein binding, V will be large (> 40L).

**Explanation:** Volume of distribution indicates whether drug resides primarily in the plasma or outside the plasma. Large volumes mean that drug has partitioned into tissue and thus, is outside of the plasma space.

If a drug is unable to cross membranes, V cannot be larger than the extracellular space.

**Explanation:** Again volume of distribution tells you where drug resides; in plasma or outside of plasma. If a drug cannot pass through membranes, it will remain outside of cells.

If plasma binding is stronger than tissue binding, V will be smaller than 40 L.

**Explanation:** Once again, volume of distribution indicates where the drug primarily resides, in plasma or outside of plasma. Small volumes mean that drug is sequestered in the blood and has not penetrated into tissue space.

Here are some examples of protein binding estimates:
### Table 3-2: Short list of drugs and their respective protein binding in blood

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>99.5%</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90% (80% in hypo-albumin)</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>90%</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>70%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>25%</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>18%</td>
</tr>
</tbody>
</table>

### Summary

To summarize, a drug’s V is determined in part by drug properties (e.g., charge, lipophilicity), physiologic factors (e.g., blood flow, membranes) and protein binding. Only unbound drug may cross membranes. The unbound concentration is in equilibrium with bound drug (this can be bound or unbound in plasma or bound and unbound in tissue. Disease state may change plasma protein concentrations, thus possibly altering unbound drug concentrations in the blood. From a clinical standpoint, changes in V will impact the drug’s half-life. For example, pregnancy will increase total body water and total body fat, and decrease serum albumin. Thus you would expect that certain drugs would exhibit a slightly larger volume of distribution during pregnancy, versus post-partum. Changes in half-life as a result of volume changes may impact dosing frequency.

### Skills Obtained

- The ability to estimate the direction of change in the volume of distribution, given changes in plasma protein binding and/or changes in tissue protein binding

### Summary Equations

Estimate volume of distribution based on protein binding:

$$V = V_p + V_T \cdot \frac{f_u}{f_{ut}}$$

Estimate the unbound fraction:

$$f_u = \frac{C_u}{C}$$
## New Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V )</td>
<td>Volume of distribution</td>
<td>The apparent volume into which a drug distributes within the body</td>
<td>Volume (e.g., L)</td>
</tr>
<tr>
<td>( f_u )</td>
<td>Unbound fraction</td>
<td>The unbound fraction of drug (typically referring in the blood). This fraction is calculated as the unbound concentration divided by the total concentration</td>
<td>Unitless</td>
</tr>
</tbody>
</table>
4) Clearance Concepts

Goals

- To understand how and why a drug is cleared from the body

Objectives

*By the end of this chapter you should be able to:*

- Define clearance and linear pharmacokinetics
- Explain and be able to estimate clearance using different types of data
- Explain the relationship between clearance and other pharmacokinetic parameters
- Explain the role of protein binding in clearance

In Brief

Clearance is the volume of blood removed of drug per unit time. It is one of the primary pharmacokinetic parameters along with the volume of distribution. The total body clearance is a sum of all clearance processes and we can calculate a patient’s clearance through a variety of ways if we know the drug’s dose and area-under the curve, the rate of removal and a single mid-point concentration or the half-life and volume of distribution. Clearance and volume together determine the drug’s half-life. Clearance and volume of distribution are both impacted by protein binding. For clearance, only unbound drug will be cleared from the body.

Introduction

We have finished discussing the first primary pharmacokinetic parameter, volume of distribution. The second primary pharmacokinetic parameter is clearance (CL). Clearance is a measure of the rate of removal of drug from a ‘reference’ fluid, usually blood (or plasma). Clearance and volume of distribution (*remember that clearance and volume of distribution are independent of each other and determine half-life, not the other way around!!*) determine a drug’s half-life according to the equation

\[ \frac{CL}{V} = K \]  
Equation 4-1

where K is a first-order rate constant and half-life \( (t_{1/2}) \) is defined as:
It is very important to remember that CL and V are independent of each other. Together these parameters determine \( t_{1/2} \). For example, if CL changes, \( t_{1/2} \) would change, but V would not change. If V changes, \( t_{1/2} \) would change, but CL would not change. The table below illustrates the independence of clearance and volume, and the fact that half-life is determined by both clearance and volume. Half-life will decrease with increasing clearance (e.g., drug gets removed faster); half-life also will decrease if volume of distribution decreases (e.g., removing drug quicker from a smaller space). Again, clearance does not impact volume and volume does not impact clearance, but they work together to impact half-life.

<table>
<thead>
<tr>
<th>Clearance (L/h)</th>
<th>Volume of Distribution (L)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>150</td>
<td>10.4</td>
</tr>
<tr>
<td>20</td>
<td>150</td>
<td>5.2</td>
</tr>
<tr>
<td>30</td>
<td>150</td>
<td>3.5</td>
</tr>
<tr>
<td>30</td>
<td>100</td>
<td>2.3</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Clearance is expressed in terms of the volume of reference fluid (e.g., blood) which is cleared of drug in a given time, therefore its units are volume per unit time (e.g. L/h, mL/min). Notice that clearance is essentially a flow parameter, and that clearance does not tell you how much drug is being removed but rather the volume of blood from which drug is removed in a given time. The rate of drug removal (dX/dt) is a function of CL and concentration because this is a first-order process.

\[
\frac{dX}{dt} = CL \cdot C
\]

Drugs are cleared or removed from the blood by different mechanisms, pathways or organs. Typically we think of the liver or kidney as our clearing organs, but some drugs can be cleared by the blood, lung, etc. Therefore clearance is the sum of the clearances from all clearance pathways.

\[
CL = CL_H + CL_R + CL_{OTHER}
\]
where CL_H is hepatic clearance (e.g., metabolism), CL_R is renal clearance (e.g., filtration), and CL_OTHER is clearance by another route.

We can look at Equation 4-3 from the reverse angle by asking the question, “How can we determine organ clearance from total clearance?”. Let us assume the mass of drug metabolized by the liver is X_M. The fraction of drug that is removed by the liver would therefore be X_M / X_0. Thus, the clearance due to the liver is:

$$ CL_H = \frac{X_M}{X_0} \cdot CL $$

The same correlations can be made for renal clearance.

$$ CL_R = \frac{X_R}{X_0} \cdot CL $$

where X_R is the amount that is removed, unchanged, by the kidney.

**Problem:** Drug X is given IV at a dose of 100 mg. The renal clearance of the drug is 7 L/h and the hepatic clearance is 23 L/h. Assuming that these are the only two routes of elimination, what is the total clearance? How much drug (in mg) was metabolized?

**Answer:**

CL = CL_H + CL_R = 23 L/h + 7 L/h = 30 L/h. Total clearance is 30 L/h

CL_H = 23 L/h and $ CL_H = \frac{X_M}{X_0} \cdot CL $ (rearrange for X_M)

$$ X_M = \frac{CL_H \cdot X_0}{CL} = \frac{23 \text{ L/h}}{30 \text{ L/h}} \cdot 100 \text{ mg} = 76 \text{ mg} $$

76 mg of drug was metabolized

In an earlier chapter we discussed the concept of area under the concentration-time curve (AUC), which reflects the body’s exposure to a drug. More exactly, AUC is the response of the system to a given dose (X_0). AUC is inversely-related to the systemic clearance (CL) of the drug and proportional to the fraction of X_0 that reaches systemic circulation.
\[
\text{AUC} = \frac{X_0}{\text{CL}}
\]

Equation 4-4

Figure 4-1: (left) Relationship between dose and AUC in a linear system (i.e., clearance is independent of dose). In this case, clearance is 20 L/h. (right) Relationship between half-life and the reciprocal of clearance. As increases (and volume of distribution does not change), half-life will decrease.

Thus, the higher the CL, the lower the AUC, and vice versa. This relationship also leads into a very important concept; linear pharmacokinetics. In linear pharmacokinetic systems, regardless of \(X_0\), the CL of a drug will remain constant.

Therefore, an increase in \(X_0\) would result in a proportional increase in AUC (e.g., double the dose, double the AUC). Please note that neither \(V\) nor the rate of absorption would affect AUC. If \(V\) changes, \(t_{1/2}\) would change but CL would not! This concept can be very important in making dose adjustments, when dealing with a drug exhibiting linear pharmacokinetics. If the blood concentration of drug X in your patient is 5 mg/L, but you want the patient to have a drug concentration of 10 mg/L, how would you change this patient’s dose? If you simply double the dose, you will double the concentration because in this case, you are dealing with a linear pharmacokinetic system. Most drugs exhibit linear pharmacokinetics, however, exceptions will be discussed in the nonlinear pharmacokinetics section of this text.
**Problem:** Drug X is given IV at a dose of 100 mg. Blood concentrations were measured and the AUC was calculated to be 3.3 mg·h/L. What is the clearance of this drug?

**Answer**

\[
CL = \frac{X_0}{AUC} = \frac{100 \text{ mg}}{3.3 \text{ mg} \cdot \text{h/L}} = 30 \text{ L/h}
\]

The clearance is 30 L/h

We now will introduce two more mathematical ways to express CL. Which equation you use to calculate CL will depend on what type of information you have.

The first alternative method we will discuss relates back to the definition of a first order process, that is, where the rate of change \(\frac{dX}{dt}\) is equal to the product of the clearance and the concentration.

\[
\frac{dX}{dt} = CL \cdot C
\]

Equation 4-5

We can rearrange this equation to solve for CL. What this relationship indicates is that the rate of elimination (or excretion) is proportional to drug concentration in the blood (higher concentration = higher rate). CL is constant in a linear system. Thus, increasing concentration will increase rate. This relationship does not apply to nonlinear pharmacokinetic systems (e.g., phenytoin), which will be discussed later.

\[
CL = \frac{dX}{dt} \div C
\]

Equation 4-6

Let us take a quick look at a one-compartment model which is a model that assumes the body is one homogenous “box”. The S-shaped line indicates instantaneous administration (i.e., an intravenous bolus inject) and the bolded arrow indicate clearance from the body – in this case let us assume that the drug is eliminated via the kidney.
Here \( X_U \) is the amount of drug excreted unchanged in the urine. The rate of excretion (\( \frac{dX_U}{dt} \)) will be a product of the renal clearance (\( CL_R \)) and the concentration in the plasma.

\[
CL_R = \frac{\frac{dX_U}{dt}}{C_{\text{MID}}}
\]  

Equation 4-7

The concentration to which this equation refers is the mid-point concentration, because it is representative of an ‘average’ concentration driving the excretion of drug. Suppose we give drug X and collect urine from 2-4 h after dosing. We would want to take a blood sample at 3 h to perform the above calculation. We will discuss this later in the context of renal clearance, but briefly, the midpoint concentration represents the median concentration during the collection of the urine. The equation illustrates the point that we can use the mass of drug outside the body (rather than only blood) to obtain an estimate of CL.

**Problem:** Drug X is administered IV at a dose of 100 mg. A blood concentration was drawn at 3 h and urine was collected from 2 to 4 hours. The blood concentration at 3 h was 2 mg/L and during the two-hour interval, 20 mg of drug was eliminated. What is the renal clearance of this drug?

**Answer**

\[
\frac{dX_U}{dt} = \frac{20 \text{ mg}}{4 \text{ h} - 2 \text{ h}} = 10 \text{ mg/h}
\]

\[
CL_R = \frac{\frac{dX_U}{dt}}{C_{\text{MID}}} = \frac{10 \text{ mg/h}}{2 \text{ mg/L}} = 5 \text{ L/h}
\]

The previous scheme we call a black box approach, because we assume little to no physiologic relevance of the body. A second method to represent these processes is more physiologic in nature. An organ that is involved in clearance has the ability to extract drug from the blood flow and eliminate it. Consider the figure below.
Blood flow (Q) perfuses the organ, and the blood contains drug at a concentration (C_{IN}). The organ then extracts drug out of blood such that the drug concentration leaving the organ (C_{OUT}) is reduced (C_{IN} \geq C_{OUT}). Another angle from which to consider this process involves rates of entry and rates of exit.

The rates of entry and exit, again assuming first order processes, are

\[
\text{Rate of entry} = (Q)(C_{IN})
\]

\[
\text{Rate of exit} = (Q)(C_{OUT})
\]

The difference between the ‘rate of entry’ and ‘rate of exit' will give us the ‘rate of elimination’ since all drug must be accounted for (mass balance).

\[
\text{Rate of entry} – \text{Rate of exit} = \text{Rate of elimination}
\]

Thus:

\[
\text{Rate of elimination} = (Q)(C_{IN}) – (Q)(C_{OUT}) \quad \text{or}
\]

\[
\text{Rate of elimination} = (Q)(C_{IN} - C_{OUT}) \quad \text{Equation 4-8}
\]

Going back to this definition of clearance

\[
Cl = \frac{dX}{dt}
\]

The rate of elimination (here as dX/dt) is proportional to the incoming concentration of drug (C_{IN}). Substituting, we get:

\[
Cl = \frac{Q \cdot (C_{IN} - C_{OUT})}{C_{IN}} \quad \text{Equation 4-9}
\]
The ability of the organ to remove or extract a drug is proportional to the amount of drug lost ($C_{IN}$-$C_{OUT}$) relative to the total amount of drug it was perfused with ($C_{IN}$). The extraction ratio ($E$) or the proportion of drug extracted by an organ through a single pass through that organ is a measure of efficiency and is calculated by:

$$E = \frac{C_{IN} - C_{OUT}}{C_{IN}}$$  \hspace{1cm} \text{Equation 4-10}

This leads to our third fundamental definition of clearance

$$CL = Q \cdot E$$  \hspace{1cm} \text{Equation 4-11}

The more efficient the organ is at extracting drug, the higher the $E$ value. Therefore if 100 mg/L of drug enters the organ and 50 mg/L of the drug leaves the organ, then the extraction ratio ($E$) is 0.5 or 50%. If the drug concentration leaving the organ is 0 mg/L, then the extraction ratio ($E$) is 1 or 100%, that is, all drug was extracted. The term $E$ is unitless; because it expresses a ratio. The extraction ratio must be in the range $0 < E < 1$ or 0-100%. To convert the extraction ratio to a clearance (with the appropriate units), simply multiply $E$ by the blood flow ($Q$). Remember that blood flow and CL have the same units: volume/time.

**Problem:** Drug X is given IV at a dose of 100 mg and is eliminated by the liver. Hepatic blood flow is 90 L/h and hepatic clearance is 60 L/h. What is the extraction ratio for this drug?

**Answer**

$$CL = Q \cdot E$$

$$E = \frac{CL}{Q} = \frac{60 \text{ L/h}}{90 \text{ L/h}} = 0.67$$

As discussed above, CL can be dependent on blood flow. The maximum rate of clearance for any organ is the same as its rate of blood flow, $Q$. For example, in humans, hepatic clearance cannot exceed 90 L/h (1500 mL/min) and renal clearance cannot exceed 60 L/h (1000 ml/min). The clearance of the organ may, however, be lower than blood flow, depending upon how efficiently it extracts drug from the blood.

Physiochemical properties of drug molecules are important determinants of drug disposition, as discussed in the chapter on volume of distribution. Relative to hydrophilic drugs, lipophilic drugs tend to distribute...
throughout the body more extensively, exhibit greater plasma protein binding, and are usually metabolized in the liver to a greater extent. Hydrophilic drugs tend not to be extensively metabolized by the liver because this type of drug can be readily excreted by the kidney into the urine. The liver and kidneys are two major organ systems responsible for eliminating drugs from the body; each system will be discussed in greater depth in a subsequent dedicated chapter.

Table 4-2: Summary of the various methods to estimate clearance

<table>
<thead>
<tr>
<th>Clearance “Definition”</th>
<th>Application/Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CL} = \text{CL}_H + \text{CL}<em>R + \text{CL}</em>{\text{OTHER}}$</td>
<td>Systemic clearance is the sum of all clearance processes</td>
</tr>
<tr>
<td>$\text{Cl} = \frac{X_0}{\text{AUC}}$</td>
<td>Systemic clearance can be calculated from the dose and the AUC. (Note: clearance and dose determine AUC)</td>
</tr>
<tr>
<td>$\text{Cl} = \frac{dX}{dt}$</td>
<td>Renal clearance can be calculated based upon the amount of drug excreted over time in urine and the concentration of drug in the blood that is acting as the &quot;driving force&quot; for elimination</td>
</tr>
<tr>
<td>$\text{CL} = Q \cdot E$</td>
<td>Hepatic clearance can be calculated based upon hepatic blood flow and the efficiency of the liver in extracting drug from the incoming blood</td>
</tr>
</tbody>
</table>

**Summary**

Clearance is one of the most important concepts in pharmacokinetics, and is one of the two primary pharmacokinetic parameters. Together, volume of distribution and clearance determine half-life. Clearance can be calculated in various ways, but it is important to understand that clearance is summative; i.e., that systemic clearance (or total clearance) is the sum of clearance processes which may include hepatic clearance, renal clearance, biliary clearance, etc. It is also important to understand that the rate of clearance for most drugs is independent of drug concentration and route of administration. In linear pharmacokinetic systems, these concepts allow the clinician to easily adjust doses to obtain therapeutic concentrations.

**Skills Obtained**

- The ability to define and correctly use the term "linear pharmacokinetics"
• The ability to estimate clearance based upon dose and AUC, rate of excretion and blood concentration, blood flow and extraction ratio and from individual organ clearances

**Summary Equations**

To determine clearance from a rate (rate of excretion, rate of metabolism) and blood concentration

\[ \text{Cl} = \frac{dX}{dt} \div C \]

To determine clearance from organ blood flow and extraction ratio

\[ \text{CL} = Q \cdot E \]

To determine clearance from dose and AUC

\[ \text{AUC} = \frac{X_0}{\text{CL}} \]

To determine clearance from individual organ clearances

\[ \text{CL} = \text{CL}_H + \text{CL}_R + \text{CL}_{OTHER} \]
### New Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>Clearance</td>
<td>Volume of fluid (usually blood) irreversibly cleared of drug, per unit time</td>
<td>Volume per time (e.g., L/h)</td>
</tr>
<tr>
<td>E</td>
<td>Extraction ratio</td>
<td>The fraction of drug removed by the body (or organ) per unit time; a measure of efficiency</td>
<td>Unitless</td>
</tr>
<tr>
<td>Q</td>
<td>Blood flow</td>
<td>Volume of blood perfusing an organ, per unit time</td>
<td>Volume per time (e.g., L/h)</td>
</tr>
<tr>
<td>CL_&lt;X&gt;</td>
<td>Organ Clearance</td>
<td>Volume of blood irreversibly cleared of drug, per unit time, by a specific organ</td>
<td>Volume per time (e.g., L/h)</td>
</tr>
<tr>
<td></td>
<td>X = H = Hepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>X = R = Renal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5) Intravenous Bolus

**Goals**

To understand the one compartment body model and how it is used to predict drug concentrations in the body over time, after an intravenous bolus dose

**Objectives**

*By the end of this chapter you should be able to:*

- Calculate a drug concentration at a given time after IV bolus
- Determine the time at which a given drug concentration will occur
- Calculate pharmacokinetic parameters (clearance, volume, half-life), given a plasma concentration-time profile
- Graph a concentration-time profile on semi-log paper

**In Brief**

The IV bolus one-compartment model is the simplest pharmacokinetic system but serves as a basis for many concepts and calculations. The initial concentration at IV bolus administration is a function of dose and the volume of distribution. Knowing the initial concentration and the drug’s half-life, you can estimate any concentration at any time point. Given appropriate information, you can estimate a patient’s clearance and volume of distribution by first estimating the half-life, initial concentration or the area-under-the-curve.

**Introduction**

The body can be represented functionally as a system of compartments, even though these compartments often have no apparent physiologic or anatomic basis. The one-compartment model depicts the body as a single homogenous unit.

A one-compartment model is the simplest model used to describe behavior of drug in the body. This model operates upon several important assumptions:

1. Drug distribution is instantaneous
2. The system is an open pharmacokinetic system
3. The system is linear
4. The system is stationary
5. Clearance is a first order process

The first assumption refers to the ability of the drug to instantly distribute throughout the body. This does not mean that each tissue has the same drug concentration; only that drug appears in tissues instantly. The second assumption is that the system is open. This means that drug that enters the body leaves the body, whether it is excreted by the kidneys, metabolized by the liver or cleared by some other pathway. The third assumption is linearity. Under this assumption, increasing the amount of drug results in a proportional increase in blood concentrations (e.g., doubling the concentration by doubling the dose). The reason for this linearity is that in this type of system, clearance is independent of dose. This is not always the case; exceptions are discussed later in this book. The system is stationary means that the pharmacokinetic parameters do not change with time or are time independent. For example, the value for clearance is the same for the first dose as it is for the 100th dose. We will discuss violations to this assumption later in this book. The final assumption is that elimination is a first-order process.

**Intravenous Bolus**

Figure 5-1 illustrates the scheme for a one-compartment model after IV bolus administration. The term “bolus” refers to the administration of a drug instantly, or over a very short period of time (as in a rapid injection). Schemes are very important because they help us build the appropriate equations that describe concentration-time profiles. Also please note the use of symbols such as \( X_0 \) for dose, \( V \) for volume of distribution and \( CL \) for clearance as these are standard notations. This scheme can be converted to mathematical equations that describe changes in drug concentrations over time.

To aid us in understanding this model, consider a case where drug has been administered via an IV bolus dose (bolus meaning all drug enters the system at once). There are 2 points in time at which the drug concentrations are automatically known. The first is immediately after we administer drug (before there is any elimination). Imagine dropping a
dose of drug, $X_0$, into a container of water with a volume, $V$. The concentration (denoted $C_0$ or the concentration at time $= 0$) is equivalent to:

$$ C_0 = \frac{X_0}{V} \quad \text{Equation 5-1} $$

where $X_0$ is the dose, $V$ is the volume into which the dose is distributed, and $C_0$ is the initial concentration at time $= 0$. If we sample blood soon after administration we can obtain a reasonable estimate of $C_0$, and since we know $X_0$, $V$ can be obtained with the above simple calculation.

The second point at which we automatically know the concentration is after an infinite amount of time – the concentration at infinite time is zero (remember that all drug that enters the body is removed eventually). Now the question arises, does drug concentration from zero time to infinite time change in a linear (straight line) or curvilinear fashion? As you may remember, drug elimination is usually a first-order process, thus a plot of drug concentration over time results in a curved relationship.

![Figure 5-2: Concentration versus time profile plotted on rectilinear coordinates (left) and on semi-log coordinates (right)](image)

The change in concentration ($dC$) with respect to changing time ($dt$) is proportional to the concentration (for review, return to our discussion of first order processes).

$$ -\frac{dC}{dt} \propto C \quad \text{Equation 5-2} $$

We typically prefer dealing with equalities rather than proportionalities. The proportionality in Equation 5-2 can be converted to an equality by multiplying the left side of the equation by the apparent volume of distribution, $V$, and the right side by clearance, $CL$. 

49
\[
\frac{dC}{dt} = -C \cdot CL \\
\text{Equation 5-3}
\]

Why do we do this? Well, if we use dimensional analysis (a fancy word meaning that our units should be the same on both sides) we see that both sides of the equation are expressed in terms of amount per unit time. For every equation, units on both sides of the equals sign should be the same – if they are not, this is an indication that you did something incorrectly!

\[
\frac{\text{amount}}{\text{Volume}} \cdot \frac{\text{Volume}}{\text{Time}} = \frac{\text{amount}}{\text{Volume}} \cdot \frac{\text{Volume}}{\text{Time}} \Rightarrow \frac{\text{amount}}{\text{Time}} = \frac{\text{amount}}{\text{Time}}
\]

We can rearrange this equation in such a way that the rate of change is equal to the concentration \(C\) and the 2 primary pharmacokinetic parameters \(CL\) and \(V\):

\[
\frac{dC}{dt} = -C \cdot \frac{CL}{V} \\
\text{Equation 5-4}
\]

At this point, we can integrate Equation 5-4 from zero time to infinite time, which yields the following equation:

\[
C = C_0 \cdot e^{\left(\frac{CL}{V} \cdot t\right)} \\
\text{Equation 5-5}
\]

Equation 5.5 is very important because it can be used to predict drug concentrations in the current system (IV bolus, 1-compartment). Our 2 primary pharmacokinetic parameters, clearance \(CL\) and volume \(V\), determine the rate constant of change \(K\) using an equation from the previous chapter:

\[
k = \frac{CL}{V}
\]

We can substitute this into the previous equation to yield a simplified equation:

\[
C = C_0 \cdot e^{(k \cdot t)} \\
\text{Equation 5-6}
\]

Here, any concentration \(C\) can be determined based upon the initial concentration \(C_0\), the first order rate constant \(k\), and the time after the initial concentration \(t\). This equation can also be transformed by taking the natural log of both sides.
\[
\ln[C] = C_0 \cdot e^{-kt}
\]
\[
\ln(C) = \ln(C_0) - K \cdot t
\]

Now, we have an equation that resembles the equation of a straight line. If you plot \(\ln(C)\) versus time, the y-intercept is \(\ln(C_0)\) and the slope is \(-k\).

Going back to our discussion of first-order processes, we learned that half-life is inversely related to \(k\) in the following manner:

\[
t_{\frac{1}{2}} = \frac{0.693}{k}
\]

We can now understand some important relationships. What happens to the concentration-time profile if we double clearance? Or double the volume of distribution? You can use Microsoft Excel to simulate these scenarios in order to check whether your predictions are correct.

In the first scenario, clearance is doubled. Clearance determines half-life, thus we expect that as clearance increases, half-life will decrease, because drug is being eliminated more rapidly.

\[
t_{\frac{1}{2}} = \frac{0.693 \cdot V}{CL}
\]

\[
\downarrow t_{\frac{1}{2}} = \frac{0.693 \cdot V}{\uparrow CL}
\]

Figure 5-3: Impact of doubling clearance on concentration-time profile after IV bolus: doubling clearance will increase the rate of drug elimination, thus resulting in a steeper slope (that is, shorter half-life)

Notice that we do not change \(C_0\) (the initial concentration); we are only changing the slope of the line.
However, if you double volume, both half-life will double AND your concentration at $C_0$ will be half as much.

$$t_{\frac{1}{2}} = \frac{0.693 \cdot V}{CL}$$

$$C_0 = \frac{X_0}{V}$$

**Figure 5-4:** Impact of doubling volume of distribution on concentration-time profile after IV bolus: doubling volume will decrease the rate of drug elimination, thus making the slope less steep (that is, larger half-life). Doubling volume will also dilute the initial concentration.

Another very important concept to reiterate is that the following equations can be useful in many ways:

$$C = C_0 \cdot e^{(-k \cdot t)}$$

$$\ln(C) = \ln(C_0) - K \cdot t$$

These equations are quite versatile. First, keep in mind that $C < C_0$. Given 2 concentrations ($C_1$ and $C_2$) where $C_2 < C_1$, the equations

$$C_2 = C_1 \cdot e^{(-k \cdot t)}$$

$$\ln(C_2) = \ln(C_1) - k \cdot t$$

can be rearranged to solve for $C_1$ or $C_2$, $t$, or $k$ in order to answer questions like: Given a concentration of 10 mg/L, how long will it take to reach a concentration of 2.5 mg/L, given a half-life of 10 hours? (The answer is 20 hours). You can also solve this problem simply by counting. If the concentration is 10 mg/L, over the course of one half-life, 50% of the drug concentration will be lost, thus, in 10 hours the concentration will be 5 mg/L. Over the course of an additional half-life, the concentration will decrease by 50% to 2.5 mg/L. Thus, over one half-life, concen-
trations will drop from 10 to 5 mg/L, and over two half-lives (or 20 hours) concentrations will drop to 2.5 mg/L.

Gathering Information from IV Bolus Data

It is important to extrapolate clearance and volume of distribution terms from pharmacokinetic data. Presently, we will limit ourselves to discussion of the 1-compartment model after IV bolus administration. There are several ways to gather information from a plot of concentration versus time data, but we will start with the simplest method. Following these step-by-step procedures will result in accurate estimations of important pharmacokinetic parameters. Let us start with the raw data presented below, determined after administration of 1000 mg of drug X.

Table 5-1: Sample concentration-time data after IV bolus administration

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Plasma [drug X] (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.2</td>
</tr>
<tr>
<td>2</td>
<td>11.8</td>
</tr>
<tr>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>4</td>
<td>5.6</td>
</tr>
<tr>
<td>5</td>
<td>3.8</td>
</tr>
<tr>
<td>10</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Step 1) On semi-log coordinates, plot time on the x-axis and plasma concentration on the y-axis. What do you notice about the shape of the curve? If this is done correctly you should have a straight line! Always start your analysis with a graph.

Step 2) Consider what type of information you need to find (e.g., volume of distribution and clearance) and what information
you can obtain from the graph, as well as any necessary
equations to accomplish this.

Step 3)
Start by finding the volume of distribution. First, find $C_0$ by
drawing a best-fit line through the points and extending the
line backwards until it intersects the y-axis. Simply read the
value at the y-axis (approximately 25 mg/L). We know that
the concentration at time=0 ($C_0$) is determined by:

$$C_0 = \frac{X_0}{V}$$

and we know the dose ($X_0 = 1000$ mg). Plugging in our
known values:

$$25 \text{ mg/L} = \frac{1000 \text{ mg}}{V}$$

and solving for $V$, we determine that $V = 40$ L.

Step 4)
Since we know $C_0$, we can calculate half-life. Simply follow
the y-axis to 50% of $C_0$ (12.5 mg/L) and observe the time at
which this concentration occurs. The half-life is a little less
than 2 hours (around 1.9 h). Since we now know half-life, we
can calculate the elimination rate constant, $K$, using the fol-
lowing equation:

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{2 \text{ h}} = 0.375 \text{ 1/h}$$

Please note that any concentration can be used, not just $C_0$
as in this example.

Step 5)
The final parameter in which we are interested is clearance,
which can be determined as follows:

$$CL = V \cdot k$$

We determined volume in step 3, and $K$ in step 4. By plug-
ing these values into the above equation, we find that $CL =
0.375 \times 40$, thus, clearance is 15 L/h.

Below are some alternative ways to find half-life and clear-
ance:

$K$ can be calculated by choosing any two points on the line
and plugging them into the following formula:

\[
k = \frac{(\ln C_2 - \ln C_1)}{(t_2 - t_1)}
\]

Subsequently, half-life is determined by:

\[
t_{1/2} = \frac{0.693}{k}
\]

Remember, you must use the natural log of concentration. Additionally, because most data will have some degree of variability or measurement error, you must be judicious in selecting data points upon which to perform this calculation. The more points you use to determine the average k value, the more accurate the estimate of half-life.

Clearance can be obtained by calculating the AUC from zero to infinity (Chapter 2), and then using the equation:

\[
Cl = \frac{X_0}{AUC}
\]

**Summary**

In one-compartment pharmacokinetic systems with IV bolus drug administration, the initial concentration is dictated by the dose and volume of distribution. The slope of the concentration-time profile is dictated by the drug’s half-life, which is determined by the volume of distribution and clearance.

**Skills Obtained**

- Ability to construct a schematic for a one-compartment system with IV bolus or IV infusion administration
- Ability to estimate V, CL, and t_{1/2} from concentration-time data obtained following IV bolus administration in a one-compartment system
- Ability to predict changes in the concentration-time profile given changes in clearance and volume
**Summary Equations**

To determine plasma concentration at time = 0 after IV bolus:

\[ C_0 = \frac{X_0}{V} \]

To determine plasma concentration at any time after IV bolus or upon cessation of an IV infusion:

\[ C = C_0 \cdot e^{(-k \cdot t)} \text{ or } \ln(C) = \ln(C_0) - K \cdot t \]

**New Symbols**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X_0)</td>
<td>Dose</td>
<td>The amount of drug administered</td>
<td>Mass (e.g., mg)</td>
</tr>
<tr>
<td>(C_0)</td>
<td>Initial concentration</td>
<td>Concentration at time zero (prior to any drug elimination), assuming instantaneous drug distribution</td>
<td>Mass per volume (e.g., ng/mL)</td>
</tr>
<tr>
<td>(K)</td>
<td>Elimination rate constant</td>
<td>First order rate constant of elimination</td>
<td>Inverse time (e.g., 1/h)</td>
</tr>
</tbody>
</table>
6) Extravascular Administration

Goals

- To understand the effect, on drug concentrations, resulting from extravascular drug administration

Objectives

By the end of this chapter you should be able to:

- Calculate clearance, volume, half-life, $C_{\text{MAX}}$ and $t_{\text{MAX}}$ from a concentration-time profile
- Discuss the variables that affect the rate and extent of drug absorption
- Determine absolute or relative bioavailability
- Describe how the ‘method of residuals’ can be used to determine the rate of absorption
- Predict the impact of changes in clearance, absorption rate, volume, or bioavailability on the concentration-time profile
- Describe “flip-flop” pharmacokinetics
- Describe how to establish that two drug products are “bioequivalent”

In Brief

Most drugs are given extravascularly (e.g., orally). The major difference between this route and IV is it now takes time for drug to enter systemic circulation and some drug may be lost during the absorption process. The time for absorption leads parameters of the absorption rate constant ($k_a$) and loss of drug leads to the fraction of drug absorbed ($F$). We also introduce the maximal drug concentration and the time at which that concentration occurs. In terms of fraction of drug absorbed, we will discuss this in terms of absolute bioavailability (i.e., in reference to IV delivery), or relative bioavailability (i.e., in reference to other non-IV dosage forms). We will touch on bioequivalence or how interchangeable two dosage forms might be and flip-flop kinetics that refers what process – absorption rate or elimination rate – is the rate-limiting step in the process.

Introduction

Thus far, we have discussed only intravenous drug administration routes. The most common routes for administration of drugs, however,
are extravascular (e.g., intramuscularly, subcutaneous, oral, etc.), mainly due to their convenience. Differences between intravenous and extravascular methods of input can substantially affect the pharmacokinetics of a drug. Drugs administered intravenously enter directly into systemic circulation, but drugs given extravascularly are, by definition, administered to a peripheral site, and must be absorbed from the site of administration into the systemic circulation. As we discuss principles of drug absorption, it will also be necessary to discuss the concept of bioavailability.

As with the other routes of administration, pharmacokinetic systems incorporating extravascular administration can be represented schematically. Since we are still dealing with a one compartment system (i.e., where drug equilibrates instantly in the body) $V$ and $CL$ will still govern distribution and elimination, as with the IV models. One new aspect, however, will be the need to develop different definitions for input into the system. Input will be represented by the first-order rate constant, $k_a$. As discussed earlier, first-order processes are concentration-dependent, and therefore the driving force for the rate of absorption is the mass of drug to be absorbed ($X_A$). $X_A$ is a function of the actual dose administered ($X_0$) and bioavailability ($F$; the fraction of the dose that enters the systemic circulation).

For the above one compartment model, input into the system is a first-order process and elimination is also first-order process. The rate of change in the mass of drug to be absorbed ($dX_A/dt$) is equal to the product of the absorption rate constant ($k_a$) and the amount in the absorption compartment ($X_a$).

$$\frac{dX_A}{dT} = -k_a X_a \quad \text{Equation 6-1}$$

A graph of the resulting mass-time profile at the site of drug administration will look exactly like the mass-time profile in the systemic circulation following administration of an IV bolus. In the example below, the initial input into the system (the dose administered) is designated $X_0$, and the
mass of drug to be absorbed, designated \( X_A \), declines in an exponential fashion.

![Figure 6-2: Mass-time relationship of drug exiting the site of administration](image)

The half-life for absorption is calculated similarly to the half-life for elimination:

\[
t_{1/2,\text{abs}} = \frac{0.693}{k_a}
\]

Equation 6-2

Taking the entire scheme (absorption and elimination) into consideration we get:

\[
\frac{dX}{dT} = k_aX_a - \text{Cl \cdot C}
\]

Equation 6-3

where the rate of change in the mass of drug over time (\( dX/dT \)) can be calculated based upon \( k_a \), the rate constant for absorption, the mass of drug remaining to be absorbed, \( X_a \), and the first-order elimination rate, \( \text{Cl \cdot C} \). By integrating this equation, we obtain two exponential terms, one for absorption (\( e^{-kat} \)) and one for elimination (\( e^{-kt} \)).

\[
C = \frac{(k_a)(F)(X_0)}{V(k_a - k)}(e^{-kt} - e^{-k_a t})
\]

Equation 6-4

The above equation describes the systemic blood concentrations at any time after administration of the drug. Recall that at time = 0, there will be no drug in the systemic circulation, as with an IV infusion. Also, at time = \( \infty \) there will be no drug remaining in the body (in an open pharmacokinetic system, it will all have been eliminated). At some time point, \( t_{\text{MAX}} \), the peak concentration (\( C_{\text{MAX}} \)) will occur, as depicted in the figure below.
Figure 6-3: Concentration versus time profile for extravascular administration plotted on rectilinear coordinates (left) and on semi-log coordinates (right)

At points prior to $C_{MAX}$, the rate of absorption is greater than the rate of elimination. At $C_{MAX}$, the rate of absorption is equal to the rate of elimination, and after $C_{MAX}$, the rate of elimination is greater than the rate of absorption. As after administration of an IV bolus, concentrations fall in a curved fashion (when plotted on rectilinear coordinates) or a straight-line (when graphed on semi-log coordinates). The equation that describes this profile incorporates the following parameter: dose ($X_0$), bioavailability ($F$), volume ($V$), absorption rate constant ($k_a$) and elimination rate constant ($k$).

The first part of the equation $\frac{(k_a)(F)(X_0)}{V \cdot (k_a - k)}$ is a constant because these values will not change with time. The two exponential terms $e^{-kt}$ and $e^{-k_a t}$ describe the rates at which drug is removed from, or enters into the body, respectively. The term, $F$, represents bioavailability, or the fraction of the administered drug which reaches the systemic circulation.

**Example:** Drug X (100 mg), administered as an intramuscular injection, has the following pharmacokinetic parameters: $t_{1/2} = 8$ h, $k_a = 1.5$ h$^{-1}$, $V = 10$ L, $F = 65\%$. What will be the concentration at 12 hours after the dose is administered?

Here is the equation for the concentration-time profile:

$$C = \frac{(k_a)(F)(X_0)}{V \cdot (k_a - k)} (e^{-kt} - e^{-k_a t})$$

Insert the above parameter values into the equation and solve:
\[
C = \frac{(1.5)(0.65)(100)}{10 \cdot (1.5 - .087)} (e^{-(0.087)(12)} - e^{-(1.5)(12)})
\]
\[
C = 6.9 \cdot (0.35 - 0.00) = 2.4 \text{mg/L}
\]

Thus, 12 h after administering the drug, blood concentration will be 2.4 mg/L

**Bioavailability**

Bioavailability refers to the rate and extent to which a drug is absorbed and available at the site of action. Rate, of course, means ‘how fast’ the drug is absorbed. Absorption rates can be zero-order \((k_0)\), as we have discussed in the context of infusions, first-order \((k_a\) where the subscript ‘a’ stands for absorption), may be a function of other more complex processes. The absorption rate will depend on factors such as dosage form and physiologic parameters (e.g., transporters etc). Typically, it is assumed that absorption rates are first-order, however, some examples of zero-order absorption processes include absorption from transdermal patches and controlled-release tablets.

Another component of bioavailability is the extent to which, or ‘how much’ of the dose enters systemic circulation. The extent of bioavailability is abbreviated by the letter ‘\(F\)’, for “fraction”. Generally, when discussing bioavailability, the primary concern is “how much of the dose enters circulation” but keep in mind that the rate of absorption is also a component of bioavailability. In the prior discussion of IV administration, it was assumed that \(F=1\), because the entire dose is injected directly into the systemic circulation via the vein. Drugs administered by any extravascular (non-IV) route must travel from the site of administration (e.g., muscle, mouth) to the systemic circulation, thus, the potential for loss of drug prior to entry into the systemic circulation is increased.
Below are examples of approximate $F$ values for various drugs:

**Table 6-1: Examples of drug bioavailabilities**

<table>
<thead>
<tr>
<th>Drug</th>
<th>$F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>1.0</td>
</tr>
<tr>
<td>Nicotine (inhaled)</td>
<td>0.90</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.88</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.80</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.57</td>
</tr>
<tr>
<td>Nicotine (oral)</td>
<td>0.30</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.24</td>
</tr>
<tr>
<td>Budesonide</td>
<td>0.12</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

What factors determine the rate and extent to which a drug is absorbed? Our discussion of factors that can affect bioavailability will focus on oral bioavailability, however, some of the barriers for oral absorption are relevant to other routes. The figure and table below summarize these important barriers.

![Figure 6-4: Potential sites of drug loss following oral administration: 1) drug is not absorbed; 2) drug undergoes metabolism or efflux in the intestine; 3) drug is metabolized in the liver](image)

Bioavailability may be affected by:
1) Physicochemical properties of the drug or formulation
2) Lability of drug to pH, enzymes, etc.
3) Membrane barriers.
Table 6-2: Examples of factors that impact the rate of absorption or the fraction absorbed

<table>
<thead>
<tr>
<th>Factors Impacting Drug Absorption Rate</th>
<th>Factors Impacting Drug Absorption Extent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transit Time</td>
<td>Enzyme degradation</td>
</tr>
<tr>
<td>Disintegration</td>
<td>pH-dependent degradation</td>
</tr>
<tr>
<td>Dissolution</td>
<td>CYP P450 metabolism (intestinal)</td>
</tr>
<tr>
<td>Mechanism of absorption / diffusion</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>P-glycoprotein</td>
<td>First-pass metabolism (liver metabolism)</td>
</tr>
<tr>
<td></td>
<td>Entero-hepatic recirculation</td>
</tr>
</tbody>
</table>

The following discussion will summarize the effect of various factors impacting (oral) bioavailability of a drug. Consider a drug tablet which is administered orally. The drug enters the stomach and subsequently moves through the small intestine, colon etc. The amount of time for this transit process to occur is referred to as gastrointestinal transit time. If the drug is targeted for colonic absorption, the absorption time will (in theory) be longer than if it is targeted for stomach absorption, because the colon is more distal than the stomach. Once the tablet is in the small intestine (or stomach) the tablet must undergo disintegration and must also dissolve into solution (dissolution). Food can affect both disintegration and dissolution, thus, some drugs include instructions to “take with food” or “take with water” or “do not take with food”. The factors influencing these processes vary by administration route; for example, following intramuscular administration, absorption time could be dependent on factors such as muscle size, blood flow, amount of adipose tissue etc.

![Disintegration and Dissolution Diagram](image)

Returning to the example of oral administration, after dissolution, drug is in solution and must pass through (or around) the cells that line the intestine before it can enter the blood supply. Absorption can occur via diffusion (a passive process) or active transport. A growing body of evidence suggests that drugs can also be ‘pumped’ back into the intestine by transporters like P-glycoprotein (PGP) and that drugs can be metabolized inside intestinal cells. Thus, the factors influencing bioavailability can be complex. Finally, the proportion of drug that escapes intestinal
metabolism and transport by PGP will reach the portal vein leading into the liver. The drug will remain in the liver for a certain period of time before it passes into the systemic circulation. All of these processes take time.

Next, we will discuss factors which influence the extent to which a given drug dose will enter systemic circulation. During the absorption process, a drug is exposed to various changes in pH, degradative enzymes (e.g., P450 enzymes in the gut and liver) and drug efflux transporters such as PGP. Enzymes and pH can degrade drugs, P450 enzymes can metabolize drugs and PGP can minimize drugs from entering the systemic circulation. If a drug survives this process, it can be absorbed by intestinal cells, however, if it is not absorbed, it will continue down the GI tract and be eliminated in the feces. These same types of processes may also be relevant for other drug administration modalities (e.g. IM injection). For example, insulin tends to degrade in the muscle; enzymes, immune cells, or muscle pH may also degrade drug, thus limiting the amount that eventually enters into the systemic circulation.

If a drug is subject to absorption by transporters, then the capacity of these transporters to move drug will in part determine how much of the drug eventually reaches the blood. Many nutrients are absorbed by transporters, thus, modulation of these transporters can constitute an important potential therapeutic approach (e.g., to regulate absorption of nutrients). Some drugs utilize endogenous transport proteins including methyldopa, valcyclovir, certain cephalosporins, and salicylic acid.

Drugs will eventually reach the portal circulation, providing exposure to the liver, where many drug metabolizing enzymes function, and other elimination processes. The remaining fraction of drug, following transit through the liver, will enter the systemic circulation. A detailed discussion of hepatic systems will be discussed later in this book, in the chapter titled Hepatic Clearance. The liver’s ability to clear drug from the body after oral administration is called the “first-pass effect”, because the first passage of drug through the liver (i.e., before entry into the systemic circulation and subsequent additional passages through the liver) can remove a significant amount of drug. For example, the oral bioavailability of testosterone is extremely low because of extensive first-pass metabolism. In order to make testosterone into an effective oral formulation, one approach is to modify the drug’s structure, thus “protecting” the testosterone from first-pass metabolism (e.g., methyltestosterone – testosterone with a methyl group at the 17-α position).

The previous sections dealt with factors that determine the rate and extent to which a drug is absorbed. Now we will discuss methods for determining a drug’s bioavailability from concentration-time data.
The AUC is a general term used to describe drug exposure; it reflects the response of the system to a given dose and clearance. In cases of extravascular administration, AUC is related to clearance and dose as well as bioavailability, as summarized in the equation below.

\[
\text{AUC}_\infty = \frac{X_0 F}{CL}.
\]

Equation 6-5

Note that this equation has appeared before, in the context of IV administration, however, in that case, it was assumed that \( F=1 \). Since the AUC is a response of the system to an amount of drug that enters into the system, we now must consider the fraction of dose that reaches the systemic circulation, that is, the \( F \) term in the equation.

The dose of drug administered is generally known, and can be used to calculate the AUC based upon a concentration-time profile in blood. For most drugs, when administered at therapeutic doses, clearance is independent of dose and independent of the route of administration. This means that clearance after an IV bolus dose is equal to the clearance after an orally-administered dose (\( \text{CL}_{\text{IV Bolus}} = \text{CL}_{\text{PO}} \)). Based upon this information we can determine \( F \) (bioavailability).

As discussed above, after extravascular administration,

\[
\text{AUC}_{\text{PO}} = \frac{X_0 F}{CL}
\]

Recall that after IV bolus administration bioavailability is 100\% (\( F=1 \))

\[
\text{AUC}_{\text{IV}} = \frac{X_0}{CL}
\]

Since CL for a given drug is the same regardless of route, it is possible to 1) rearrange the above equations to solve for CL, 2) set the equations equal to each other, and 3) solve for \( F \):

Step 1)

\[
\text{AUC}_{\infty \text{PO}} = \frac{X_0 F}{CL} \rightarrow \text{CL} = \frac{X_0 F}{\text{AUC}_{\text{PO}}}
\]

\[
\text{AUC}_{\infty \text{IV}} = \frac{X_0}{CL} \rightarrow \text{CL} = \frac{X_0}{\text{AUC}_{\text{IV}}}
\]
Step 2)

$$\frac{X_0}{AUC_{IV}} = \frac{X_0 F}{AUC_{PO}}$$

Step 3)

$$F = \frac{AUC_{PO} \cdot X_{0,IV}}{AUC_{IV} \cdot X_{0,PO}}$$  \hspace{1cm} \text{Equation 6-6}$$

Where $F$ is the bioavailability, $AUC_{PO}$ is the AUC after oral administration; $AUC_{IV}$ is the AUC after IV administration; $X_{0,IV}$ is the dose given IV; and $X_{0,PO}$ is the dose given orally. When both doses are equal:

$$F = \frac{AUC_{PO}}{AUC_{IV}}$$  \hspace{1cm} \text{Equation 6-7}$$

This equation determines \textit{absolute bioavailability}, which refers to the difference between AUC resulting from extravascular administration ($F<1$) vs. intravenous data ($F = 1$). Thus, the effect of a non-IV administration route on the proportion of drug reaching the systemic circulation can be definitively determined. Absolute bioavailability will range from zero through 1 (or 100%).

It also is possible to determine \textit{relative bioavailability}, by comparing two different extravascular formulations (e.g., tablet vs. solution, subcutaneous vs. intramuscular, generic vs. standard). The theory and calculations are nearly the same, however, the selection of the reference and test compounds depends on the experimental objective, as discussed below.

$$\frac{F_{\text{TEST}}}{F_{\text{STAND}}} = \frac{AUC_{\text{TEST}}}{AUC_{\text{STAND}}} \Rightarrow$$

$$F_{\text{TEST}} = \frac{AUC_{\text{TEST}}}{AUC_{\text{STAND}}}$$  \hspace{1cm} \text{Equation 6-8}$$

In the case above, relative bioavailability refers to the difference between AUC associated with a test product ($AUC_{\text{TEST}}$) and some standard product ($AUC_{\text{STAND}}$) to which the test product is being compared. Thus, bioavailability is expressed in terms relative to another product rather than relative to an identical product delivered by an intravenous admin-
After extravascular administration, we represent clearance as \( \text{Cl/F} \) because we do not know bioavailability.

Do NOT forget about \( F \) when do you calculations!!!

Example: The following data were obtained after intramuscular (IM) and intravenous (IV) administration of drug Z. Determine the bioavailability of the drug after IM injection.

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>IC</th>
<th>CL (mL/min)</th>
<th>V (L)</th>
<th>( t_{1/2} ) (h)</th>
<th>AUC (mg h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>1000</td>
<td>---</td>
<td>---</td>
<td>2</td>
<td>115.5</td>
</tr>
<tr>
<td>IV</td>
<td>500</td>
<td>115</td>
<td>20</td>
<td>2</td>
<td>72.1</td>
</tr>
</tbody>
</table>

Beginning with the equation for \( F \)

\[
F_{\text{IM}} = \frac{\text{AUC}_{\text{IM}} \times X_0_{\text{IV}}}{\text{AUC}_{\text{IV}} \times X_0_{\text{IM}}}
\]

Insert the known values

\[
F_{\text{IM}} = \frac{(115.5)(500)}{(72.1)(1000)} = 0.80
\]

Bioavailability is 80%

Now, consider a case in which extravascular administration data alone is available. The value of \( X_0 \) (the administered dose) is known, and the AUC can be determined from blood concentration-time data, thus, values for 2 of the 4 components of the following equation can be determined.

\[
\text{AUC}_{\infty \text{PO}} = \frac{X_0 F}{\text{Cl}}
\]

Rearranging the equation:

\[
\frac{\text{Cl}}{F} = \frac{X_0}{\text{AUC}_{\text{PO}}}
\]

Equation 6-9

After extravascular administration, we represent clearance as \( \text{Cl/F} \) because we do not know bioavailability.
It is impossible, based on extravascular data alone, to estimate F. Therefore, in this case, it is necessary to report clearance and volume values relative to the (unknown) bioavailable fraction of the dose. The appropriate terms are thus CL/F (the apparent oral clearance) and V/F (the apparent oral volume of distribution).

Consider the following situation in which drug interactions may be responsible for changes in bioavailability. In this situation, 100 mg of drug X is administered orally, alone, or in combination with drug Y (also oral). When drug X is administered alone, the resulting AUC is 10 ng*h/mL. When 100 mg of drug X is administered in combination with drug Y, the resulting AUC for drug X drops to 5 ng*h/mL. Did drug Y increase the clearance of drug X (induce metabolism) or did drug Y decrease the amount of drug X that was initially absorbed into the systemic circulation? Both are feasible explanations, however, the answer cannot be determined unless additional data (such as IV data) are collected. Again, this is why, for non-intravenous routes, clearance is appropriately reported as CL/F.

**Flip-Flop Kinetics**

In pharmacokinetic systems, the concept of a rate-limiting step is particularly important. The rate-limiting step of a process is the slowest component of the process, when it is not possible for the entire process to proceed faster than the slowest step. To conceptualize, when you are driving down the highway and you are the only person on the road, the rate limiting factor determining your trip duration is how fast your car can go (in theory, if you do not obey traffic laws). However, in traffic, the rate limiting factor may be the speed of slower cars in front of you. This concept is relevant to our discussion of “flip-flop” kinetics.

For most extravascularly-administered drugs, the absorption rate constant (k_a) is significantly larger than the elimination rate constant (k); \((k_a >> k)\). What this means is that absorption proceeds at a much faster rate than elimination. Thus, elimination (the slower process) is the rate limiting step in the disposition of the drug. As a result, at some time after administration, the term \(e^{-k_a t}\) approaches zero faster than the elimination term approaches zero. For example, if the absorption half-life (t_{1/2, abs}) is 30 min (k_a = 1.4 h\(^{-1}\)) and the elimination half-life (t_{1/2}) is 6 hours (k = 0.126 h\(^{-1}\)), absorption should be complete within 5 half-lives or 150 min. The terminal slope of the resulting concentration-time profile (as seen below) is representative of the cases which we have considered up to this point, that is, where the absorption rate exceeds the elimination rate.
Sometimes the rate of absorption is much slower than the rate of elimination (k >> kₐ), such as is the case for certain extended-release formulations or depot injections. This phenomenon, wherein k >> kₐ, is termed ‘flip-flop’ kinetics, wherein the terminal slope is no longer representative of the elimination rate (k), because elimination is no longer the slowest step in the process. The terminal slope in the “flip-flop” case actually represents the absorption rate constant, kₐ. Again, what this means is that the rate-limiting step, (whether absorption or elimination), determines the terminal slope of the concentration-time profile.

So how is it possible to identify a system with flip-flop kinetics? The only way to determine this is by examining concentration-time data collected following an IV bolus injection of the drug in question. In the case of IV bolus administration, drug enters the systemic circulation directly, thus, no absorption phase exists, and therefore the slope is always representative of elimination only. The slope of the concentration-time profile resulting from IV bolus administration should be equal to the terminal slope associated with extravascular administration, if kₐ >> k (that is if elimination is the rate-limiting process).

**Example.** The following pharmacokinetic parameters were calculated after an IV push (treat as an IV bolus) and subcutaneous administration of erythropoietin α (EPO).

<table>
<thead>
<tr>
<th>Route</th>
<th>(X₀) (U/kg)</th>
<th>AUC (U*h/mL)</th>
<th>(t_{1/2}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>50</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>SubQ</td>
<td>50</td>
<td>2</td>
<td>45</td>
</tr>
</tbody>
</table>
Note the difference between the half-life of IV- vs. subcutaneously- administered EPO. In theory, half-life should be the same because CL and V, which determine the elimination rate constant K, do not depend upon the route of administration. Because the rate of absorption from the subcutaneous injection site is much slower than the rate of elimination of EPO, the terminal half-life is not representative of an elimination process. This situation is typical for drugs with very fast elimination half-lives.

An important note – even though the half-life is different, AUC is still determined by the bioavailable dose (X₀F) and clearance, so regardless of the absorption kinetics, AUC will still be proportional to the fraction of dose entering the systemic circulation. Here the bioavailability of EPO via subcutaneous injection is ~17%.

The main impact of flip-flop pharmacokinetics is upon the physiological interpretation of half-life in this case. Regardless of route, a drug will always have the same clearance and volume of distribution, thus half-life should always be the same. If a drug displays flip-flop kinetics, changes that alter either parameter will not impact the half-life, thus, in the case of a drug interaction that reduces clearance, AUC may change, but half-life will not. In addition, because the estimated half-life does not reflect elimination, calculating volume (or clearance) based upon the relationship $K = \frac{CL}{V}$ will result in error because the K term in this equation represents the elimination rate constant!

The figure below represents the impact of a slow absorption rate (relative to the elimination rate), on a concentration time profile. In this example, the half-life of the immediate-release product has the same half-life as the IV bolus-administered drug – this is to be expected. The extended release formulation, however, has a much slower absorption rate than the immediate-release formulation, which leads to flip-flop pharmacokinetics. Note that the half-life of the extended-release product is much longer than that of the immediate-release product. Recall as well that it takes 5 half-lives to approximately reach steady-state, so extended-release products may take longer to reach steady-state than immediate release products. The benefit of an extended-release product, however, is that fewer doses must be administered, which increases compliance.
Figure 6-7: Illustration of flip-flop pharmacokinetics. Drug X was administered as an IV bolus injection, or extravascularly as either an immediate release formulation (IR) or extended-release formulation (ER). The ER formulation results in an absorption rate much slower than the elimination rate, resulting in flip-flop behavior.

**Bioequivalence**

The final topic we will discuss in this chapter is bioequivalence. Bioequivalence is defined as “the absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of action when administered at the same dose”. The main issue addressed by bioequivalence studies is “switchability”, that is, whether one product (e.g., a proprietary product like Prozac) can be replaced with another product (e.g., a generic like fluoxetine) without any significant impact on the compound’s pharmacokinetics. “Switchable” products are given ratings of “AB” by the US FDA, and are listed as such in the FDA’s Orange Book (http://www.fda.gov/cder/ob/default.htm). Products are deemed bioequivalent based mainly upon equivalence in AUC and C\text{MAX}, and to a lesser extent, t\text{max}.

**Impact of parameters on concentration-time profile**

Finally, we will briefly discuss how changes in bioavailability, clearance, volume of distribution, and absorption rate will affect the shape of the plasma concentration-time profile. These relationships can be determined using the equations presented in this chapter, and by using a program such as Microsoft Excel to observe the effects of each of these parameters in a simulated pharmacokinetic system.

**Bioavailability (F):** Bioavailability indicates the fraction of the administered dose which enters the systemic circulation. An change in F is func-
tionally equivalent to administering a different dose, and will thus alter $C_{\text{MAX}}$ (i.e., $\uparrow F = \uparrow C_{\text{MAX}}$) and $\text{AUC}$ (i.e., $\uparrow F = \uparrow \text{AUC}$). A change in $F$ will not affect $t_{\text{MAX}}$ or $t_{1/2}$. In the figure below, the dotted line represents the original concentration-time profile, the solid line represents a 2-fold increase in $F$.

**Figure 6-8: Impact of increasing $F$ on the concentration-time profile, plotted on rectilinear (left) and semi-log (right) coordinates. Dotted is the original profile. Solid line is with increased bioavailability.**

**Clearance ($\text{CL}$):** Clearance indicates the volume from which a drug is completely eliminated per unit time (essentially, the elimination rate). A change in clearance will change $t_{1/2}$ (and $k$) and $C_{\text{MAX}}$ (i.e., $\uparrow \text{CL} = \downarrow t_{1/2}$ and $\downarrow C_{\text{MAX}}$). $T_{\text{MAX}}$ is, in part, determined by $k$, and therefore $t_{\text{MAX}}$ also changes with clearance (i.e., $\uparrow \text{CL} = \downarrow t_{\text{MAX}}$). In the figure below, the dotted line represents the original concentration-time profile, and the solid line represents the profile that would result if clearance was doubled.
Figure 6-9: Impact of increasing CL on the concentration-time profile, plotted on rectilinear (left) and semi-log (right) coordinates. Dotted is the original profile. Solid line is with increased clearance.

**Effects of ↑ CL:**
- \( C_{\text{max}} = \downarrow \)
- \( T_{\text{max}} = \downarrow \)
- \( \text{AUC} = \downarrow \)
- \( t_{1/2} = \downarrow \)

**Volume:** The apparent volume of distribution, which does not necessarily reflect a physiological volume, functions in some cases as a “fudge factor” for converting a given dose to a concentration. A change in volume will change \( t_{1/2} \) (and \( k \)), for example, \( \uparrow V = \uparrow t_{1/2} \). \( T_{\text{MAX}} \) is, in part, determined by \( k \) and therefore \( t_{\text{MAX}} \) will also change with volume (e.g., \( \uparrow V = \uparrow t_{\text{MAX}} \)). The effect of a change in volume on \( C_{\text{MAX}} \) is somewhat more complicated. The terminal elimination rate, \( k \), will decrease with increasing volume, but increasing volume will lower plasma concentration. The direction in which \( C_{\text{MAX}} \) changes will depend on the degree to which each of these parameters changes, but in general, \( \uparrow V = \downarrow C_{\text{MAX}} \). In the figure below, the dotted line represents the original concentration-time profile, and the solid line represents the effect of doubling volume. If volume changes, the AUC will NOT change – the only factors that will impact AUC are CL or F!
Figure 6-10: Impact of increasing V on the concentration-time profile, plotted on rectilinear (left) and semi-log (right) coordinates. Dotted is the original profile. Solid line is with increased volume of distribution.

Absorption rate ($k_a$): Finally, how does the absorption rate constant affect other pharmacokinetic parameters? $k_a$ will NOT affect $t_{1/2}$ but it will affect $t_{\text{MAX}}$ and $C_{\text{MAX}}$ (e.g., $\uparrow k_a = \uparrow C_{\text{MAX}}$ and $\downarrow t_{\text{MAX}}$). In the figure below, the dotted line represents the original concentration-time profile, and the solid line represents the effect of doubling the absorption rate. As with changes in V, a change in $k_a$ will NOT change AUC.

Figure 6-11: Impact of increasing absorption rate, plotted on rectilinear (left) and semi-log (right) coordinates. Dotted is the original profile. Solid line is with increased absorption rate constant.
The table below summarizes the effects of changes in F, CL, V or kₐ on various pharmacokinetic parameters, under conditions of extravascular drug administration.

Table 6-3: Summary of how parameter changes influence each other

<table>
<thead>
<tr>
<th>Parameter Changed</th>
<th>t½</th>
<th>CMAX</th>
<th>tmax</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>☒</td>
<td>☑</td>
<td>☒</td>
<td>☑</td>
</tr>
<tr>
<td>CL</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>V</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☒</td>
</tr>
<tr>
<td>kₐ</td>
<td>☒</td>
<td>☑</td>
<td>☑</td>
<td>☒</td>
</tr>
</tbody>
</table>

Using Microsoft Excel, simulate different scenarios to test your ability to predict changes in the concentration-time profile, given a change in any pharmacokinetic parameter.

**Gathering information from a one compartment pharmacokinetic system after extravascular administration**

The following data were obtained after drug X was administered orally as a 1000 mg tablet. Determine the clearance (CL/F), half-life, volume (V/F), maximum concentration (C_MAX), time to maximal concentration (t_MAX) and the absorption rate constant (assume kₐ>>k).

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>19.85</td>
</tr>
<tr>
<td>2</td>
<td>21.92</td>
</tr>
<tr>
<td>4</td>
<td>14.42</td>
</tr>
<tr>
<td>6</td>
<td>7.75</td>
</tr>
<tr>
<td>8</td>
<td>3.96</td>
</tr>
</tbody>
</table>

**Step 1)** As always, plot the data on semi-log coordinates.
Step 2) The simplest parameters to find first are $C_{\text{MAX}}$ and $t_{\text{MAX}}$ because they can be read directly from the graph. Here, $C_{\text{MAX}}$ is 21.92 mg/L and $t_{\text{MAX}}$ is 2 hours.

Step 3) Determine half-life by drawing the best fit line through the terminal slope (straight portion of the profile) and read from the graph the time it takes for concentrations to fall by half. In this case, half-life is approximately 2 h.

Confirm the half life value: note that it takes about 2 h for concentrations to drop from 14.42 mg/L to 7.75 (around half of 14.42). Be sure that you base these calculations on the
part of the profile where drug concentrations are falling!

**Alternative:** This can also be done mathematically using any two points on the straight line portion of the profile (that is, the terminal slope):

$$k = \frac{\ln(C_2) - \ln(C_1)}{t_2 - t_1}$$

$$k = \frac{\ln(14.42) - \ln(7.75)}{6 - 4} = 0.31 h^{-1}$$

$$t_{1/2} = 2h$$

The above equation is not new—it is simply the equation describing the slope of a straight line ($\Delta y/\Delta x$).

**Step 4**) Clearance can be determined using the following equation

$$CL = \frac{X_0 F}{AUC_{\infty}}$$

The administered dose is known, and we can calculate AUC using the trapezoidal method (remember to include the terminal portion of the AUC).

$$AUC_t = 101 mg*h/L$$

$$AUC = 113.3 mg*h/L$$

Here, clearance is

$$\frac{CL}{F} = \frac{1000}{113.3} = 8.8 L/h$$

Note that clearance and AUC are independent of the route of administration, and that the rate of absorption does not influence AUC.

**Step 5**) Now that half-life and clearance have been calculated, it is possible to determine volume.

$$V = \frac{CL}{k} = \frac{8.8}{0.347} = 25.4 L$$

**Step 6**) The absorption rate constant, $K_a$, can be calculated using
the method of residuals (description in Appendix D). Below is a graphical representation of this method. (1) The terminal portion of the profile is extrapolated backward (toward t=0). This terminal slope reflects the rate of elimination only. (2) The contribution of the elimination process is subtracted from the concentration-time profile, resulting in a “residual line” representing the contribution of only the absorption process to the concentration-time profile. (3) The slope of this residual line reflects the absorption half-life.

![Graphical representation of the method of residuals]

The absorption half-life is approximately 0.5 h, so $k_a = 1.4 \text{ h}^{-1}$

**Summary**

We have finished our discussion of the concentration-time profile in a one-compartment pharmacokinetic system following extravascular administration. The term bioavailability was introduced to represent the fraction of the drug that enters systemic circulation; this is an important factor when designing dosing regimens. Bioequivalence is a term used to indicate that two dosage forms can be interchanged without loss of therapeutic effect; bioequivalence is determined based upon pharmacokinetic equivalence. Although absorption can add a level of complication to the concentration-time profile (relative to systems with intravenous administration), systemic exposure is not impacted by the absorption profile unless the fraction of the dose absorbed is changed.

**Skills Obtained**

- Calculating absolute and relative bioavailability.
- Estimating changes in the concentration-time profile resulting from changes in $k_a$, $CL$, $F$, or $V$. For example, will a drug interaction that reduces clearance change a drug’s $C_{MAX}$?
• Determining CL/F, V/F and t₁/₂ from concentration-time data.
• Using the method of residuals to estimate the absorption rate constant (kₐ).

**Summary Equations**

To determine plasma concentration after extravascular administration at any time:

\[ C = \frac{(k_a)(F)(X_0)}{V \cdot (k_a - k)} \left( e^{-kt} - e^{-k_at} \right) \]

To determine the AUC after extravascular administration:

\[ \text{AUC} = \frac{X_0F}{CL} \]

To determine absolute bioavailability:

\[ F = \frac{\text{AUC}_\text{PO}}{\text{AUC}_\text{IV}} \cdot \frac{X_{0,IV}}{X_{0,PO}} \]

To determine relative bioavailability (assuming the same dose is administered):

\[ F_{\text{TEST}} = \frac{\text{AUC}_{\text{TEST}}}{\text{AUC}_{\text{STAND}}} \]

**New Symbols**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>kₐ</td>
<td>Rate constant for absorption</td>
<td>The first order rate at which a drug is absorbed into systemic circulation</td>
<td>Inverse time (e.g., 1/h)</td>
</tr>
<tr>
<td>F</td>
<td>Bioavailability</td>
<td>The fraction of the administered dose that reaches systemic circulation</td>
<td>Unitless</td>
</tr>
</tbody>
</table>
7) Intravenous Infusion

Goals

To understand the one compartment model and how it is used to predict drug concentrations in the body over time after intravenous infusion

Objectives

* By the end of this chapter you should be able to:
  * Calculate a drug concentration at a given time after IV infusion
  * Calculate the time at which a given drug concentration occurs
  * Calculate pharmacokinetic parameters (clearance, volume, half-life) given a plasma concentration-time profile
  * Graph a concentration-time profile on semi-log coordinates
  * Estimate the time to reach steady-state with an infusion
  * Explain the term steady-state
  * Calculate a loading dose and explain why a loading dose is necessary

In Brief

In a clinical setting we can administer drugs via an infusion – that is, giving a mass of drug over time into a vein. In this situation we can now discuss the time to achieve steady-state, where concentrations do not fluctuate over time, the steady-state concentration, the concentration achieved at a constant infusion rate, and how we may achieve steady-state more quickly by using a loading dose or loading infusion. Our time to steady-state is a function of half-life (5 to be exact) and the steady-state concentration is a function of the infusion rate and the clearance of the drug. We also can use data from infusions to recover patient specific parameters of half-life, clearance and volume.

Introduction

We have already discussed how to obtain pharmacokinetic parameters after IV bolus in a one-compartment body model. However, not many drugs are administered as an IV bolus. More often, drugs that are administered intravenously are given as an infusion rather than a bolus. The main advantage of an IV infusion is the ability to maintain constant plasma drug concentrations, referred to as steady-state drug concentrations. Steady-state refers to the condition in which the RATE of drug entering the system is equal to the RATE of drug leaving the system. Infusions
are zero-order processes, because they deliver a fixed amount of drug per unit time (e.g., mg/min).

In the above schematic depicting a one compartment pharmacokinetic system, input into the system is represented as a zero-order process, but elimination is depicted as a first order process. The following equations can be developed based upon the above scheme:

\[
\begin{align*}
V \frac{dC}{dt} &= k_0 - CL \cdot C \\
\frac{dC}{dt} &= \frac{k_0}{V} - \frac{CL}{V} \cdot C
\end{align*}
\]

Equation 7-1

where the rate of change in amount of drug with respect to time (dC/dt) is equal to the difference between the zero order input rate, \( k_0 \), and the first-order elimination rate of drug, \( \frac{CL}{V} \cdot C \). Integrating this equation yields:

\[
C = \frac{k_0}{CL} \cdot (1 - e^{-kt})
\]

Equation 7-2

where \( C \) is the concentration at time, \( t \); \( CL \) is clearance; \( k_0 \) is the infusion rate, and \( k \) is the elimination rate constant. The term \((1-e^{-kt})\) gives the fraction of steady-state concentration achieved by a given time, \( t \). As time increases, this term approaches 1, and we reach a steady-state level as seen in the figure below.
So how long does it take to reach steady-state? Half-life is an important parameter required to answer this question. Suppose that a drug has a half-life of 4 hours (k=0.173 h\(^{-1}\)). We can examine how the factor \((1-e^{-kt})\) changes with time:

Table 7-1: Example of how the values within the equation for an infusion changes over time.

<table>
<thead>
<tr>
<th>Time after starting infusion (h)</th>
<th>Value of (1-e(^{-kt}))</th>
<th>Drug Elapsed (Half-Lives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>0.29</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>0.50</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0.75</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>0.87</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>0.97</td>
<td>5</td>
</tr>
</tbody>
</table>

As illustrated above, it takes 5 half-lives to reach approximately steady-state concentrations (we usually approximate steady-state to within 10% of the true value; since the fraction of steady-state vs. time relationship is asymptotic, the fraction will approach, but never actually reach 100%). This relationship also can be used to determine how long it takes for a drug to be eliminated from the body (also 5 half-lives). This idea will be important when we examine the concept of a loading dose.

Looking back at the equation:

\[
C = \frac{k_0}{CL} \cdot (1 - e^{-kt})
\]

**CSS** is the average drug concentration at steady-state.
when steady-state conditions are attained, \((1-e^{-kt}) = 1\) and therefore, the steady-state concentration \(C_{SS}\) is determined by:

\[
C_{SS} = \frac{k_0}{CL} \quad \text{Equation 7-3}
\]

This equation gives the concentration at steady-state. Therefore, the equation can be rearranged to calculate an infusion rate, given a target concentration \(C\) and the rate of clearance \(CL\).

\[
k_0 = C_{SS} \cdot CL \quad \text{Equation 7-4}
\]

It should now be possible to predict the effect of changes in clearance or volume. If volume is doubled, half-life will be doubled, therefore, it will take twice as long to reach steady-state.

\[
t_{\frac{1}{2}} = \frac{0.693 \cdot V}{CL}
\]

\[
\uparrow t_{\frac{1}{2}} = \frac{0.693 \cdot V}{CL}
\]

\[
\downarrow t_{\frac{1}{2}} = \frac{0.693 \cdot V}{CL}
\]

Figure 7-4: Impact of doubling volume of distribution on time to steady-state and steady-state concentrations. Closed and open circles represent concentrations under conditions of 1x and 2x volume, respectively. Volume impacts time to steady-state, but not steady-state concentration.

If we double clearance, we will decrease half-life by half, and therefore will reach steady-state twice as fast.

\[
t_{\frac{1}{2}} = \frac{0.693 \cdot V}{CL}
\]

\[
\downarrow t_{\frac{1}{2}} = \frac{0.693 \cdot V}{\uparrow CL}
\]

Clearance and dose dictate steady-state concentrations.

Half-life dictates time to steady-state. It takes 5 half-lives to reach steady-state.
Additionally, doubling the clearance will halve the steady-state concentration, because:

$$C_{ss} = \frac{k_0}{CL}$$

$$\downarrow C_{ss} = \frac{k_0}{CL}$$

This is very important; clearance dictates steady-state concentrations, but not volume. Be sure that you understand both scenarios. Microsoft Excel spreadsheets found on the Blackboard page can help illustrate these points.

**Loading Dose - Bolus**

We have learned that it takes approximately 5 half-lives to reach steady-state. If a drug has a long half-life, or if therapeutic levels must be attained immediately, an IV bolus loading dose can be administered. For example, the antiarrhythmic lidocaine is usually administered with an IV bolus loading dose. How do we calculate a loading dose? In the previous section we learned that the concentration at time = 0 (referred to as $C_0$) can be determined by:

$$C_0 = \frac{X_0}{V}$$

Substituting the term $C_0$ with our desired steady-state concentrations ($C_{ss}$), and designating our dose as a loading dose ($X_{LD}$) for clarity, we can rearrange this equation to determine the loading dose as a function of the desired steady-state level ($C_{ss}$) and volume of distribution ($V$):
Let us look back at the earlier example. Suppose a drug has a half-life of 4 hours ($k=0.173 \ 1/h$). Upon administration of the loading dose as an IV bolus at the start of the infusion, observe how the amount of drug from the infusion increases over time and the amount of drug from the IV bolus decreases over time:

**Table 7-2: Example of the contributions of the amount of drug from the infusion and a loading IV bolus**

<table>
<thead>
<tr>
<th>Time after starting infusion (h)</th>
<th>Amount of Drug from Infusion</th>
<th>Amount of Drug from IV Bolus</th>
<th>Total Drug in Body (infusion+bolus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>20.00</td>
<td>20.00</td>
</tr>
<tr>
<td>2</td>
<td>5.86</td>
<td>14.14</td>
<td>20.00</td>
</tr>
<tr>
<td>4</td>
<td>10.00</td>
<td>10.00</td>
<td>20.00</td>
</tr>
<tr>
<td>8</td>
<td>15.00</td>
<td>5.00</td>
<td>20.00</td>
</tr>
<tr>
<td>12</td>
<td>17.50</td>
<td>2.50</td>
<td>20.00</td>
</tr>
<tr>
<td>20</td>
<td>19.37</td>
<td>0.63</td>
<td>20.00</td>
</tr>
</tbody>
</table>

Not only does it take 5 half-lives to reach steady-state but it takes 5 half-lives to completely eliminate a given dose of drug from the body.
Loading Dose Example

The desired steady-state concentration of drug X is 5 mg/L. Clearance of drug X is 30 L/h and its volume of distribution is 150 L. What infusion rate will be necessary to reach the target concentration? How long will it take to reach steady-state? What loading dose will be required to instantaneously achieve steady-state?

Determination of Infusion Rate

Starting with the equation:

\[ C_{ss} = \frac{k_0}{CL} \]

rearrange the equation to solve for \( k_0 \), the infusion rate

\[ k_0 = C_{ss} \cdot CL \]

Knowing that \( CL = 30 \) L/h and \( C_{ss} \) is 5 mg/L, it can be determined that \( k_0 = 150 \) mg/h

Determination of Time to Steady-State

Steady-state is attained after approximately 5 half-lives, so begin by estimating half-life based upon clearance and volume of distribution

\[ t_{\frac{1}{2}} = \frac{0.693 \cdot V}{CL} \]

Half-life is 3.5 h, thus, steady state will be attained in approximately 17 hours.

Determination of Loading Dose

Using the equation for a loading dose:

\[ X_{LD} = V \cdot C_{ss} \]

Insert the volume of distribution and the desired concentration. In this case, the appropriate IV bolus loading dose is 750 mg
Loading Dose - Infusion

In clinical practice, the loading dose is not always given as an IV bolus but by an infusion, because a bolus-loading dose may cause “speed shock” or precipitation/crystallization at the site of injection. Thus, it may be necessary to instead calculate a loading dose infusion rate \( k_{0,L} \) and infusion duration \( T \). Note that infusion time is designated ‘\( T \)’ whereas clock time in general is designated with a lower case ‘\( t \)’. Generally, loading dose infusions are administered at a rate close to the maximum infusion rate (the highest rate which does not compromise patient safety). This maximum infusion rate, \( k_{0,L} \), is \textit{drug specific}; for example, dopamine has a maximum infusion rate of 50 \( \mu \text{g/min} \). Also note that bolus loading doses are generally administered at the start of infusion, however, loading infusions are given first; the rate is subsequently decreased to the maintenance infusion rate in order to maintain concentrations. Using the IV infusion formula:

\[
C = \frac{k_0}{CL} \cdot (1 - e^{-kt})
\]

replace time, \( t \), with infusion time, \( T \), and calculate the shortest infusion time necessary to reach the desired concentration. The goal is to reach the steady-state concentration, \( C_{ss} \) as rapidly as possible, without exceeding the maximum infusion rate. Substituting \( k_{0,L} \), the maximum loading infusion rate, into the equation:

\[
C_{ss} = \frac{k_{0,L}}{CL} \cdot (1 - e^{-kT})
\]

and solving for infusion time \( T \):

\[
T = -\frac{1}{k} \cdot \ln \left(1 - \frac{C_{ss} \cdot CL}{k_{0,L}}\right) \quad \text{Equation 7-6}
\]

Parameters which will usually be known \textit{a priori} include: half-life (and therefore, \( k \)), the target concentration (\( C_{ss} \)), clearance, and \( k_{0,L} \) (the maximum infusion rate recommended for the drug). Suppose that for drug X, the minimum necessary infusion time, \( T \), is determined to be 12 minutes. Clinically, this is not a typical infusion duration (infusions times would generally be rounded up, to the nearest convenient unit, e.g. 5, 10 or 15 minutes). Infusion times must always be rounded UP (that is, to a longer infusion time). NEVER round the value of \( T \) down, because reducing the infusion duration will necessitate increasing the infusion rate above the maximal infusion rate at which the drug can be safely administered. In
the above example, infusion time might be rounded up to 15 minutes. The loading infusion rate should thus be recalculated, using T=15 min, by rearranging the above equation to solve for $k_{0,L}$.

![Figure 7-7: Impact of an infusion and loading infusion on drug concentrations. Lines indicate concentrations resulting from infusion alone (dotted/dashed), loading infusion alone (dashed) and from simultaneous infusion plus loading infusion (solid). Note that steady state is attained more rapidly with the combined infusions vs. either infusion alone.](image)

\[
k_{0,L} = \frac{C_{ss} \cdot CL}{(1 - e^{-kT})}
\]

Equation 7-7

**Loading Infusion Example**

Returning to the above example of drug X ($C_{ss} = 5$ mg/L, CL = 30 L/h and V = 150 L), what will be the minimum loading infusion duration necessary to achieve the desired steady-state blood concentration, assuming that the maximal infusion rate is 200 mg/h?

**Determination of Loading Infusion Duration (T)**

Starting with the equation

\[
T = \frac{1}{k} \cdot \ln \left(1 - \frac{C_{ss} \cdot CL}{k_{0,L}}\right)
\]

insert the following known values: maximum infusion rate ($k_{0,L}$), desired concentration, clearance, and elimination rate constant ($k = 0.2$ h$^{-1}$).

\[
T = -\frac{1}{0.2} \cdot \ln \left(1 - \frac{5 \cdot 30}{200}\right)
\]

In this case, $T = 6.9$ h. This value would generally be rounded to a more convenient duration. Note what happens when this value is rounded down instead of up (keeping in mind that the maximum infusion rate is 200 mg/h). For example, insert a value of $T = 5$ h into the equation below:


\[ k_{0L} = \frac{C_{ss} \cdot CL}{(1 - e^{-kT})} \]

\[ k_{0L} = \frac{5 \cdot 30}{(1 - e^{-0.2 \cdot 5})} = 237 \text{ mg/h} \]

The required loading infusion rate is now 237 mg/h. This rate exceeds the maximum safe infusion rate of 200 mg/h, which is unacceptable! Repeat the calculation, instead rounding the infusion duration up (that is, to the next highest convenient unit of time) from 6.9 h, such as \( T = 10 \text{ h} \).

\[ k_{0L} = \frac{5 \cdot 30}{(1 - e^{-0.2 \cdot 10})} = 173 \text{ mg/h} \]

The loading infusion rate is 173 mg/h, which is below the maximum rate of 200 mg/h. The appropriate loading infusion is thus 173 mg/h for 10 h.

---

**Short Term Infusion**

We will now switch gears a little and consider what happens to drug concentrations when an infusion is stopped after a certain time (designated \( T \), for infusion time). To begin, let \( T \) be equal to some time after the acquisition of steady-state (5 half-lives). After the infusion is stopped, note that drug concentrations fall in a manner similar to the decline in concentrations following an IV bolus dose, as depicted below.

![Figure 7-8: Concentration versus time after a short-term infusion on linear coordinates (left) and semi-log coordinates (right)](image)
Gathering Data from Short Term Infusion: Scenario 1 – Stopping the Infusion After Reaching Steady State

Given the data below, can clearance and volume terms be calculated? Determine the clearance, half-life and volume for the system illustrated below.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>3</td>
<td>1.26</td>
</tr>
<tr>
<td>5</td>
<td>1.40</td>
</tr>
<tr>
<td>7</td>
<td>1.43</td>
</tr>
<tr>
<td>8</td>
<td>0.72</td>
</tr>
<tr>
<td>9</td>
<td>0.36</td>
</tr>
</tbody>
</table>

\( K_0 \quad 5 \text{ mg/h} \)

**Step 1)** First plot the data on semi-log coordinates. Estimate the steady-state drug level from the graph (or from the data) and use this value to calculate the clearance rate, given the \( K_0 \) value listed above, by rearranging the steady-state equation:

\[
C_L = \frac{k_0}{C_{ss}}.
\]

As visually estimated from the graph, the steady-state concentration is \(~1.43\text{ mg/L}\). Thus, when \( k_0 = 5 \text{ mg/h} \), clearance is 3.5 L/h.

*Alternative approach:* Estimate clearance using the equation below, by finding the AUC and the dose \( (X_0 = (k_0)(T)) \):

\[
C_L = \frac{X_0}{AUC}
\]

**Step 2)** Next, calculate half-life just as you would following an IV bolus dose, by simply estimating the time it takes for \( C_{peak} \) to be reduced by half. Be careful to determine this value based on concentrations after the infusion has stopped. Again, if \( C_{peak} \) is 1.43 mg/L, concentrations decline to half of that value (0.72 mg/L) one hour later, therefore, half-life is 1 hour.
Step 3) Based upon the half-life (and k) values determined during step 2, and clearance values determined during step 1, calculate volume using the following equation:

\[ CL = k \times V \]

by rearranging to solve for volume. \( V = \frac{3.5}{0.693} \) or \(~5.1\) L.

Gathering Information from Short Term infusion – Scenario 2- Stopping the Infusion Before Reaching Steady State

Consider a situation in which an infusion is stopped at a time, \( T \), before steady state concentrations are attained. This situation is typical for the administration of, for example, aminoglycosides. As before, drug concentrations fall as they would after an IV bolus. How can clearance and volume be calculated when the steady state concentration has not yet been attained? Consider the case of drug X, given at 10 mg/h for 3 h. Calculate clearance, half-life and volume based upon the concentration-time data presented below.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>3</td>
<td>1.26</td>
</tr>
<tr>
<td>5</td>
<td>0.32</td>
</tr>
<tr>
<td>7</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Step 1) Again, begin by graphing the data on semi-log coordinates. Calculate half-life, as before, by estimating the time required for drug concentrations to fall by half. In this case, use $C_T (1.26 \text{ mg/L})$ as the reference concentration, and estimate the interval over which concentrations fall to half of that value. In the current example, concentrations fall to 0.63 mg/L in ~1 hour, therefore, half-life is one hour.

Step 2) Next, calculate clearance, using the equation that describes drug concentrations DURING the infusion:

$$C = \frac{k_0 \cdot (1 - e^{-kT})}{CL}$$

by rearranging to solve for clearance. The value of $k$ can be calculated based upon the half-life value determined in step 1. $T$ (the infusion time) is simply the time at which the infusion was stopped, and $C$ is the concentration at time $T$ ($C_{peak}$): both of these values can be estimated visually from the graphed data. The infusion rate ($k_0$), was given as 10 mg/h. Thus, the equation below can be rearranged to calculate clearance.

$$CL = \frac{k_0 \cdot (1 - e^{-kT})}{C_T} \cdot * \text{ see note below}$$

Clearance is 6.9 L/h

* Note: Although this is an acceptable way to determine clearance, the estimate is not very precise since it is based upon only one time point, $C_T$. A better alternative is to calculate clearance based upon AUC, by using Eq. 4.6, with dose as the infusion rate, $k_0$ and the infusion time, $T$. Remember that AUC can be calculated using the trapezoidal rule (see chapter 2), and must include the area from the tail region (from $C_T$ to infini-
Step 3) The clearance and half-life values determined above can subsequently be used to calculate volume, as we have done previously, using the equation $CL = k \cdot V$. In this case, $V \approx 10$ L

Summary

We have finished our discussion of the one-compartment model with intravenous infusion administration. In the case of IV infusions, the time required to attain steady-state is determined by half-life, and the steady-state concentration is determined by the drug’s clearance and dosing rates. After termination of the infusion, concentrations decline as they would after an IV bolus dose, that is, in a manner dictated by the volume of distribution and clearance.

Skills Obtained

- Drawing a schematic for a one-compartment model for IV infusion
- Estimating $V$, $CL$ and $t_{1/2}$ from IV infusion concentration-time data
- Calculating steady-state concentrations given appropriate pharmacokinetic data
- Estimating the time it takes to reach steady-state
- Calculating the appropriate loading dose to produce a desired $C_{ss}$

Summary Equations

To determine plasma concentration during an IV infusion:

$$C = \frac{k_0}{CL} \cdot (1 - e^{-kt})$$

To determine steady-state concentration during IV infusion:

$$C_{ss} = \frac{k_0}{CL}$$

To determine infusion rate given a desired steady-state level:

$$k_0 = C_{ss} \cdot CL$$
To determine a bolus loading dose for an infusion:

\[ X_{0,L} = C_{ss} \cdot V \]

To determine a loading infusion rate:

\[ k_{0,L} = \frac{C_{ss} \cdot CL}{(1 - e^{-kT})} \]

To determine the dose of an infusion:

\[ X_0 = k_0 \cdot T \]

**New Symbols**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K_0 )</td>
<td>Infusion rate</td>
<td>Amount of drug infused per unit time; ( K_0 = X_0 / T )</td>
<td>Mass per time (e.g., mg/h)</td>
</tr>
<tr>
<td>( T )</td>
<td>Infusion time</td>
<td>Duration over which an infusion is maintained</td>
<td>Time (e.g., h)</td>
</tr>
<tr>
<td>( t' )</td>
<td>Time after infusion stops</td>
<td>Amount of time after the infusion ends; ( t' = t - T ) (where ( t ) is time)</td>
<td>Time (e.g., h)</td>
</tr>
</tbody>
</table>
8) Multiple Dosing

Goals

To understand the effect on drug levels of multiple doses of a drug and how dose amount, dosing interval, clearance and volume will affect steady-state drug concentrations.

Objectives

By the end of this chapter you should be able to:

- Describe how dosing rate, clearance and apparent volume of distribution impact average steady-state concentrations, steady-state peaks and troughs
- Define the “principle of superposition”
- Calculate average steady-state concentrations, given dose amount, dosing interval and clearance values
- Predict time to steady-state and describe factors that will impact time to steady-state
- Develop a dosing regimen (dose amount, dosing interval) given patient parameters
- Evaluate and revise a dosing regimen to target a given drug level

In Brief

Most drugs are given on a regular schedule (e.g., once a day). When we do this, drug can accumulate in the body but this accumulation depends on how frequent the drug is administered relative to the half-life of the drug. We will discuss how design a dosing regimen – what dose and how frequently to give that dose- to target desired steady-state concentrations. Generally we have to know our concentration targets to determine a dosing interval. Once we know how often, we can determine how much to give. We also will discuss how with the appropriate data you can estimate patient specific parameters of half-life, clearance and volume of distribution.

Introduction

Rarely is a drug administered as a single dose. Most often, multiple doses are administered, in part, to produce a consistent level of drug in the body, similar to the effect of a continuous intravenous infusion. An important parameter associated with multiple dosing is the dosing interval (τ), which is a fixed value.
Typical dosing intervals (e.g., 6, 8, 12 h) are used because they are convenient and are factors of 24 (the number of hours in one day). Dosing intervals of 4, 6 or 8 h are common for intravenous administration and 6, 8, 12, and 24 h dosing intervals are typical for oral administration. Dosing intervals as short as $\tau = 2$ h are very rare, because such a dosing frequency would be inconvenient. A dosing interval of 7.7 h would generally be rounded to either 6 or 8 h for convenience. Remember, the fewer doses the patient has to take in a day, the higher the compliance rate. The pharmaceutical industry attempts to develop drugs that are BID, QD, q week etc. to increase patient compliance.

**Multiple Intravenous Bolus**

We will begin our discussion of multiple dosing with the case of IV bolus multiple dosing, as this is the simplest example. However, keep in mind that the concepts discussed in this section will apply to all multiple dosing situations. When a dose ($X_0$) is given, the resulting maximum concentration is referred to as $C_{MAX}$. In the case of IV bolus administration, $C_{MAX}$ is equal to $C_0$. Drug concentrations will fall until the next dose is administered, at time = $\tau$. The Greek letter $\tau$ (pronounced ‘tau’) represents the dosing interval, or the time elapsed between administration of each dose. Minimum concentrations, or $C_{MIN}$ (also called a trough or $C_{TROUGH}$) thus occur immediately prior to the administration of each subsequent dose.

![Figure 8-1: Concentration-time profile after the first IV dose administered in a multiple dosing scenario.](image)

If another dose is administered before the entire previous dose is eliminated, the concentration at the start of the next dose will be equal to the amount of drug already in the body (that is, the amount remaining from the first dose, $C_{MIN}$, denoted as $C_\tau$ above), plus the $C_{MAX}$ resulting from a single IV bolus dose (or $C_0$) (Figure 8-2. This summation of concentrations resulting from drug already in the body from a previous dose plus concentrations resulting from additional doses is termed the principle of...
superposition, meaning simply that each dose will additively influence concentrations, as seen below.

Figure 8-2: Concentration-time profile after IV bolus for the first and second doses in a multiple dosing scenario. Dotted line indicates the concentrations resulting from the first dose alone.

Note that here we use the term $C_\tau$, which is really the same as $C_{\text{MIN}}$ or $C_{\text{TROUGH}}$. With the addition of the second dose, concentrations have risen from $C_\tau$ to $C_0 + C_\tau$, which is the new $C_{\text{MAX}}$. Concentrations will subsequently fall to a new $C_{\text{MIN}}$, illustrated above as $C_{2\tau}$.

Upon administration of multiple doses, a mathematical pattern develops, as illustrated in the table below, with "n" indicating the dose number; $C_{\text{MAX}}$ as the peak concentration for dose n, and $C_{\text{MIN}}$ as the minimum concentration following dose n (which occurs immediately before the next dose is given). Again, each dose simply combines additively with any drug remaining from previous doses.

Table 8-1

<table>
<thead>
<tr>
<th>n</th>
<th>$C_{\text{MAX}}$</th>
<th>$C_{\text{MIN}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\frac{X_0}{V}$</td>
<td>$\frac{X_0}{V}e^{-k\tau}$</td>
</tr>
<tr>
<td>2</td>
<td>$\frac{X_0}{V}e^{-k\tau} + \frac{X_0}{V}$</td>
<td>$\left(\frac{X_0}{V}e^{-k\tau} + \frac{X_0}{V}\right)e^{-k\tau}$</td>
</tr>
<tr>
<td>3</td>
<td>$\frac{X_0}{V}e^{-2k\tau} + \frac{X_0}{V}e^{-k\tau} + \frac{X_0}{V}$</td>
<td>$\left(\frac{X_0}{V}e^{-2k\tau} + \frac{X_0}{V}e^{-k\tau} + \frac{X_0}{V}\right)e^{-k\tau}$</td>
</tr>
</tbody>
</table>

This mathematical pattern can be generalized in algebraic terms:

$$C_{\text{MAX}} = \frac{X_0}{V} \cdot \left(1 - \frac{e^{-nk\tau}}{1 - e^{-k\tau}}\right)$$

Equation 8-1
\[ C_{\text{MIN}} = \frac{X_0}{V} \left( \frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right) e^{-k\tau} \quad \text{Equation 8-2} \]

The above equations describe the \( C_{\text{MAX}} \) and \( C_{\text{MIN}} \) associated with any dose during a bolus multiple dosing regimen. The parenthesized elements of the equation describe accumulation of drug in the body. Note that as “n” increases, i.e., more doses are administered, \( (1 - e^{-nk\tau}) \rightarrow 1 \), thus, the system approaches steady-state conditions.

**Accumulation Factor**

With the attainment of steady-state conditions, a parameter termed the accumulation factor \( (R_a) \) becomes relevant.

\[ R_a = \frac{1}{1 - e^{-k\tau}} \quad \text{Equation 8-3} \]

Incorporation of this accumulation factor into the equation describing concentrations following a single IV bolus dose results in the equation below.

\[ C = \left( \frac{1}{1 - e^{-k\tau}} \right) \cdot C_0 e^{-kt} \quad \text{or} \quad C = R_a \cdot C_0 e^{-kt} \quad \text{Equation 8-4} \]

This accumulation factor is used to calculate, based upon the concentrations resulting from the first dose, the concentration at any point during steady-state administration. For example, if the \( C_0 \) associated with the first dose of drug X is 10 mg/L, the drug’s half-life is 8 hours \( (k = 0.087 \text{ h}^{-1}) \) and the dosing interval, \( \tau \), is 8 h, what will the \( C_{\text{MAX}} \) be at steady-state? In this case, \( R_{\text{atolera}} = 2 \) (based on \( k \) and \( \tau \)), thus, the \( C_{\text{MAX}} \) at steady-state will be equal to the \( C_{\text{MAX}} \) associated with the first dose, times the accumulation factor; \([ (10 \text{ mg/L}) \times (2) ]\) or 20 mg/L.

The principles of drug accumulation under steady-state multiple dosing conditions are very similar to the principles which apply to infusions to steady-state. If a drug is administered at a rate more rapid than the elimination rate, drug will accumulate in the body. In a first-order pharmacokinetic system, eventually the mass of drug exiting the body over a given dosing interval will equal the mass of drug administered during that dosing interval and steady-state conditions will be attained. The accumula-
tion ratio, in a sense, reflects how much drug has accumulated in the body.

The degree of drug accumulation, as indicated in the equation describing \( R_a \), depends on the \( t_{1/2} \) and the dosing interval (\( \tau \)). The more frequent the drug administration, relative to the drug’s half-life, the more drug will accumulate in the system, as illustrated below. Stated simply, if the rate of input into the body is faster than the rate of output, drug will “pile up” in the body, thus, half-life is indicative of the elimination rate, and the dosing interval reflects the input rate. The smaller the ratio of the dosing interval to half life (the last column in the table below), the greater the level of drug accumulation.

Table 8-2: Impact of dosing interval to half-life on the extent of drug accumulation

<table>
<thead>
<tr>
<th>Dosing Interval ( (t_{1/2} = 8 \text{ h}) )</th>
<th>( R_a )</th>
<th>Dosing Interval to Half-life Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3.4</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>1.54</td>
<td>1.5</td>
</tr>
<tr>
<td>24</td>
<td>1.14</td>
<td>3</td>
</tr>
<tr>
<td>48</td>
<td>1.02</td>
<td>6</td>
</tr>
</tbody>
</table>

As the dosing interval increases, the accumulation factor approaches 1. Recall that half-life determines the time to reach steady state, so despite increases in the drug administration frequency, steady-state cannot be attained faster, however, the steady-state concentrations will be higher. What happens if your dosing interval is >5 half-lives? Simply put, you will not accumulate drug in the body!
Figure 8-3: Concentration-time profile associated with IV bolus administration to steady-state. Note that the height of the peaks and troughs remains constant over time during steady-state conditions.

As illustrated in the above graph, as multiple doses of drug are administered, drug accumulates in the body and the accumulation level eventually plateaus as steady-state is attained. Recall that steady-state conditions are attained when the rate of drug entering the system (dose per unit time) equals the rate of drug exiting the system (the product of clearance and drug concentration). Under conditions of multiple bolus doses, however, the concentration fluctuates (peaks and troughs) whereas under infusion conditions, concentrations remain static.

Table 8-3: Comparison of symbols and equations for infusion and multiple dosing

<table>
<thead>
<tr>
<th></th>
<th>Infusion</th>
<th>Multiple Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate in</td>
<td>$k_0$</td>
<td>$\frac{X_0}{\tau}$</td>
</tr>
<tr>
<td>Steady-state concen-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tration</td>
<td>$C_{SS} = \frac{k_0}{C_l}$</td>
<td>$\frac{X_0}{\tau}$</td>
</tr>
</tbody>
</table>

The above table compares infusion administration to multiple dosing administration. Note that the average steady-state concentration is a function of dosing rate (dose and dosing interval) and clearance.

In the above examples, all doses of drug were administered BEFORE the entire drug from the previous dose was eliminated. If each dose of the drug were administered AFTER the entire previous dose was eliminated, no accumulation of drug would occur (see above Table with $R_a$ values), as illustrated in the following graph of simulated vancomycin concentrations. Vancomycin has a half-life of approximately 7 hours. If vancomycin was administered every other day (i.e., q48 h), drug would not accumulate in the body, because all drug from the previous dose would have been eliminated prior to the next dose. If instead the drug were administered q24 h (solid lines), a small portion of drug would ac-
cumulate in the body. Under conditions of q8h administration (dotted lines), much greater drug accumulation would occur. This example illustrates the importance of dosing rate with respect to half-life, and how changing dosing rate (a factor which is under a clinician's control) will impact accumulation and steady-state drug levels.

**Figure 8-4**: Dosing more frequently relative to the drug's half-life will increase the amount of drug that accumulates in the body. The dotted line indicates administration every 8 h; the solid line indicates administration every 24 h; the drug’s half-life is 7 h.

**The impact of dosing interval on peak, trough and average concentrations**

As stated earlier, the dosing interval is the time elapsed between administration of each dose. Additionally, the dosing interval is related to half-life. The dosing interval is also related to the therapeutic window of a drug.

If a drug’s therapeutic window occurs between 100 mg/L and 50 mg/L, over the course of one half-life, the drug concentration will decline from 100 mg/L to 50 mg/L. Thus, the appropriate dosing interval would be equal to the half-life of this drug.

If the therapeutic range spans 100 mg/L to 25 mg/L, concentrations will decline from 100 to 25 mg/L over the course of two half-lives. The appropriate dosing interval would therefore be equal to two half-lives.

Assuming a therapeutic window between 100 and 12.5 mg/L, concentrations will decline from 100 to 12.5 mg/L over the course of three half-lives (100 to 50 mg/L is one half-life, 50 to 25 mg/L is two half-lives, 25 to 12.5 mg/L is three half-lives). Let us assume that the half-life of the drug is 8 h. The appropriate dosing interval would thus be three half-lives or 24 h. The table below illustrates the impact of the dosing interval on peak and trough concentrations, relative to the therapeutic concen-
tration range. Note the effect on maximum and minimum concentrations (assume that V is 100 L and that the administration route is IV bolus injection).

Table 8-4: Impact of dosing interval on maximum and minimum concentrations at steady-state. Therapeutic range is 12.5 to 100 mg/L

<table>
<thead>
<tr>
<th>Dosing Interval (hr)</th>
<th>Dose (mg)</th>
<th>Maximum Concentration (mg/L)</th>
<th>Minimum Concentration (mg/L)</th>
<th>In Therapeutic Range?</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>8750</td>
<td>175</td>
<td>87</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>8750</td>
<td>135</td>
<td>47</td>
<td>No</td>
</tr>
<tr>
<td>24</td>
<td>8750</td>
<td>100</td>
<td>12.5</td>
<td>Yes</td>
</tr>
<tr>
<td>48</td>
<td>8750</td>
<td>89</td>
<td>1.4</td>
<td>No</td>
</tr>
</tbody>
</table>

Administration of the same dose at different intervals affects the maximum and minimum concentrations observed. In the current case, dosing intervals shorter than 24 h will cause excessive accumulation of drug, resulting in concentrations above the upper end of the therapeutic range. Dosing intervals longer than 24 h will cause insufficient accumulation of the drug, resulting in concentrations below the lower end of the therapeutic range (again therapeutic range is 100 to 12.5 mg/L).

Consider a final situation, in which the dose and clearance rates remain constant and only the dosing interval changes. The relationship between dosing interval and average steady-state concentration is characterized by an asymptotic approach of steady-state concentration to the time axis.

The shape above is characteristic of an inverse relationship; as $\tau$ (see the steady-state equation below) increases, the average $C_{ss}$ will approach zero.
AUC at Steady-State and Average Concentrations

By definition, when steady-state has been attained, the first dose has been virtually eliminated. Recall that following a single dose of drug, it takes 5 half-lives to eliminate almost all (~98%) of the dose. In addition, during infusion or multiple dose administration, it takes 5 half-lives to attain concentration that are within 98% of the steady-state value. At steady state, the AUC during one dosing interval is identical to the AUC\(_\infty\) resulting from the first dose alone.

\[
\text{AUC}_\infty = \text{AUC}_{0 \rightarrow \infty} \quad \text{Equation 8-5}
\]

The equivalency of the AUC during one dosing interval at steady-state to the AUC for the first dose through infinite time depends upon the assumption that the rate of clearance does not change. This is not always the case. For example, carbamazepine auto-induced its metabolism, thus increasing its own rate of clearance over time.

Sometimes, it is useful to calculate the average steady state concentration. AUC is a cumulative term, describing the product of concentration and time. Thus, dividing AUC by the time over which the AUC was determined, we obtain \(C_{\text{average}}\) or \(C_{ss}\).

\[
C_{ss} = \frac{\text{AUC}_\tau}{\tau} = \frac{X_0}{CL \cdot \tau} \quad \text{Equation 8-6}
\]
Note that average concentration depends only on clearance and drug dosing rate \((X_{0}/\tau)\) and not on \(V\). \(V\), however, will affect the peak and trough concentrations because this change will alter the half-life, relative to the dosing interval.

Often, the \(C_{SS}\) equation is used to calculate the dose required to produce a desired average concentration in a patient. This calculation requires determination of the clearance of the drug. In cases where drugs are monitored regularly (e.g., digoxin, lithium, aminoglycosides), it is possible to calculate clearance based upon drug-specific equations. Note also that if drug X is administered at 8 mg, q8h, the resulting \(C_{SS}\) is the same as if the drug were administered at 4 mg, q4h. This is due to linear pharmacokinetics (i.e., dose-proportional pharmacokinetics), where increases in the dosing rate result in a proportional increase in \(C_{SS,\text{AVERAGE}}\).

Designing a Dosing Regimen – IV Bolus

Designing a dosing regimen is, for clinicians, one of the most important applications of pharmacokinetics. There are two important components to designing a dosing regimen; the dose and the dosing interval. We will begin with a discussion of how to determine the appropriate dosing interval.

The half-life of a drug is an important determinant of not only the time required to reach steady state, but also of the appropriate dosing interval required to produce a desired steady-state concentration. For example, suppose that for drug X, the desired peak concentration is 100 mg/L and the desired trough concentration is 50 mg/L (i.e., the drug concentration should be reduced by half before administration of the next dose). Therefore, the dosing interval should be equal to the half-life of drug X, because by definition, half-life is the time it takes to eliminate...
50% of a given dose of drug. To prove this mathematically, rearrange the equation describing change in concentrations following administration of an IV bolus dose (below) to solve for time (Eq. 8-7)

$$\ln(C) = \ln(C_0) - kt$$

$$t = \frac{\ln\left(\frac{C_0}{C}\right)}{k}$$

Equation 8-7

Insert the relevant dosing interval, \(\tau\), for the term \(t\), and insert the desired \(C_{\text{MAX,SS}}\) and \(C_{\text{MIN,SS}}\) for \(C_0\) and \(C\), respectively, to solve for \(\tau\).

$$\tau = \frac{\ln\left(\frac{C_{\text{MAX,SS}}}{C_{\text{MIN,SS}}}\right)}{k}$$

Equation 8-8

As an example, when dosing aminoglycosides, the desired peak concentrations are ~8 mg/L and desired troughs are 0.5 mg/L. How long should the dosing interval be? This can be determined rapidly by simply counting. A decrease from 8 to 4 mg/L will require one half-life; 4 to 2 mg/L a second half-life; 2 to 1 mg/L a third half-life, and 1 to 0.5 mg/L a fourth half-life. Therefore, the appropriate dosing interval would be equal to approximately 4 half-lives (note: aminoglycosides have half-lives around 2 h). To calculate the dosing interval using the equation above, simply insert the known values (and assume \(k = 0.35\ h^{-1}\)).

$$\tau = \frac{\ln\left(\frac{8}{0.5}\right)}{0.35} = 7.9h$$

The first step in designing a dosing regimen is determination of the appropriate dosing interval, discussed above. The next step is to determine the appropriate dose to administer. The appropriate dose will depend upon whether the goal is to target (1) peak concentrations at steady-state (e.g., aminoglycosides), (2) trough concentrations at steady-state (e.g., lithium or antiretrovirals), or (3) average steady-state concentrations (e.g., digoxin). Note that the target concentration is dependent on drug.

To target a peak concentration, begin with equation for the peak concentration at steady-state:
\[ C_{\text{MAX,SS}} = \frac{X_0}{V} \cdot R_a \text{ or } \frac{X_0}{V} \cdot \frac{1}{(1 - e^{-k\tau})} \]

Rearrange to solve for dose:

\[ X_0 = C_{\text{MAX,SS}} \cdot V \cdot \left(1 - e^{-k\tau}\right) \]

To target a trough concentration, begin with the equation for the trough concentration at steady-state:

\[ C_{\text{MIN,SS}} = \frac{X_0}{V} \cdot e^{-k\tau} \cdot R_a \text{ or } \frac{X_0}{V} \cdot e^{-k\tau} \cdot \frac{1}{(1 - e^{-k\tau})} \]

Rearrange to solve for dose:

\[ X_0 = C_{\text{MIN,SS}} \cdot \frac{V}{e^{-k\tau}} \cdot \left(1 - e^{-k\tau}\right) \]

To target an average steady-state concentration, begin with the equation for average steady-state concentrations:

\[ \bar{C}_{\text{SS}} = \frac{X_0}{\text{CL} \cdot \tau} \]

Rearrange to solve for dose:

\[ X_0 = \bar{C}_{\text{SS}} \cdot \text{CL} \cdot \tau \quad \text{Equation 8-9} \]

NOTE: The true average steady-state concentration is actually slightly higher than the calculated arithmetic mean of the maximum and minimum concentrations, although this latter calculation produces a good approximation of the true value. When using average steady-state concentrations, try to keep the ratio of \( X_0 \) to \( \tau \) (i.e., the dosing rate) constant, particularly when fine tuning the regimen.

After determining the appropriate dosing interval and dose, check your work to ensure that the peaks and troughs are within the therapeutic window!

The equations above are used to design an initial therapeutic regimen, however, the dose or dosing interval may subsequently be adjusted based upon a patient’s blood drug levels determined via routine monitoring. For example, when administering aminoglycosides, if the trough

**Clinical Tidbit**

For aminoglycosides, troughs are related to toxicity because high trough concentrations can cause accumulation of drug in tissues such as the kidney or ear which is potentially damaging. Low troughs help prevent drug from accumulating in those tissues.

Always check your peaks and troughs after you calculate the dose and dosing interval!!!
concentrations (which are related to toxicity (see Clinical Tidbit) are too high, extension of the dosing interval (e.g., from 8 to 12 h) will allow concentrations to fall further before the next dose (decrease trough concentrations).

---

**Example – target peaks and troughs:** Drug X has the following pharmacokinetic parameters: CL = 25 L/h, V = 200 L, t₁/₂ = 5.5 h. The desired peak and trough concentrations are 1 and 0.25 mg/L, respectively. Design a dosing regimen to target the desired peak concentration.

**Step 1)** Calculate the appropriate dosing interval. The simplest method is by counting. For example, the time required for concentrations to decline from 1 to 0.5 mg/L is 1 half-life, and from 0.5 to 0.25 mg/L is another half-life, so with a half-life of 5.5 h, the required dosing interval is 11 h (round up to 12 h for convenience).

Alternatively, use the following equation, where \( C_{\text{MAX,SS}} \) is 1 mg/L, \( C_{\text{MIN,SS}} \) is 0.25 mg/L and \( k = 0.126 \text{ 1/h} \) (derived from half-life). Insert the appropriate values and solve for \( \tau \).

\[
\tau = \frac{\ln\left(\frac{1 \text{mg/L}}{0.25 \text{mg/L}}\right)}{0.126 \text{h}^{-1}} = 11 \text{h}
\]

Round this value to 12 h.

**Step 2)** Calculate the appropriate dose to target peak concentrations. Use the equation for \( C_{\text{MAX,SS}} \), rearranging to solve for dose:

\[
X_0 = C_{\text{MAX,SS}} \cdot V \cdot \left(1 - e^{-k\tau}\right)
\]

Where \( C_{\text{MAX,SS}} \) is 1 mg/L, \( V = 200 \text{ L} \), \( k = 0.126 \text{ 1/h} \) and \( \tau = 12 \text{ h} \) (from step 1).

\[
X_0 = 1 \text{mg/L} \cdot 200 \text{L} \cdot \left(1 - e^{-0.126\cdot12 \text{h}}\right) = 156 \text{mg}
\]

If the dose will be administered as a bolus, 156 mg is an appropriate dose, however, it may be necessary to round this
value when dealing with extravascular administration.

The dosing regimen calculated above is thus 156 mg Q 12h.

Step 3) Check your work: confirm that concentrations fall within the desired range of peaks and troughs (1 to 0.25 mg/L). For example, administration of 156 mg Q 12 h will result in the following peak concentrations at steady state:

\[
C_{\text{MAX,SS}} = \frac{X_0}{V} \cdot R_a = \frac{156 \text{ mg}}{200 \text{ L}} \cdot 1.28 = 1 \text{ mg/L}
\]

Steady-state trough concentrations will be:

\[
C_{\text{MIN,SS}} = \frac{X_0}{V} \cdot e^{-kt} \cdot R_a = \frac{156 \text{ mg}}{200 \text{ L}} \cdot e^{-0.126 \cdot 12 \text{ h}} \cdot 1.28 = 0.22 \text{ mg/L}
\]

Thus, the dosing regimen produces peak concentrations which are on target, but trough concentrations which are somewhat low.

If these low trough concentrations are problematic (this will depend upon the drug in question, and the level of precision desired), the dosing interval could be shortened to 8 h and the dose recalculated via step 2 (Answer: 127 mg Q 8h produces peaks of 1 mg/L and troughs of 0.36 mg/L). The reason behind shortening the dosing interval vs. increasing the dose is that increasing the dose will increase both \(C_{\text{MAX}}\) and \(C_{\text{MIN}}\). As \(C_{\text{MAX}}\) was on target initially, increasing the dose would have been inappropriate. Shortening the interval and recalculating the dose would have produced a lower peak concentration.

NOTE: \(R_a\) was estimated based upon the equation:

\[
R_a = \frac{1}{(1 - e^{-kt})} = \frac{1}{(1 - e^{-0.126 \cdot 12})} = 1.28
\]

Next, design a regimen to target trough concentrations. (Answer: 177 mg Q 12h, predicted \(C_{\text{MAX}} = 1.13 \text{ mg/L}\), predicted \(C_{\text{MIN}} = 0.25 \text{ mg/L}\). If a peak concentration of 1.13 mg/L is unacceptably high, simply shorten the dosing interval and recalculate the dose.
Example – target average steady-state: Drug X has the following pharmacokinetic parameters: CL = 25 L/h, V = 200 L, \( t_{1/2} = 5.5 \) h. The desired peak and trough concentrations are 1 and 0.25 mg/L. Design a dosing regimen to target an average steady-state concentration of 0.5 mg/L.

**Step 1)** Determine the appropriate dosing interval. Simply count: the decline of concentrations from 1 to 0.25 mg/L will require 2 half-lives, so if the half-life is 5.5 h, the dosing interval is 11 h.

Alternatively, use the equation:

\[
\tau = \frac{\ln \left( \frac{C_{\text{MAX,SS}}}{C_{\text{MIN,SS}}} \right)}{k}
\]

where \( C_{\text{MAX,SS}} \) is 1 mg/L, \( C_{\text{MIN,SS}} \) is 0.25 mg/L and \( k = 0.126 \) 1/h (derived from half-life).

\[
\tau = \frac{\ln \left( \frac{1 \text{mg/L}}{0.25 \text{mg/L}} \right)}{0.126 \text{h}^{-1}} = 11 \text{h}
\]

This value would be rounded to 12 h.

**Step 2)** Identify the appropriate dose to target the desired average concentrations. Use the equation describing average steady-state concentrations, rearranging to solve for dose:

\[
X_0 = \frac{C_{ss} \cdot CL \cdot \tau}{\tau}
\]

where \( C_{ss} \) is 0.5 mg/L, \( CL = 25 \) L/h, and \( \tau = 12 \) h (from step 1).

\[
X_0 = 0.5 \text{mg/L} \cdot 25 \text{L/h} \cdot 12 \text{h} = 150 \text{mg}
\]

Because this the dose will be administered as a bolus, there is no need to round this value.
Step 3) Check your work: a therapeutic regimen of 150 mg Q 12 h, will result in the following peaks concentrations:

$$C_{\text{MAX,SS}} = \frac{X_0}{V} \cdot R_a = \frac{150 \text{ mg}}{200 \text{ L}} \cdot 1.28 = 0.96 \text{ mg/L}$$

and trough concentrations:

$$C_{\text{MIN,SS}} = \frac{X_0}{V} \cdot e^{-k\tau} \cdot R_a =$$

$$C_{\text{MIN,SS}} = \frac{150 \text{ mg}}{200 \text{ L}} \cdot e^{-0.126 \cdot 12} \cdot 1.28 = 0.21 \text{ mg/L}$$

Again, these calculations confirm that the dosing regimen is appropriate, since the peak concentrations are acceptably near the target concentrations. In order to maintain concentrations within the range of desired peaks and troughs, shorten the dosing interval to 8 h and recalculate the dose.

$$\frac{X_0}{\tau} = \frac{150 \text{ mg}}{12 \text{ h}} = \frac{X \text{ mg}}{8 \text{ h}} = 100 \text{ mg}$$

A regimen of 100 mg Q 8h will produce peak and trough concentrations of 0.79 and 0.29 mg/L.

NOTE: $R_a$ was estimated based upon the equation:

$$R_a = \frac{1}{(1-e^{-k\tau})} = \frac{1}{(1-e^{-0.126 \cdot 12})} = 1.28$$
**Loading Dose**

As with infusions, sometimes it is necessary to produce steady-state concentrations instantly. This can be accomplished with an IV bolus loading dose. When dealing with infusions we targeted the loading dose to achieve a given $C_{SS}$. In the case of multiple dosing, concentrations fluctuate, i.e., have peaks and troughs, so instead, we want to target $C_{MAX,SS}$. The loading dose ($X_L$) can be estimated as follows:

$$C_{MAX,SS} \cdot V = X_L$$

Equation 8-10

Remember that $C_{MAX,SS}$ is a function of the accumulation factor and $C_0$:

$$\frac{X_0}{V} \cdot R_a \cdot V = X_L$$

Equation 8-11

The volume terms cancel out, resulting in the equation below. Note the substitution of $X_0$ with $X_{MD}$ (the maintenance dose):

$$X_{MD} \cdot R_a = X_L$$

Equation 8-12

![Figure 8-8: Impact of an IV bolus loading dose during multiple dosing. Lines indicate concentration-time profiles for a loading dose followed by multiple dosing (solid) multiple dosing without a loading dose (black dashes) and the loading dose alone (gray dashes).](image)

**Multiple Intravenous Infusions**

Once you understand the basic concepts underlying bolus multiple dosing, it is easy to apply the same principles to other routes, such as intravenous infusions or extravascular dosing (e.g., oral, buccal, IM). The steps for calculating the dosing regimen are the same as discussed.
above, however, additional factors to consider include infusion time, absorption time and bioavailability. In general, using IV bolus equations to design dosing regimens for other routes will over-estimate $C_{\text{MAX}}$ at steady-state and under-estimate $C_{\text{MIN}}$ at steady-state, however, since the calculations are fairly simple they can still be somewhat useful.

Intermittent infusions, while clinically very important, are probably one of the most confusing types of therapeutic regimens to design, because of all the different “times” that are involved.

Table 8-5: Definitions of various time parameters for multiple infusions

<table>
<thead>
<tr>
<th>Time</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t$</td>
<td>General time</td>
</tr>
<tr>
<td>$T$</td>
<td>Infusion time – duration of the infusion</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Dosing interval – duration between start of each infusion</td>
</tr>
<tr>
<td>$t'$</td>
<td>Time from the stop of the infusion through general time ($t-T$) – time explaining the fall in drug concentrations after we stop the infusion</td>
</tr>
</tbody>
</table>

The equations for multiple IV infusions are nearly identical to those for a single dose IV infusion, except that in the case of multiple infusions, it is necessary to include the accumulation factor $R_a$. 

Figure 8-9: Concentration-time profile for intermittent IV infusions
To calculate the maximum plasma concentration at steady-state:

\[
C_{\text{MAX,SS}} = \frac{k_0}{\text{Cl}} \left(1 - e^{-kT}\right) + \left(1 - e^{-kT}\right) \cdot R_a \tag{8-13}
\]

To calculate the minimum plasma concentration at steady-state:

\[
C_{\text{MIN,SS}} = \frac{k_0}{\text{Cl}} \left(1 - e^{-kT}\right) \cdot e^{-k't'} \tag{8-14}
\]

Recall that \(t'\) is the amount of time between the end of one infusion and the start of the next infusion. When calculating \(C_{\text{MIN}}\), the relevant time term is \(t'\), calculated as \(\tau - T\).

Calculate the dosing interval for IV infusion using the equation below, which is nearly identical to the IV bolus situation, except that it includes a term indicating the infusion time.

\[
\tau = \frac{\ln\left(\frac{C_{\text{MAX}}}{C_{\text{MIN}}}ight)}{k} + T \tag{8-15}
\]

Example – Aminoglycoside: Gentamicin, an aminoglycoside antibiotic, has the following pharmacokinetic parameters: \(\text{CL} = 7.5 \text{ L/h}\), \(V = 17.5 \text{ L}\), \(t_{1/2} = 2 \text{ h}\). The desired peak concentration should be greater than 8 mg/L and the desired trough concentration is 0.5 mg/L. Gentamicin is given as a 30 min infusion. Design a dosing regimen to target peak concentrations.

Step 1) Find an appropriate dosing interval. The simplest method is to count the number of half lives which will be required for concentrations to drop from 8 to 0.5 mg/L (8→4→2→1→0.5 mg/L; 4 half lives). With a half-life of 2 h, the dosing interval is 8 h. Recall that the infusion time is 0.5 h, thus the dosing interval is 8.5 h. (Round to 8 h for convenience.)
Alternatively, use the equation:

\[
\tau = \frac{\ln\left(\frac{C_{\text{MAX,SS}}}{C_{\text{MIN,SS}}}\right)}{k} + T
\]

where \(C_{\text{MAX,SS}}\) is 8 mg/L, \(C_{\text{MIN,SS}}\) is 0.5 mg/L, \(T\) is 0.5 h and \(k = 0.347 \text{ h}^{-1}\) (derived from half-life).

\[
\tau = \frac{\ln\left(\frac{8 \text{ mg/L}}{0.5 \text{ mg/L}}\right)}{0.347 \text{ h}^{-1}} + 0.5 \text{ h} = 8.5 \text{ h}
\]

Round this value (e.g., to 8 or 12 h).

**Step 2)** Determine an appropriate dose to target average concentrations. Use the following equation, rearranging to solve for dose:

\[
C_{\text{MAX,SS}} = \frac{k_0 \cdot \left(1 - e^{-kT}\right)}{\text{Cl} \cdot \left(1 - e^{-k\tau}\right)}
\]

Or

\[
C_{\text{MAX,SS}} = \frac{X_0 / T \cdot \left(1 - e^{-kT}\right)}{\text{Cl} \cdot \left(1 - e^{-k\tau}\right)}
\]

\[
X_0 = C_{\text{MAX,SS}} \cdot \text{Cl} \cdot T \cdot \frac{\left(1 - e^{-kT}\right)}{\left(1 - e^{-k\tau}\right)}
\]

where \(C_{\text{MAX,SS}}\) is 8 mg/L, \(\text{Cl} = 7.5 \text{ L/h}\), \(\tau = 8 \text{ h}\) (from step 1), \(T = 0.5 \text{ h}\)

\[
X_0 = 8 \text{ mg/L} \cdot 7.5 \text{ L/h} \cdot 0.5 \text{ h} \cdot \frac{\left(1 - e^{-0.347 \cdot 8 \text{ h}}\right)}{\left(1 - e^{-0.347 \cdot 0.5 \text{ h}}\right)} = 175 \text{ mg}
\]

Because this is an infusion it is not necessary to round the dose from 175 mg. Thus the infusion regimen will deliver 175 mg over 30 min, every 8 h.
Step 3) Check your work: under an infusion regimen of 175 mg Q 8 h, peak concentrations will be:

\[
C_{\text{MAX,SS}} = \frac{k_0}{Cl}(1 - e^{-kT}) \cdot R_a
\]

\[
\frac{175\text{mg}}{7.5\text{L/h}} \cdot (1 - e^{-0.347 \cdot 0.5\text{h}}) \cdot 1.07 = 8\text{mg/L}
\]

and trough concentrations will be:

\[
C_{\text{MIN,SS}} = \frac{k_0}{Cl}(1 - e^{-kT}) \cdot R_a \cdot e^{-kT}
\]

\[
C_{\text{MIN,SS}} = 8.0\text{mg/L} \cdot e^{-0.347 \cdot 7.5\text{h}} = 0.59\text{mg/L}
\]

Note that the trough concentration is higher than the desired value of 0.5 mg/L. Because high trough concentrations are associated with toxicity, recalculation is necessary. The next step might be to try a dosing interval of 12 h, recalculating to determine the appropriate dose (step 2). This infusion scheme would consist of 190 mg infused over 30 min every 12 h, which will result in peak concentrations of 8 mg/L and trough concentrations of 0.15 mg/L.

NOTE: \( R_a \) was estimated using the equation below.

\[
R_a = \frac{1}{(1 - e^{-kT})} = \frac{1}{(1 - e^{-0.347 \cdot 8\text{h}})} = 1.07
\]

**Extravascular Administration**

The equations required to design a multiple extravascular administration regimen can become very complex because they must account for the impact of absorption on drug accumulation. Below is the complete equation for multiple extravascular dose calculations.

\[
C = \frac{F \cdot X_0 \cdot k_a}{V \cdot (k_a - k)} \cdot \left( \frac{e^{-kT}}{1 - e^{-kT}} - \frac{e^{-k_aT}}{1 - e^{-k_aT}} \right) \quad \text{Equation 8-16}
\]

For extravascular dosing, use IV bolus equations as a short cut, but be sure to incorporate bioavailability.

NEVER FORGET F!
Please note that when dealing with oral absorption, the accumulation factor incorporates the absorption rate constant \((k_a)\) as well as the elimination rate constant \((K)\). However, because this is a rather unwieldy equation, some assumptions can be made to simplify the design of an extravascular dosing regimen. The assumptions which will generally apply are that absorption is rapid, and that each dose will be administered after the majority of the previous dose is absorbed.

Although the administration route in question is extravascular, IV bolus equations may be used, keeping in mind that the peak and trough concentrations calculated will not be accurate. Predicted peaks will be higher under conditions of IV bolus vs. extravascular administration. As well, it is necessary to incorporate bioavailability \((F)\), since not all of each extravascularly-administered dose will be absorbed. The table below illustrates the result of the assumption that extravascular doses behave like IV bolus doses.

**Table 8-6: Impact of estimating concentrations after multiple extravascular doses by using IV bolus equations with a bioavailability**

<table>
<thead>
<tr>
<th>Absorption Rate</th>
<th>Extravascular Equation</th>
<th>IV Bolus with Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_a)</td>
<td>(C_{MAX}) (mg/L)</td>
<td>(C_{MIN}) (mg/L)</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>6.1</td>
</tr>
<tr>
<td>0.8</td>
<td>9.4</td>
<td>6.1</td>
</tr>
<tr>
<td>0.4</td>
<td>7.4</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Values used in calculations: \(K = 0.1 \text{ h}^{-1}\); \(V = 100 \text{ L}\); \(F = 0.75\); \(X_0 = 1000 \text{ mg}\)

In cases where absorption is very rapid \((k_a = 1 \text{ h}^{-1})\) IV bolus dose equations can be used to generate a fairly accurate estimation of drug concentrations under extravascular administration conditions. When absorption is slower, IV bolus equations overestimate \(C_{MAX}\) but \(C_{MIN}\) is fairly accurate. Thus, the shortcut of using IV bolus equations incorporating a bioavailability term generally results in a good approximation of concentrations. The tendency toward overprediction can be a benefit, since if your predicted peak is at the top of the therapeutic range, the actual concentration will be slightly lower than that value.

**Example:** Drug Y has the following pharmacokinetic parameters: \(CL = 15 \text{ L/h}\), \(V = 500 \text{ L}\), \(t1/2 = 24 \text{ h}\), \(F = 0.80\). The desired peak and trough concentrations are 10 and 5 \(\mu\text{g/L}\). Design an oral dosing regimen to target peak concentrations.
Step 1) Find an appropriate dosing interval. Simply count: concentrations will decline from 10 to 5 \( \mu g/L \) during 1 half-life (24 h).

Alternatively, use the equation:

\[
\tau = \frac{\ln\left(\frac{C_{\text{MAX,SS}}}{C_{\text{MIN,SS}}}\right)}{k}
\]

where \( C_{\text{MAX,SS}} \) is 10 \( \mu g/L \), \( C_{\text{MIN,SS}} \) is 5 \( \mu g/L \) and \( k = 0.029 \) 1/h (derived from half-life).

\[
\tau = \frac{\ln\left(\frac{10\mu g/L}{5\mu g/L}\right)}{0.029 \text{h}^{-1}} = 24 \text{h}
\]

Step 2) Determine the appropriate dose to target average concentrations. Use the equation below, rearranging to solve for dose.

\[
C_{\text{MAX,SS}} = \frac{X_0 \cdot F \cdot 1}{V \cdot \left(1 - e^{-k\tau}\right)}
\]

Notice that \( F \) (bioavailability) has been incorporated into the equation

\[
X_0 = C_{\text{MAX,SS}} \cdot \frac{V}{F} \cdot \left(1 - e^{-k\tau}\right)
\]

\[
X_0 = 10\mu g/L \cdot \frac{500L}{0.8} \cdot \left(1 - e^{-0.029 \cdot 24h}\right) = 3.1 \text{mg}
\]

where \( C_{\text{MAX,SS}} \) is 10 \( \mu g/L \), \( V = 500 \text{ L} \), \( \tau = 24 \text{ h} \) (from step 1).

Since the administration route was oral, it would be necessary to take into account the dose sizes which might be available. Assuming that a 3 mg tablet exists, the therapeutic regimen would consist of 3 mg QD.

Step 3) Check your work: under an administration scheme of 3 mg QD, peak concentrations will be:
Gathering Information from multiple dose data

Calculation of important pharmacokinetic parameters (e.g., CL, V, \( t_{1/2} \), \( C_{SS} \), \( C_{MAX} \), \( C_{MIN} \), \( R \)) from multiple dose data can be somewhat complicated, so below are some general guidelines.

**Step 1)** Graph data on semi-log coordinates, or, if you have limited information, sketch the general shape of the anticipated concentration-time profile.

**Step 2)** Half-life can be determined by reading from the graph the time elapsed when drug concentrations fall by 50%. It does not matter which dose you base your estimate upon, because both \( V \) and \( CL \) (and thus half-life) will be constant with time. Of course, the estimate should always be based upon data from the terminal portion (the straight part) of the concentration-time profile.

In a clinical setting, few blood concentration samples may be available. For example (illustrated below) two steady-state concentrations might be available, sampled from within the same dosing interval (case 1) or from different dosing intervals (case 2). In either case, the following equation can be used to determine \( k \), and thus half life (where \( C_{MAX} \) is the higher concentration, \( C_{MIN} \) is the lower concentration, and time is the time elapsed between the two concentrations).

\[
C_{MAX,SS} = \frac{X_0 \cdot F \cdot R_a}{V} = \frac{3\ mg \cdot 0.8 \cdot 3}{500\ L} = 9.6\ ug/L
\]

and trough concentrations will be:

\[
C_{MIN,SS} = \frac{X_0 \cdot F \cdot e^{-k_T} \cdot R_a}{V} = \frac{3\ mg \cdot 0.8 \cdot e^{-0.029\ 24h} \cdot 2.0}{500\ L} = 4.8\ ug/L
\]

**NOTE:** \( R_a \) was estimated using the equation below.

\[
R_a = \frac{1}{(1 - e^{-k_T})} = \frac{1}{(1 - e^{-0.029\ 24h})} = 2.0
\]
In case 2, the samples were collected from two different dosing intervals, as is common with multiple short term infusions. Note that at steady-state, by definition, concentrations sampled at the same time point post-dose (regardless of the dosing interval) will be the same. Thus, a concentration determined during one dosing interval can be extrapolated to the latter (as seen below).
Now case 2 can simply be treated like case 1.

A third way to determine half-life would be to approximate based upon the amount of time it takes for the system to attain steady-state conditions. If steady-state is attained in 10 h, then half-life is approximately 2 h (10 h / 5 half-lives to reach steady-state).

Step 3) Clearance can always be calculated via AUC. Calculate either the AUC (from 0 through infinity) associated with the first dose only, or AUC at steady-state over the course of one dosing interval.

Step 4) Volume is slightly more difficult to calculate from data collected after extravascular administration (relative to, for example, IV bolus administration). For systems with IV bolus input as discussed earlier, volume can be calculated based upon the \( C_0 \) and \( X_0 \). For systems with any other administration route, it will be necessary to rearrange the appropriate equations and input known parameter values (e.g., \( k \), \( \tau \), \( CL \), \( X_0 \)), or use the relationship \( V = CL/k \).

When a drug is administered via intermittent infusions, the following equation often is used to estimate the volume of distribution. The \( C_{MIN} \) in this case is the trough concentration before a subsequent dose is given, and \( C_{MAX} \) is the maximum concentration at the end of that next infusion. Note that this equation only works in certain scenarios, as discussed in the examples below.

\[
V = \frac{k_0}{k} \left( 1 - e^{-kT} \right) \left( \frac{C_{MAX} - C_{MIN} \cdot e^{-kT}}{C_{MAX} - C_{MIN} \cdot e^{-kT}} \right)
\]
Step 5) CSS can be calculated based upon either the AUC (AUC/τ) or based upon CL (X₀/CL*τ).

Step 6) CMAX and CMIN can be estimated directly from the graph.

Step 7) The accumulation ratio can be determined by the equation below, if k and τ are known, or based upon the ratio of CMAX at steady-state to CMAX after a single dose.

\[ R_a = \frac{1}{(1 - e^{-k\tau})} \]

Example – Aminoglycoside: Gentamicin, an aminoglycoside antibiotic, is administered at a dose of 100 mg over 30 min every 12 h. Under steady-state conditions, a blood sample is drawn right before the start of the next infusion, and the concentration of drug in the sample is 0.86 mg/L. A second blood sample is drawn when the infusion stops, and the drug concentration in the sample is 6.3 mg/L. Determine the drug’s half-life, clearance and volume of distribution.

Step 1) Sketch the concentration-time profile (similar to case 2 above):

Step 2) To determine half-life, use the two data points available, but remember that since the system is at steady-state, the trough concentrations are identical from dosing interval to dosing interval. Thus it is possible to redraw the figure so that the two
concentrations appear within the same dosing interval.

By plotting these data on semi-log coordinates, it is possible to draw a best fit line through the points in order to estimate half-life. In this case, use the equation below.

$$k = \frac{\ln\left(\frac{C_{\text{MAX},SS}}{C_{\text{MIN},SS}}\right)}{t}$$

This equation is a simple rearrangement of the IV bolus equation. $C_{\text{MAX},SS}$ and $C_{\text{MIN},SS}$ are known. It will be necessary to calculate $t$; this can be somewhat tricky. The trough concentration was obtained at 12 h from the start of the infusion. The peak concentration was obtained at the end of the infusion. Since the duration of the infusion was 0.5 h, the total time elapsed between the peak and trough concentrations was 11.5 h (12 - 0.5).
Half-life is determined as indicated below.

\[
\ln\left(\frac{6.3}{0.86}\right) = \ln\left(\frac{6.3}{0.86}\right) = 0.173\text{h}^{-1}
\]

**Step 2)** Either the volume of distribution or clearance can be calculated next (although both require the use of equations). In this instance we will find clearance first. Simply rearrange the equation describing \(C_{\text{MAX,SS}}\) in order to solve for CL.

\[
C_{\text{MAX,SS}} = \frac{k_0}{\text{Cl}} \cdot (1 - e^{-kT}) \cdot R_a
\]

\[
R_a = \frac{1}{1 - e^{-kT}} = \frac{1}{1 - e^{-0.173(12)}} = 1.14
\]

Insert the known values for each parameter and solve.

\[
\text{Cl} = \frac{100}{6.3} \cdot \frac{0.5}{(1 - e^{-0.173(0.5)} \cdot 1.14) \cdot 3 \text{ L/h}}
\]

**Step 3)** Estimate volume by using the equation below, rearranging to solve for volume.

\[
k = \frac{\text{Cl}}{V}
\]

\[
V = \frac{\text{Cl}}{k} = \frac{3}{0.173} = 17.3\text{L}
\]
To solidify your understanding of the pharmacokinetic principles associated with multiple dose drug administration schemes, conduct simulations using Microsoft Excel. Some ideas for simulations are:

1) Effect of clearance: simulate the effect on pharmacokinetic parameters of decreases in renal or liver function.

2) Effect of dose: most clinical decisions, for pharmacists, involve making changes to the dose or dosing rate of a therapeutic regimen.

3) Effect of dosing interval: most clinical decisions, for pharmacists, involve making changes in the dose or dosing rate. For example, when high trough concentrations are associated with toxicity (as in aminoglycoside therapy), a therapeutic regimen which results in high trough concentrations (but on-target peak concentrations) can be improved by extending the dosing interval.

4) Effect of volume: Although not clinically relevant, it is helpful to understand how volume impacts peak, trough and steady-state drug concentrations.

5) Compare the effects of administration route (e.g., IV bolus vs. oral) under multiple-dose conditions: the calculations are simpler for systems with IV bolus vs. oral administration. Thus, certain calculations may be simplified by assuming that the two systems behave similarly. Simulate both types of data in order to observe differences (e.g., in peak and trough concentrations) between the two administration routes.

**Skills Obtained**

- Calculating average steady-state concentrations
- Estimating the effects of changing clearance, volume or dosing interval on steady-state concentrations
- Calculating an accumulation factor
- Estimating the amount of time required to reach steady-state
- Estimating CL, V and t_{1/2} from concentration-time data
- Designing a dosing regimen to achieve a certain average, peak or trough concentration

**Summary Equations**

Equation to determine concentration at steady-state (IV bolus administration):
\[
C = \frac{1}{(1 - e^{-k\tau})} \cdot C_0 e^{-kt}
\]

Equation to determine average steady-state concentration:

\[
\overline{C}_{ss} = \frac{\text{AUC}}{\tau} = \frac{X_0}{\text{CL} \cdot \tau}
\]

Equation to determine dosing interval:

\[
\tau = \frac{\ln\left(\frac{C_{\text{MAX}}}{C_{\text{MIN}}}\right)}{k} \quad \text{or} \quad \tau = -\frac{\ln\left(\frac{C_{\text{MAX}}}{C_{\text{MIN}}}\right)}{k} + T
\]

Equation to determine maximum concentration at steady-state after IV infusion:

\[
C_{\text{MAX}} = \frac{k_0}{\text{Cl}} \cdot \frac{(1 - e^{-kT})}{1 - e^{-k\tau}} \quad \text{or} \quad C_{\text{MAX}} = \frac{k_0}{\text{Cl}} \cdot (1 - e^{-kT}) \cdot R_a
\]

Equation to determine minimum concentration at steady-state after IV infusion (where \( t' = \tau - T \)):

\[
C_{\text{MIN}} = \frac{k_0}{\text{Cl}} \cdot \frac{(1 - e^{-kT})}{1 - e^{-k\tau}} \cdot e^{-kt'} \quad \text{or} \quad C_{\text{MIN}} = \frac{k_0}{\text{Cl}} \cdot (1 - e^{-kT}) \cdot e^{-kt'} \cdot R_a
\]

Equation to determine concentration at steady-state after oral (extravascular) administration:

\[
C = \frac{F \cdot X_0 \cdot k_a}{V \cdot (k_a - k)} \left( \frac{e^{-k_0 t} - e^{-k_0 \tau}}{1 - e^{-k_0 \tau}} \right)
\]

Much more practical form of the equation above (based on IV bolus):

\[
C_{\text{MAX}} = \frac{F \cdot X_0}{V} \cdot \left( \frac{1}{1 - e^{-k_0 \tau}} \right)
\]

\[
C_{\text{MIN}} = \frac{F \cdot X_0}{V} \cdot \left( \frac{e^{-k_0 \tau}}{1 - e^{-k_0 \tau}} \right)
\]
New Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \tau )</td>
<td>Dosing Interval</td>
<td>The time elapsed between administration of each dose of a drug</td>
<td>time (e.g., h)</td>
</tr>
<tr>
<td>( R_a )</td>
<td>Accumulation ratio</td>
<td>The amount of drug that accumulates in the body (function of the half-life of the drug and the frequency with which the drug is administered)</td>
<td>unitless</td>
</tr>
</tbody>
</table>
9) Hepatic Clearance

<table>
<thead>
<tr>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>• To understand how drug disposition is impacted by hepatic clearance.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>By the end of this chapter you should be able to:</td>
</tr>
<tr>
<td>• Differentiate between a low extraction ratio and high extraction ratio drug.</td>
</tr>
<tr>
<td>• Determine the effects (on total and unbound drug concentrations) of changes in protein binding, intrinsic clearance or liver blood flow rate, for intravenous and orally administered drugs.</td>
</tr>
<tr>
<td>• Calculate the bioavailability of a drug and describe how alterations in hepatic function can influence bioavailability.</td>
</tr>
<tr>
<td>• Define the term enterohepatic recycling.</td>
</tr>
</tbody>
</table>

In Brief

The liver is one of the most essential organs in the body related to the clearance of a drug or toxin. In this chapter we will look at the different variables of clearance that affect a hepatically cleared drug, which include hepatic blood flow, protein binding, and efficiency of an enzyme to metabolize a drug or toxin. We can combine these factors into an equation that allows us to more easily predict drug behavior at the extreme ends of the extraction ratio (or the efficiency a drug is removed by the liver). Hepatic clearance concepts is one of the most difficult concepts in pharmacokinetics.

Introduction

General concepts related to clearance have been discussed earlier in the book. In this and the next chapter, respectively, the body’s two main clearing organs, the liver and the kidney, will be discussed in greater detail.

The liver is involved in numerous functions including storage and filtration of blood, secretion and excretion processes and metabolism. The rate of blood flow through the human liver (hepatic blood flow rate; \( Q_H \)) is 90 L/h (1500 mL/min), with \( \sim 75\% \) of the blood coming from the portal vein and \( \sim 25\% \) from the hepatic artery. The metabolic functions of this
organ are of interest in pharmacokinetics because these functions include, among other enzymatic reactions, the biotransformation of drugs. Hundreds of enzyme systems metabolize drugs and most can be classified into phase I or phase II reactions. Phase I reactions are referred to as “preparatory reactions”, and include reactions such as oxidations, reductions, and hydrolyses accomplished by major enzyme families such as the cytochrome P450 and flavinoid monooxygenase (FMO) systems. Phase I reactions generally result in small increases in hydrophilicity. Phase II reactions are referred to as “synthetic” or “conjugate reactions” and result in very polar molecules that are easily excreted by the kidney. The table below summarizes some of these processes.

Table 9-1: Examples of phase I and phase I biotransformation reactions

<table>
<thead>
<tr>
<th>Phase I Reactions</th>
<th>Phase II Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation</td>
<td>Glucuronide conjugation</td>
</tr>
<tr>
<td>Aromatic hydroxylation</td>
<td>Ether glucuronide</td>
</tr>
<tr>
<td>Side chain hydroxylation</td>
<td>Ester glucuronide</td>
</tr>
<tr>
<td>N-, O- and S- dealkylation</td>
<td>Amide glucuronide</td>
</tr>
<tr>
<td>Deamination</td>
<td>Peptide conjugation</td>
</tr>
<tr>
<td>Sulfoxidation, N-oxidation</td>
<td>Glycine conjugation (hippurate)</td>
</tr>
<tr>
<td>N-hydroxylation</td>
<td></td>
</tr>
<tr>
<td>Reduction</td>
<td>Methylation</td>
</tr>
<tr>
<td>Azoreduction</td>
<td>N-methylation</td>
</tr>
<tr>
<td>Nitroreduction</td>
<td>O-methylation</td>
</tr>
<tr>
<td>Alcohol dehydrogenase</td>
<td></td>
</tr>
<tr>
<td>Hydrolysis</td>
<td>Acetylation</td>
</tr>
<tr>
<td>Ester hydrolysis</td>
<td>Sulfate conjugation</td>
</tr>
<tr>
<td>Amide hydrolysis</td>
<td>Mercapturic acid synthesis (glutathione conjugation)</td>
</tr>
</tbody>
</table>

The topic of cytochrome P450 reactions has become increasingly complex with the discovery of various subclasses and polymorphs of the enzymes in this family. In addition, many of these enzymes may be induced or inhibited by drugs like phenobarbital, rifampin, ritonavir and fluoxetine, by dietary supplements like St. John’s Wort and even by foods and exercise. Since so many factors can potentially modulate hepatic function, it is important to understand the basic principles of hepatic clearance and how factors like enzyme function can impact systemic exposure to a drug. In the following sections, a basic model of hepatic function will be introduced, followed by a discussion of important components of this model. On the remainder of the chapter will focus on the impact of hepatic clearance on the total and unbound drug concentrations of drug in the body after intravenous and oral administration.

The well-stirred model assumes that drug instantaneously distributes through the liver, and that all metabolic enzymes have equal access to drug.
The Well-Stirred Model

Various models have been developed to describe the liver’s ability to clear drugs. The venous equilibrium model or the well-stirred model is the most commonly-used and most generally-applicable model. Although physiologically, the liver is highly structuralized, this simplistic model operates on the assumption that all hepatic regions have instantaneous, equal access to the drug (i.e., that the liver is “well-stirred”). Structurally, this model is similar to the organ clearance model presented earlier, in the Clearance chapter.

\[\text{Liver} \quad C_{\text{IN}} \quad C_{\text{OUT}}\]

\[Q_H \quad \text{Elimination} \quad \text{Cl}'_I \quad Q_H\]

Figure 9-1: Schematic of the well-stirred model for hepatic clearance

This model incorporates the following parameters: 1) the hepatic blood flow rate \(Q_H\), 2) unbound intrinsic clearance \(\text{CL}_I';\) read as “CL_I prime”), which is the maximum rate at which drug can be metabolized, in the absence of protein binding or blood flow rate limitations; and 3) the degree of protein binding, as the unbound fraction of drug, \(f_u\). Other parameters include the concentration of drug in the blood entering the liver \(C_{\text{IN}}\) and exiting the liver \(C_{\text{OUT}}\). Note that the unbound intrinsic clearance \(\text{CL}_I'\) is different than \(\text{CL}\). \(\text{CL}\) refers to systemic clearance, while \(\text{CL}_I'\) (the unbound intrinsic clearance rate) refers to the maximum rate at which enzymes in an organ can clear drug, in the absence of all factors which might limit the rate of metabolism (i.e., protein binding and blood flow rate). An additional, similar term, \(\text{CL}_U\), refers to the total intrinsic clearance rate, (clearance of both bound and unbound drug), in the absence of blood flow rate limitations only \((\text{CL}_I = f_u * \text{CL}_I')\).

These new clearance terms reflect the fact that both protein binding and blood flow rate will impact the ability of enzymes to metabolize drug. Only unbound drug is accessible to enzymes. Blood flow rate influences clearance because if drug is flowing through an organ very rapidly, it may be more difficult for an enzyme to access the drug to metabolize it. For this discussion, please keep in mind we are assuming drug concentrations are low enough such that the kinetics follow a first-order process. The relevant clearance terms are summarized below.
Table 9-2: Symbols and definitions related to hepatic clearance

<table>
<thead>
<tr>
<th>Term</th>
<th>Verbiage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>(Systemic) Clearance</td>
<td>Volume of reference fluid (usually blood) from which drug is completely, irreversibly removed, per unit time. (Reflects the sum of all clearance processes.)</td>
</tr>
<tr>
<td>CL_H</td>
<td>Hepatic Clearance</td>
<td>Volume of blood from which drug is completely, irreversibly removed by the liver per unit time. (One component of systemic clearance.)</td>
</tr>
<tr>
<td>CL_I</td>
<td>Intrinsic Clearance</td>
<td>Rate at which enzymes, in the absence of limitation by blood flow rate can metabolize total (bound and unbound) drug.</td>
</tr>
<tr>
<td>CL_I'</td>
<td>Unbound Intrinsic</td>
<td>Rate at which enzymes, in the absence of limitation by blood flow rate and protein binding can metabolize unbound drug.</td>
</tr>
</tbody>
</table>

Equations describing the above scheme can be derived mathematically, or can be approximated (as discussed below) by using some logic. When a drug molecule enters the liver, two possible routes are available. Route 1 is to leave the liver unchanged, and Route 2 is to undergo metabolism and elimination. The mass of drug which will eventually enter the systemic circulation depends on the fraction of drug which moves by each route. If all drug follows Route 2 upon a single pass through the liver, would any systemic pharmacologic response occur? The answer is no, because all drug would be eliminated before reaching the systemic circulation.

Figure 9-2: Scheme depicting possible routes a drug might take upon entering the liver.
The effects of altering the proportion of drug moving by each route are illustrated in the table below. The first column, \((C_{IN})\) indicates the concentration of drug coming into the liver, and the second column, \((C_{OUT})\), indicates the drug concentration coming out of the liver. If all drug exits the liver unchanged \((C_{OUT} = 100)\), then the liver did not remove or extract any drug, so the fraction “lost” due to hepatic metabolism is 0. Alternatively, if no drug exits the liver \((C_{OUT} = 0)\), 100% of the drug is lost via hepatic metabolism.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Situation & \(C_{IN}\) & \(C_{OUT}\) & Fraction Lost \\
\hline
1 & 100 & 100 & 0.0 \\
2 & 100 & 50 & 0.5 \\
3 & 100 & 0 & 1.0 \\
\hline
\end{tabular}
\caption{Examples of extraction ratios based on concentrations coming into and out of the liver}
\end{table}

The above table, although somewhat intuitive, can be generated by using the following equation:

\[
\text{Fraction Lost} = \frac{C_{IN} - C_{OUT}}{C_{IN}}
\]

Where \(C_{IN}\) is the concentration entering the liver and \(C_{OUT}\) is the concentration exiting the liver. Because both the numerator and denominator are composed of concentration terms, the fraction lost is unitless. The idea that a certain fraction of drug is lost during a single pass through an organ, underlies the next concept we will discuss; extraction ratio.

The fraction of drug that is eliminated upon a single pass through an organ can be expressed as the mass of drug which undergoes elimination, normalized for the total mass of drug moving by both possible routes.

\[
\text{Fraction of Drug Eliminated} = \frac{\text{Route 2}}{\text{Route 1} + \text{Route 2}}
\]

This fraction is termed the extraction ratio \((E)\). The extraction ratio reflects the ability of the liver to extract drug from the systemic circulation upon a single pass through the liver. Assume that the extraction ratio is 0.25, that is, 25% of the drug in the blood will be extracted by the liver.
upon a single pass through the liver. The table below illustrates the resulting drug concentrations over time, given a 0.25 extraction ratio.

**Table 9-4: Example of the difference between extraction ratio and extent removed by the liver**

<table>
<thead>
<tr>
<th># of passes through the liver</th>
<th>Concentration in blood</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>25%</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>25%</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>25%</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>25%</td>
</tr>
</tbody>
</table>

In the case of a drug that is eliminated by hepatic metabolism only, the entire administered dose will eventually be eliminated by the liver. Even though a drug may be extracted inefficiently (i.e., may have a low extraction ratio), the liver will still (with sufficient time) achieve removal of 100% of the administered dose of drug.

Next, we will discuss physiologic parameters underpinning drug movement by the above-discussed routes. Movement of drug by route 1, (wherein unchanged drug exits the liver), is determined by the hepatic blood flow rate ($Q_H$). Recall from earlier discussions that blood flow and clearance have the same units, that is, volume per time. Hepatic blood flow can “clear” or remove drug from the liver into the body. Movement of drug by route 2, on the other hand, is governed by the intrinsic capacity of hepatic enzymes to metabolize drug (the rate of unbound intrinsic clearance; $CL_I'$). Since some fraction of the drug in the blood is generally bound to proteins, it is necessary to incorporate the drug-specific unbound fraction ($f_U$) into the intrinsic clearance term. Thus, movement of drug by route 2 can be described as being governed by $f_U \cdot CL_I$, or the innate ability of hepatic enzymes to metabolize unbound drug.

Returning to the idea of extraction ratio, in this “well-stirred” model, the extraction ratio ($E$) is:

$$E = \left( \frac{f_U \cdot CL_I'}{Q_H + f_U \cdot CL_I'} \right)$$

Equation 9-1

$E$ is a ratio, thus, it has no units, and the value is restricted to $0 \leq E \leq 1$. That is, no more than 100% of the administered dose of drug can be extracted. This ratio essentially reflects the ratio of the mass of drug metabolized by the liver (Route 2, governed by $f_U \cdot CL_I'$) to the total mass of drug.
drug cleared by metabolism and blood flow combined (Route 1 + Route 2, governed by \( f_u \cdot CL_i + Q_H \)).

Earlier, we defined clearance in terms of blood flow and extraction ratio:

\[
\text{Cl} = Q \cdot E
\]

Equation 9-2

When the above definition of E is incorporated into the equation:

\[
CL_H = Q_H \cdot \left( \frac{f_u \cdot CL_i'}{Q_H + f_u \cdot CL_i'} \right)
\]

Equation 9-3

The above equation describes the well-stirred model. Recall that E is the ratio of the concentration of drug coming into the liver vs. leaving the liver in a single pass. Note that because \( E \leq 1 \), it follows that hepatic clearance (\( CL_H \)) cannot exceed hepatic blood flow (\( Q_H \)). To illustrate the principles discussed above, including how each of the equations' parameters affects clearance, consider the following two cases, representing the extreme ends of the extraction ratio scale.

**High and Low Extraction Ratio Drugs: Discussion of Extremes**

First, we will discuss the case of a low extraction ratio drug (\( E < 0.3 \)). Low extraction ratio drugs are also sometimes called “restrictively cleared” or “capacity-limited”, because the rate at which the liver can remove drug from the blood is limited by the rate of hepatic enzyme intrinsic activity. In this case, the rate at which enzymes can metabolize drug is much less than the rate at which blood flows through the organ (\( f_u CL_i' \ll Q_H \)). Again, Q and CL have the same units, this comparison can be made relatively easily. Since \( Q_H \) is so much greater than \( f_u CL_i' \), the \( f_u CL_i' \) term can simply be removed from the denominator. The principle behind this simplification is that the addition of a very small number to a very large number has little impact on the sum e.g., 10,000 + 0.1 \( \approx \) 10,000. Therefore, the equation for hepatic clearance can be simplified to:

\[
CL_H = Q_H \cdot \left( \frac{f_u \cdot CL_i'}{Q_H} \right)
\]

Equation 9-4

The \( Q_H \) terms will cancel out, leaving:

\[
CL_H = f_u \cdot CL_i'
\]

Equation 9-5

Hepatic Clearance cannot exceed hepatic blood flow.
For drugs which are extracted inefficiently by the liver (i.e. drugs which are classified as “low extraction” or as undergoing “restricted clearance”), alterations in the expression level of enzymes, or the function of existing enzymes (e.g., enzyme induction, inhibition), as well as any changes in the fraction of unbound drug (i.e., resulting in more ‘free’ drug to metabolize) will alter the rate of systemic clearance. It may be helpful to think about the situation presented by low hepatic extraction in terms of rate-limiting steps. Imagine that the enzymes are not very good at metabolizing the drug in question (much like the Chicago Cubs are not very good at either hitting or catching baseballs). One way to improve systemic clearance is to increase the rate of drug metabolism by increasing the amount of enzyme present in the liver. The other option is to increase the unbound fraction of the drug, thus facilitating access of the drug to the metabolic enzymes.

As a second case, consider drugs that have a high extraction ratio (E>0.7), resulting in “nonrestrictive clearance” or “flow-limited” clearance. In this scenario, the rate of blood flow is much lower than the rate at which enzymes can metabolize drug (Q_H<< f_u·CL_i'). Again, since f_u·CL_i’ is so much greater than Q_H, the equation for hepatic clearance can be simplified to:

\[
CL_H = Q_H \cdot \left( \frac{f_u \cdot CL_i'}{f_u \cdot CL_i} \right)
\]

Equation 9-6

The f_u·CL_i’ term cancels out, resulting in the following equation:

\[
CL_H = Q_H
\]

Equation 9-7

For high extraction ratio drugs, CL will depend on the rate at which blood flows through the liver (rate of presentation of drug to the liver). Since the metabolic efficiency of the enzymes is high, the only way to increase CL is to increase the rate of presentation of drug to them (increasing Q increases the mass of drug presented to the hepatic enzymes).

**Low E and High E: Intravenous Administration**

The following table presents the equations relevant to these two cases (low and high extraction ratio), as well as the effect of each type of extraction ratio on total and unbound drug concentration. It is necessary to differentiate between total and unbound drug concentrations because
only the unbound concentrations govern pharmacologic activity (although typically, total drug concentrations are measured in patients). Is it possible for unbound concentrations to change while total concentrations remain the same?

Table 9-5: Summary table of low and high E drugs

<table>
<thead>
<tr>
<th>General Equation</th>
<th>Low Extraction (E&lt;0.3)</th>
<th>High Extraction (E&gt;0.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( CL_H )</td>
<td>( CL_H = Q_H \cdot \left( \frac{f_U \cdot CL'_i}{Q_H + f_U \cdot CL'_i} \right) )</td>
<td>( CL_H = f_U \cdot CL'_i )</td>
</tr>
<tr>
<td>( CSS ) (TOTAL)</td>
<td>( CSS = \frac{k_0}{CL} )</td>
<td>( CSS = \frac{k_0}{f_U \cdot CL'_i} )</td>
</tr>
<tr>
<td>( CSS ) (unbound)</td>
<td>( CSS,U = \left( \frac{k_0}{CL} \right) \cdot f_U )</td>
<td>( CSS,U = \left( \frac{k_0}{CL'_i} \right) )</td>
</tr>
<tr>
<td>Half-life</td>
<td>( t_{1/2} = \left( \frac{CL}{V CL} \right) \cdot 0.693 )</td>
<td>( t_{1/2} = \left( \frac{V}{f_U \cdot CL'_i} \right) \cdot 0.693 )</td>
</tr>
</tbody>
</table>

In response to the above question, it is possible to have a situation where the total drug concentration changes but the unbound concentration remains the same. Consider the low extraction ratio example in the table above. If protein binding changes, thus changing \( f_U \), the total steady-state concentration will change but the unbound steady-state concentration will not, since there is no \( f_U \) term in the latter equation. If the unbound concentration does not change then we do not need to adjust the dose since the unbound concentration drives response.

The following graphs illustrate how changing either intrinsic clearance (\( CL'_i \)) or blood flow (\( Q_H \)) will affect blood concentrations after IV bolus administration.
In the above graphs, the parameter that is changing in the first row is intrinsic clearance. The systemic clearance for a low extraction ratio drug is affected by the intrinsic clearance because enzyme activity is the rate-limiting step. Increasing the rate of the rate-limiting step increases the rate of the overall clearance process. Because high extraction drugs are so efficient, increasing their activity rate will have very little impact on the rate of the overall clearance process. As discussed earlier in the context of IV bolus kinetics, note that clearance impacts the drug’s half-life but does not impact the initial concentration, $C_0$.

The parameter that is changing in the second row is hepatic blood flow. High extraction ratio drugs are limited, in terms of overall clearance rate, by the hepatic blood flow rate, which governs the rate of drug presentation to the hepatic enzymes. Increasing the rate of presentation of drug to these enzymes will increase the rate of the overall clearance process. For a low extraction ratio drug, alterations in hepatic blood flow will have very little impact on the rate of the overall clearance process. The maximum rate at which the enzymes can metabolize drug is very low, thus, the intrinsic metabolic rate, rather than the drug presentation rate, is the limiting step in the overall clearance process.
The following graphs illustrate how changes in the degree of protein binding (e.g., resulting from physiologic changes such as pregnancy, or from addition of another drug to a therapeutic regimen), will affect unbound and total steady-state drug concentrations. Recall that at steady-state, an equilibrium exists between bound and unbound drug concentrations in the plasma and in the cell. In addition, an equilibrium exists between unbound drug concentrations in the plasma and in the cells. Thus, when binding is perturbed, a period of ‘readjustment’ will exist before a new equilibrium is established.

Figure 9-4: Impact of changes in protein binding on total and unbound drug concentrations

For a drug with a low extraction ratio, the rate of metabolism is primarily limited by the low intrinsic activity of the enzymes themselves. Thus, increasing the unbound fraction of drug causes a temporary rise in unbound concentrations. Because only the unbound portion of drug is accessible to enzymes, as the unbound concentration increases, the rate of metabolism will increase. This increase in metabolic rate causes the unbound concentration to return to its previous level, and also results in a reduction in the total concentration.

For a drug with a high extraction ratio, the intrinsic metabolic clearance is so high that bound drug is removed from protein and cleared from the liver on a single pass through the organ. Thus, the total concentration serves as the driving force for drug metabolism. Therefore, an increase in unbound fraction will not result in an increase in hepatic clearance, and total drug concentrations will remain unchanged. Because total concentrations have not changed, and unbound fraction has increased, the unbound concentration will rise.

The influence of protein binding on unbound concentrations at steady-state is important because in almost every case, the unbound concen-
tration will govern pharmacologic response. If a change in protein binding does not result in a change in unbound concentration at steady-state, no dosage adjustment would be required, even if total concentrations change. Note that in clinical settings, total rather than unbound concentrations are generally measured. However, changes (or lack thereof) in total concentration may not reflect the manner in which unbound concentrations are impacted (for example, by a physiologic change or addition of another drug to a therapeutic regimen). It is critically important for the clinician to understand the fundamental relationships between unbound fraction, extraction ratio, and unbound concentration at steady-state, and to be knowledgeable about the pharmacokinetic and protein binding characteristics of all drugs in a given patient’s therapeutic regimen.

The table below summarizes the interaction between three factors; blood flow rate, protein binding and unbound intrinsic clearance, and impact half-life, $C_{SS}$ total and unbound (or AUC) and clearance.

**Table 9-6: Summary table for low extraction ration and high extraction ratio drugs after intravenous administration**

<table>
<thead>
<tr>
<th></th>
<th>Low Extraction (E&lt;0.3)</th>
<th>High Extraction (E&gt;0.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q</td>
<td>$f_u$</td>
</tr>
<tr>
<td>CL</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>$C_{SS}$ (TOTAL)</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>$C_{SS}$ (unbound)</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Half-life</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

* may not see a change because $f_u$ will impact both $V$ and $CL$

**Low E and High E: Oral administration**

Thus far, our discussion of hepatic clearance has focused on systems with intravenous administration input. We will now discuss hepatic clearance in relation to systems with oral administration input. Under conditions of oral administration, it is important to take into account the bioavailability ($F$) of the administered dose, as discussed in the Extravascular Administration chapter. One of the main factors determining bioavailability is the capacity of the liver to remove drug during the first pass of the drug through the liver. Recall that after a drug is absorbed, the first organ it will enter is the liver. If the liver removes much of that drug, little will remain to subsequently enter the systemic circulation.
Recall the schematic illustrating the possible routes a drug can take once it enters the liver:

![Schematic of drug routes in liver](image)

**Figure 9-5: Schematic of the routes a drug can take once in the liver.**

Drug that exits the liver via route 2 (i.e., is metabolized) is effectively eliminated from the body. However, the fraction of drug which exits the liver via route 1 (i.e., is excreted unmetabolized) will become available (bioavailable) to the rest of the body. Thus, bioavailability is related to extraction (E) in the following manner:

\[
F = 1 - E \quad \text{Equation 9-8}
\]

To obtain an equation describing bioavailability under the assumptions of the well-stirred model, (that is, including terms to describe protein binding, blood flow and enzyme activity), there are two approaches. One is to simply incorporate an equation describing E into the above equation, and simplify, as illustrated below.

\[
F = 1 - \left( \frac{f_U \cdot CL_i^*}{Q_H + f_U \cdot CL_i^*} \right) \quad \text{Equation 9-9}
\]

Expand the equation to obtain a common denominator on both sides of the subtraction sign

\[
F = \left( \frac{Q_H + f_U \cdot CL_i^*}{Q_H + f_U \cdot CL_i^*} \right) - \left( \frac{f_U \cdot CL_i^*}{Q_H + f_U \cdot CL_i^*} \right)
\]

Subtract to obtain the equation below

\[
F = \left( \frac{Q_H}{Q_H + f_U \cdot CL_i^*} \right) \quad \text{Equation 9-10}
\]
An alternative approach to arrive at this equation, is to consider the two possible routes by which a drug may exit the liver. The fraction of a dose of drug that will exit the liver via route 1 (become bioavailable) is:

**Fraction of Drug that is Bioavailable** = \( \frac{\text{Route 1}}{\text{Route 1} + \text{Route 2}} \)

Simply re-write the equation in terms of the parameters governing drug movement by each of these routes (discussed earlier):

\[
F = \left( \frac{Q_H}{Q_H + f_u \cdot CL'_i} \right)
\]

**Impact of Protein Binding, Blood Flow and Enzyme Activity on the Concentration-Time Profile Following Oral Administration**

Previously, we have considered the ways in which factors such as protein binding, blood flow rate and enzyme activity impact pharmacokinetic parameters in systems with IV bolus input. The effects of these factors are similar in systems with oral administration input, however, in this case it is necessary to take bioavailability into account. Recall that drugs which have a low extraction ratio are cleared from the blood at a rate much lower than the rate of blood flow (\( f_uCL'_i << Q_h \)) and drugs which have a high extraction ratio are cleared at a rate much greater than the rate of blood flow (\( Q_H << f_uCL'_i \)). When calculating bioavailability for a drug with a very low extraction ratio, \( f_uCL'_i \) is very small relative to \( Q_H \), thus, the \( f_uCL'_i \) term can be simply dropped from the denominator.

\[
F = \left( \frac{Q_H}{Q_H + f_u \cdot CL'_i} \right)
\]

\[
F = \left( \frac{90}{90 + 0.0001} \right)
\]

\[
F = \left( \frac{Q_H}{Q_H} \right) = 1
\]

The bioavailability for a drug with a very low extraction ratio is thus nearly 100%. Note that alterations to any of the three parameters in the equation (\( Q_H, f_u \), and \( CL'_i \)) will have essentially no effect on \( F \).
Now consider the case of drug with a high extraction ratio. Assume that the intrinsic clearance rate is much greater than the rate of blood flow \( Q_H << f_u \cdot CL_i' \), such that again, the much smaller term in the denominator can be dropped. Thus, the relevant equation describing bioavailability becomes:

\[
F = \left( \frac{Q_H}{Q_H + f_u \cdot CL_i'} \right)
\]

\[
F = \left( \frac{1}{1 + 10000} \right)
\]

\[
F = \left( \frac{Q_H}{f_u \cdot CL_i'} \right)
\]

For drugs with a high extraction ratio, alteration of any of the three parameters in the equation would alter bioavailability. As blood flow increases, more drug will be cleared, unchanged, from the liver and thus reach the systemic circulation. As intrinsic clearance increases, the capacity of the liver to remove drug from the blood increases, thus bioavailability decreases. Drugs that have a high extraction ratio typically exhibit particularly low and variable bioavailability.

The table below summarizes the equations that are relevant for compounds with high and low extraction ratios.

### Table 9-7: Summary of equations for low extraction ratio drugs

<table>
<thead>
<tr>
<th>General Equation</th>
<th>Low Extraction (E&lt;0.3)</th>
<th>High Extraction (E&gt;0.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( CL_H )</td>
<td>( CL_H = Q_H \cdot \left( \frac{f_u \cdot CL_i'}{Q_H + f_u \cdot CL_i'} \right) )</td>
<td>( CL_H = f_u \cdot CL_i' )</td>
</tr>
<tr>
<td>( F )</td>
<td>( F = \left( \frac{Q_H}{Q_H + f_u \cdot CL_i'} \right) )</td>
<td>( F = 1 )</td>
</tr>
<tr>
<td>( C_{ss} ) (TOTAL)</td>
<td>( \bar{C}_{ss} = \frac{k_0}{CL} \cdot F )</td>
<td>( \bar{C}_{ss} = \frac{k_0}{f_u \cdot CL_i'} )</td>
</tr>
<tr>
<td>( C_{ss} ) (FREE)</td>
<td>( \bar{C}_{ss} = \frac{k_0}{CL} \cdot f_u \cdot F )</td>
<td>( \bar{C}_{ss} = \frac{k_0}{CL_i'} )</td>
</tr>
</tbody>
</table>
Note that under conditions of extravascular administration, the equations describing unbound and total drug concentrations remain unchanged by the extraction ratio of the drug. It is important to realize that the bioavailability of drugs with low extraction ratios is essentially independent of blood flow, protein binding or intrinsic clearance, as demonstrated in the following example.

**Example:** In the case of a drug that has a low extraction ratio \((E=0.1)\), how will bioavailability change if the extraction ratio decreases by 50% \((E=0.05)\)?

\[
\begin{align*}
\text{If } E &= 0.1, \text{ then } F = 0.90 \\
\text{If } E &= 0.05, \text{ then } F = 0.95 \\
\text{Pre-Post Change} &= 100 \times \frac{0.90 - 0.95}{0.90} = 5.6\%
\end{align*}
\]

Thus, a 50% decrease in the extraction ratio causes a 5.6% increase in bioavailability.

**Example:** In the case of a drug that has a high extraction ratio \((E=0.9)\), how will bioavailability change if the extraction ratio decreases by 10% \((E=0.8)\)?

\[
\begin{align*}
\text{If } E &= 0.9, \text{ then } F = 0.10 \\
\text{If } E &= 0.8, \text{ then } F = 0.2 \\
\text{Pre-Post Change} &= 100 \times \frac{0.10 - 0.20}{0.10} = 100\%
\end{align*}
\]

A 10% decrease in the extraction ratio causes a 100% increase in bioavailability.

Below are graphs of the concentration-time profiles from orally-administered drugs with either high or low extraction ratios. The effects, on the concentration-time profile, of altering either \(\text{CL}_i\) or \(Q_i\) are also illustrated.
Figure 9-6: Example graphs for the impact of changes in intrinsic clearance or hepatic blood flow on high or low extraction ratio drugs after oral administration

<table>
<thead>
<tr>
<th>Change</th>
<th>Low Extraction (E=0.1)</th>
<th>High Extraction (E=0.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ CL\text{INT}'</td>
<td><img src="before.png" alt="Graph 1" /></td>
<td><img src="after.png" alt="Graph 1" /></td>
</tr>
<tr>
<td>↓ Q_h</td>
<td><img src="before.png" alt="Graph 2" /></td>
<td><img src="after.png" alt="Graph 2" /></td>
</tr>
</tbody>
</table>

Altering the rate of hepatic blood flow does not substantially impact the concentration-time profile of drugs with low extraction ratios, because this change does not affect clearance or bioavailability. Blood flow does, however, impact both clearance and bioavailability for compounds with high extraction ratios. In this latter case, a decrease in the hepatic blood flow rate will decrease both clearance and bioavailability. Although the shapes of the two concentration-time profiles are different, the resulting AUCs are similar. Conversely, altering the rate of intrinsic clearance affects the concentration-time profile of both types of drugs, although the effects are different in each situation. In the case of the drug with a low extraction ratio, the increase in intrinsic clearance changes the concentration-time profile by increasing total systemic clearance. A change in intrinsic clearance will not impact the clearance of a high extraction ratio drug but it will impact the drug's bioavailability. As intrinsic clearance increases, bioavailability will decrease (thus decreasing AUC).

The graphs below illustrate the impact of protein binding on steady-state total and unbound drug concentrations in the context of oral administration of drugs with high or low extraction ratios. Note that the relationships illustrated in these graphs apply strictly to the case of oral admin-
istration, and cannot be extrapolated to systems with other types of extravascular input. In the case of oral administration (unlike intravenous administration, which was discussed earlier) drugs with high and low extraction ratios behave similarly.

**Figure 9-7: Example graphs for the impact of changes in protein binding on high or low extraction ratio drugs after oral administration**

<table>
<thead>
<tr>
<th>Low E</th>
<th>High E</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenytoin</td>
<td>lidocaine</td>
</tr>
</tbody>
</table>

In the specific case of oral administration, the average steady-state concentration of unbound drug is equal to the ratio of the dose rate divided by the unbound intrinsic clearance. Therefore, changes in the unbound fraction will not affect unbound concentrations for any drug administered orally, regardless of the extraction ratio. The total concentration, however, will be influenced by changes in unbound fraction as illustrated in the graphs above.

The table below provides a summary of the relationship between the three key parameters governing hepatic clearance and their impact on bioavailability, half-life, and steady-state concentrations after oral administration.
Table 9-8: Summary of expected changes for low and high extraction ratio drugs given changes in hepatic blood flow, unbound fraction and intrinsic clearance.

<table>
<thead>
<tr>
<th></th>
<th>Low Extraction (E&lt;0.3)</th>
<th>High Extraction (E&gt;0.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>f_U</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CL'_I</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>F</td>
<td>☒</td>
<td>✓</td>
</tr>
<tr>
<td>C_SS (TOTAL)</td>
<td>☒</td>
<td>✓</td>
</tr>
<tr>
<td>C_SS (unbound)</td>
<td>☒</td>
<td>✓</td>
</tr>
<tr>
<td>Half-life</td>
<td>☒</td>
<td>✓</td>
</tr>
</tbody>
</table>

* may not see a change because fu will impact both V and CL

Hepatic clearance concepts can be summarized as follows:

Table 9-9: Summary table of concepts related to low and high extraction ratio drugs.

<table>
<thead>
<tr>
<th></th>
<th>Low Extraction Ratio</th>
<th>High Extraction Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance Category</td>
<td>Restrictive</td>
<td>Non-restrictive</td>
</tr>
<tr>
<td>Systemic Clearance</td>
<td>Tends to be low</td>
<td>Tends to be high</td>
</tr>
<tr>
<td></td>
<td>(close to Q_h)</td>
<td></td>
</tr>
<tr>
<td>Oral Bioavailability</td>
<td>Tends to be high</td>
<td>Tends to be low</td>
</tr>
<tr>
<td>Clearance appears to be restricted to unbound drug</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rate of drug dissociation from plasma protein</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Other name</td>
<td>Intrinsic clearancelimited</td>
<td>Flow-limited</td>
</tr>
</tbody>
</table>

**Biliary Clearance**

Thus far, we have considered drug metabolism to be the only mechanism by which drugs may be eliminated by the liver. There is, however, a second mechanism by which drugs may be removed by the liver: biliary excretion. Hepatic cells produce bile, which consists of water, bile salts, bile pigments, electrolytes, cholesterol, and fatty acids. Drugs with certain physicochemical properties (anions, cations, polar compounds)
may be excreted into bile. Drugs that undergo biliary excretion tend to be large (MW > 500 Da); metabolites excreted into bile may include glucuronide conjugates since glucose is a large, polar group. Most compounds that enter bile are substrates for active transporters, and do not move into bile via passive diffusion because they are too polar or charged to permeate cellular membranes.

Bile (and drug within the bile) accumulates in the gallbladder and is expressed into the intestine where it can either: 1) be excreted with feces or 2) be reabsorbed from the intestine back into blood. Reabsorption is an important mechanism by which bile salts can be reclaimed. This cycle of excretion into bile and reabsorption from the intestine into systemic blood is termed enterohepatic recycling. In the case of drug disposition, enterohepatic recycling can lead to small secondary peaks in the concentration-time profile.

For example, mycophenolate mofetil, an immunosuppressant, evidences a double peak after oral administration, as shown below. This drug is excreted into the bile and subsequently reabsorbed. This type of behavior can impact pharmacologic outcome by sustaining blood concentrations.

![Figure 9-8: Illustration of enterohepatic recycling resulting in a secondary peak.](image)

**Summary**

Hepatic clearance is a very important contributor to drug disposition. Metabolic clearance is the primary pathway of drug removal for most pharmacologic agents. The well-stirred model is a simplistic representation of the liver with respect to drug removal. Protein binding, hepatic blood flow and the intrinsic activity of metabolic enzymes all play an important role in determining bioavailability after oral administration, and systemic clearance. Drugs can be classified based upon the degree of extraction (low vs. high) on a single pass through the liver. Hepatic clearance for drugs that have low extraction ratios depends upon both
protein binding and intrinsic clearance, whereas for drugs which have high extraction ratios, clearance depends primarily upon the hepatic blood flow rate. When administered orally, the hepatic extraction ratio determines bioavailability. Drugs with a low extraction ratio have a bioavailability close to 1; drugs with a high extraction ratio have bioavailabilities that may approach zero. Although metabolism is the primary mode of drug removal by the liver, some drugs (and many conjugated metabolites) are excreted into bile and have the potential to undergo enterohepatic recycling.

Skills Obtained

- The ability to compare and contrast high and low extraction drugs based on the well-stirred model.
- Predicting changes in hepatic clearance, AUC and/or average steady-state concentrations for low and high extraction drugs based on changes in protein binding, intrinsic clearance or blood flow during IV and oral dosing.
- Deciding whether a change in protein binding would necessitate a dosage adjustment when the drug is administered orally or by the intravenous or any other non-oral route.

Summary Equations

Estimate the extraction ratio in the Well-Stirred Model

\[
E = \left( \frac{f_u \cdot CL_i}{Q_H + f_u \cdot CL_i} \right)
\]

Estimate hepatic clearance based on the Well-stirred model

\[
CL_H = Q_H \cdot \left( \frac{f_u \cdot CL_i}{Q_H + f_u \cdot CL_i} \right)
\]

Definition of bioavailability in reference to extraction ratio

\[
F = 1 - E
\]

Estimate bioavailability based on the Well-stirred model
# New Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Cl'$</td>
<td>Unbound Intrinsic Clearance</td>
<td>Intrinsic metabolic activity of enzymes in the absence of limitations imposed by blood flow rate and protein binding</td>
<td>Volume per time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intrinsic metabolic activity of enzymes in the absence of limitations imposed by blood flow</td>
<td>(e.g., L/h)</td>
</tr>
<tr>
<td>$Cl$</td>
<td>Intrinsic clearance</td>
<td></td>
<td>Volume per time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(e.g., L/h)</td>
</tr>
<tr>
<td>$E$</td>
<td>Extraction Ratio</td>
<td>The fraction of drug removed by the liver in a single pass through the liver. $E$ is a measure of the efficiency with which organ eliminates a drug</td>
<td>Unitless</td>
</tr>
</tbody>
</table>

$$ Cl' = f_u \cdot Cl'$$

$$ E = \frac{Cl}{Q_u} $$
10) Metabolite Kinetics

Goals

- To understand how drug disposition is impacted by hepatic clearance

Objectives

By the end of this chapter you should be able to:

- Discriminate between formation-limited and elimination-limited metabolite-time profiles
- Explain the importance of understanding the pharmacokinetics of metabolites

In Brief

The formation of drug metabolites is an important part of patient care because metabolites can have therapeutic activity or be toxic – not all metabolites are innocuous. Within this chapter we will touch on the rate of metabolite formation and elimination, and the differences in activity between a parent and metabolite profiles. We will differentiate between formation-limited – where the rate limiting step of the concentration-time profile is the formation of the metabolite – and the elimination-rate-limited – where the rate limiting step is concentration-time profile is the removal of metabolite from the system.

Introduction

The previous chapter dealt with the topic of metabolism in the context of hepatic elimination routes. Although some metabolites are simply the inactive products of elimination, this is not always the case. Metabolites can be also pharmacologically active, (e.g., prodrugs such as valcyclovir or lovastatin), produce toxicity (e.g., normeperidine), prolong pharmacologic activity (e.g., morphine-6-glucuronide), or alter the activity of other drugs by inhibit their activity or displacing them from their binding sites.

Consider the scheme below, which describes the process of metabolite formation following IV bolus administration of a drug.
Figure 10-1: Schematic representing metabolite formation after IV bolus administration. CLf is the formation clearance rate and CLm is the clearance rate of the metabolite.

This scheme appears similar to the scheme for extravascular administration presented earlier, but in this case, systemic clearance of the parent drug is achieved via metabolism, governed by the formation clearance rate (CLf). The metabolite, which has its own volume of distribution (VM), is in turn cleared by a process (e.g., biliary excretion, subsequent metabolism, or renal elimination) which is governed by a clearance rate, CLm. Before discussing the equations that describe this system, it is important to note several assumptions upon which this metabolism scheme is based. These assumptions are that the parent and metabolite each constitute a single pharmacokinetic compartment, the system is operating under linear conditions, there is no accumulation of drug in any clearing organ, and metabolism is not reversible. In addition, all amounts are expressed in molar units.

Thus, based upon the schematic and assumptions above, the rate of change in metabolite concentration (dCM/dt) can be described in terms of the process of formation of the metabolite from the parent (CLf*C) and the process of elimination of metabolite (CLm*C) according to the equation presented below.

\[ V \cdot \frac{dC_M}{dt} = CL_f \cdot C - CL_m \cdot C_M \]  

Equation 10-1

Once again, the concept of rate-limiting steps becomes important. What is the rate-limiting step (i.e., the slowest step) in the disposition of metabolite? Is the formation of metabolite slower than the elimination of metabolite or is the elimination of the metabolite slower than its formation? Either situation is possible. Generally, the metabolite concentration-time profile, following administration of the parent drug (in the current case, as an IV bolus dose), will be similar to one of the two profiles illustrated below.
The left panel illustrates formation rate limited disposition of a metabolite, which means that the rate of metabolite formation is much lower than the rate of metabolite elimination ($\text{CL}_f << \text{CL}_M$). Note that the terminal phase of the parent and metabolite disposition profile are parallel (the slopes are equal), reflecting the fact that the rates of clearance of the parent and metabolites are the same (essentially, elimination is so rapid that metabolite is cleared almost as soon as it is formed). This is a key feature of formation rate limited kinetics.

The right panel illustrates the elimination rate limited disposition of a metabolite, as occurs when $\text{CL}_M << \text{CL}_f$. In this case, the rate of metabolite elimination is much lower than the rate of metabolite formation. Thus, parent drug is eliminated relatively rapidly, but metabolite accumulates in the system. For this reason, the terminal portion of the metabolite’s disposition profile is not parallel to that of the parent drug; it reflects the slowest step in the metabolite disposition process, elimination.

Since in the case of formation rate limited metabolism, the apparent rate at which the metabolite is eliminated simply reflects the (slower) rate of formation from the parent compound, how can the actual metabolite elimination rate be determined? The graphs below illustrate the disposition profile of metabolites administered alone by IV bolus (solid lines), as well as the disposition profile of the same metabolite following administration of an IV bolus dose of parent compound alone (dashed lines).
Figure 10-3: Metabolite concentration-time profile after IV administration of the metabolite (solid line) and after administration of the parent (dashed line). The left and right panels illustrates formation rate limited and elimination rate limited metabolism, respectively.

When administering the metabolite directly, the observed half-life reflects the true elimination half-life. In the case of formation rate limited metabolism (left), the metabolite half-life (as reflected by the terminal phase of the disposition profile) is shorter after direct IV administration of the metabolite (vs. formation from IV-administered parent drug). This reflects the fact that the rate of formation of the metabolite from parent is the slower component of the disposition process. The panel on the right illustrates elimination rate limited metabolism. Note that the half-life (as reflected by the slope of the terminal phase of the disposition profile) is similar regardless of whether the metabolite was administered directly, or formed from parent, indicating that elimination is the rate limiting step in the disposition process.

Another way to describe the differences between these two types of metabolite disposition is to examine the ratio between the concentration of the metabolite \(C_M\) and the parent \(C_P\) during multiple dose administration. The relevant metabolite:parent ratio vs. time relationships are illustrated in the figures below.

Figure 10-4: Schematic of the metabolite / parent ratio during multiple dosing, under conditions of formation rate limited (left) and elimination rate limited (right) metabolism.
In the case of formation rate limited disposition, the metabolite is cleared almost as soon as it is formed. Thus, the metabolite to parent ratio very quickly becomes constant or time-independent (left). In the case of elimination rate limited disposition, the metabolite is eliminated slowly, accumulating in the system over time. Thus, the metabolite to parent ratio rises relatively slowly (reaches a constant value more slowly), and therefore can be considered time-dependent.

Table 10-1: Summary of metabolite kinetic concepts

<table>
<thead>
<tr>
<th>Rate Limiting Step</th>
<th>Formation-Limited</th>
<th>Elimination-Limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal Slope</td>
<td>Formation of Metabolite</td>
<td>Elimination of Metabolite</td>
</tr>
<tr>
<td>Shorter Half-life</td>
<td>Reflects CLf</td>
<td>Reflect CLM</td>
</tr>
<tr>
<td>Time-Dependent Formation</td>
<td>Metabolite</td>
<td>Parent</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Summary

Many metabolites can be pharmacologically active, or can influence the disposition or pharmacologic activity of other drugs. Thus, it is important to understand the principles underlying metabolite disposition kinetics. The two primary categories of metabolite disposition kinetics are distinguished based upon the slowest (rate-limiting) step in the disposition process; either the rate of formation of metabolite from parent (formation rate limited kinetics) or the rate of elimination of metabolite (elimination rate limited kinetics).

Skills Obtained

- The ability to differentiate between formation rate limited and elimination rate limited metabolites

New Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClM</td>
<td>Metabolite elimination clearance</td>
<td>The volume of blood from which metabolite is completely and irreversibly cleared, per unit time</td>
<td>Volume per time (e.g., L/h)</td>
</tr>
<tr>
<td>ClF</td>
<td>Metabolite formation clearance</td>
<td>The volume of blood from which parent is completely and irreversibly converted to metabolite, per unit time</td>
<td>Volume per time (e.g., L/h)</td>
</tr>
</tbody>
</table>
11) Renal Clearance

Goals

- To understand the principles which dictate clearance of a drug from the body via the kidney

Objectives

By the end of this chapter you should be able to:

- Explain the role of the kidney in drug elimination
- Determine, based upon pharmacokinetic data, whether a drug is filtered, secreted or reabsorbed in the kidney
- Describe the factors that impact filtration, secretion and reabsorption processes in the kidney
- Estimate renal clearance based upon pharmacokinetic data
- Calculate the rate of creatinine clearance using the Cockroft-Gault equation

In Brief

In this chapter we discuss another important organ for the elimination of drug, the kidney and renal clearance. We will discuss the three major processes of filtration, reabsorption, and active tubular secretion which will determine the excretion rate and clearance of a drug. These factors can be determined if we know the drug’s protein binding, the kidneys normal filtration rate, and the drug’s renal clearance – the volume of drug removed unchanged per unit time by the kidney. We will discuss some basic methods for calculating a drug’s renal clearance by using both urinary data and blood or plasma data.

Introduction

As stated earlier, the two organs responsible for the majority of drug elimination from the body are the liver and the kidney. Renal clearance processes, which are generally lower in efficiency than hepatic clearance processes, reflect the net movement of drug and metabolites from blood into urine via four types of mechanisms. These mechanisms include glomerular filtration (whereby unbound substrate is eliminated passively), active tubular secretion (an energy-dependent, saturable process by which drug is transferred from blood into urine), tubular reabsorption (movement of substrate back into blood from urine) and me-
The impact of metabolism, however, is often ignored, because of its very minor contribution to renal drug clearance.

Some standard parameter values which thus bear on renal clearance processes include the rate of blood flow to the kidney (60 L/h; ~20% of cardiac output or 1000 mL/min), the glomerular filtration rate (GFR; 7.5 L/h or 125 mL/min) and the rate of urine flow (typically is 1-2 mL/min). T

The figure below illustrates the three major mechanisms by which a drug or drug metabolite may be cleared from the body by the kidney.

![Potential pathways by which a drug may be cleared by the kidney. Drug can be filtered, secreted or reabsorbed. A: unbound drug, AP: bound drug, A +/- : ionized drug.]

Note that protein-bound drug (AP) in blood cannot enter the renal tubule. Only unbound drug (A) can enter the tubule from blood, either passively through the process of glomerular filtration or via active tubular secretion. Once unbound drug enters the tubule it may move into the urine or undergo tubular reabsorption back into the blood. The extent to which a drug will be reabsorbed depends primarily upon whether drug is ionized.

**Filtration**

There are two mechanisms by which drug can enter the urine. One mechanism is filtration and the other is secretion. Solutes in blood are passively filtered through the glomerulus, with hydrostatic pressure constituting the primary driving force for this passive movement. The rate at which solute is filtered through the glomerulus depends upon 1) the mass of the molecule, 2) the number of functional nephrons, 3) the rate of plasma flow, and 4) the extent of protein binding. Small molecules
(MW ≤ 500 Da) can undergo glomerular filtration, however, large molecules (MW ≥ 60,000 Da; the mass of albumin and other plasma proteins) cannot, as they are too large to enter the glomerulus. Only unbound drug is filtered, again, because proteins are typically too large to enter the glomerulus (the presence of protein in urine is usually an indicator of kidney damage). Kidney disease may alter the number of functional nephrons, thus, disease could contribute to a reduction in the glomerular filtration rate.

Figure 11-2: Passive filtration of a drug: hydrostatic pressure drives unbound drug into the renal tubule through the glomerulus

The rate at which a substrate will undergo filtration is typically calculated based upon the rate of creatinine clearance (see below in “Assessment of Renal Function”). This filtration rate is a function of the degree to which the drug is protein-bound, the GFR, and the plasma concentration of drug, as defined below:

\[
\text{Rate of filtration} = \text{GFR} \times f_u \times C
\]

Equation 11-1

If a drug is eliminated only by filtration, then renal clearance (CL\text{REN}) is equal to the product of the unbound fraction (f_u) of drug and GFR. Recall that only unbound drug can be filtered. Renal clearance can be obtained by dividing the rate of filtration by the driving force concentration:

\[
\text{Cl}_{\text{REN}} = \text{GFR} \times f_u
\]

Equation 11-2

If a drug undergoes filtration only (no secretion, reabsorption or metabolism), its renal clearance is proportional to GFR, with f_u as the proportionality factor.

If filtration was the only process mediated by the kidney, how much urine would we produce in one day? Since GFR is 7.5 L/h, the volume produced over 24 h would be 180 L per day! Luckily, because of the reabsorption of much of the water and salt in the urine, the actual volume of urine produced in one day is approximately 1-1.5 L/d. The process of reabsorption not only determines the volume of urine eliminated each
day, but also can affect the chemical composition of urine (including the urinary concentration of drugs and metabolites).

**Reabsorption: Active and Passive**

Reabsorption can occur as either a passive or an active process. Diuretics exert their pharmacologic effect by impacting these reabsorption processes. Osmotic diuretics, such as mannitol, minimize passive reabsorption of water and salts by maintaining high osmotic pressure in the tubules. Thiazide, a loop diuretic, impacts active reabsorption processes, resulting in increased elimination of water.

![Figure 11-3: Drug can be reabsorbed after entering the renal tubule.](image)

Consider a drug that enters the tubule via filtration, and subsequently is reabsorbed into the blood (reabsorption thus reduces the mass of drug in the tubule). The renal clearance of this drug will be lower than the renal clearance of a drug that undergoes filtration alone. Although filtration moves drug into the kidney tubule, reabsorption returns drug to the blood. Thus, the amount of drug cleared from the body in urine is lower than the amount that was filtered:

\[ C_{\text{REN}} < f_U \times GFR \]  
*Equation 11-3*

If a drug undergoes complete reabsorption, then renal clearance will approach the rate of urine flow. The flow of urine hinders reabsorption by shortening the contact time required for drug to diffuse back into blood. Thus, if urine flow increases, renal clearance would increase due to the reduced time available for reabsorption to occur.

\[ f_U \times GFR > C_{\text{REN}} > f_U \times Q_U \]  
*Equation 11-4*

Normally, most nutrients are not present in the urine (or are only present in trace amounts). For example, glucose undergoes filtration, but subsequently is fully reabsorbed, thus, healthy individuals do not have glucose in their urine. Diabetics, on the other hand, have so much glu-
cose in the blood (and thus in the urine), that not all of it can be reab-
sorbed. Glucose in the urine is a positive indicator of diabetes. Certain
nutrient (such as glucose) are reabsorbed by active processes. Most
drugs, however, tend to be reabsorbed passively.

Passive reabsorption is dependent upon 1) urine pH (as ionized mole-
cules will not be passively reabsorbed), 2) the pKa of the drug, 3) the
rate of urine flow, and 4) the octanol:water partition coefficient (log P) of
the drug. Ionized drugs have a difficult time passing through membranes
compared to their non-ionized counterparts.

For example, in the case of a drug that is a weak acid (i.e., anions), re-
absorption increases as the pH of the urine decreases (i.e., the more
unionized drug we produce).

Urine flow can be increased in a number of ways, including by consump-
tion of ethanol, caffeine, or large volumes of fluid. Increased urine flow
can cause an increase in renal clearance due to reduced drug reabsorp-
tion. Increases in urine flow decrease the contact time of the drug with
the tubule, thus reducing the opportunity for reabsorption and increasing
the amount of drug which is eliminated from the body in urine.

![Figure 11-4: The impact of pH on the ionization of weak acids and
weak bases. Ionized drug will be reabsorbed at a low rate, or not at all.
Thus, changes in urinary pH can impact renal clearance.](image)

As indicated in the figure above, as pH decreases, the concentration of
hydrogen ions (H\(^+\)) also increases. Acids are negatively charged at
physiologic pH and will thus associate with hydrogen ions as pH de-
creases and will become uncharged. Conversely, bases are uncharged
at physiologic pH, so as pH decreases, bases will accept ions and thus
become positively charged. Charged molecules do not readily penetrate
physiologic membranes, thus, these molecules will tend to remain in
urine. Any factor that alters the pH of the urine can thus potentially also
alter the clearance of drugs.
**Active Tubular Secretion**

As discussed earlier, drug can enter the renal tubule either through filtration or secretion. Secretion of drugs is an active process dependent on transporters. For example, p-aminohippurate (PAH) is used to estimate renal blood flow because it is actively transported and exhibits essentially no protein binding (it is one of the few examples of a compound evidencing a high extraction ratio across the kidney). Secretion is a capacity-limited process that may become saturated at high concentrations of drug. Renal clearance for a drug that is secreted is greater than the renal clearance for a drug that is only filtered:

\[ \text{Cl}_{\text{REN}} > f_u \cdot \text{GFR} \]  

Equation 11-5

![Figure 11-5: Certain drugs undergo both secretion and filtration.](image)

Note that drugs that undergo secretion cannot have a clearance rate higher than the rate of renal blood flow. Because secretion is an active process, it is subject to potential drug interactions. In the case of two compounds that are competitive substrates for the same transporter (a situation analogous to the competition of two drugs for the same metabolizing enzyme), there is potential for one compound to reduce the secretion rate of the other compound. For example, digoxin and quinidine are competitive substrates for the same transporter. Thus digoxin clearance is reduced when co-administered with quinidine. Many of the same factors that influence hepatic disposition according to the well-stirred model also influence the process of active tubular secretion. These factors include 1) blood flow, 2) protein binding, and 3) the intrinsic activity of the transporter (i.e., intrinsic clearance). The digoxin-quinidine interaction essentially lowers the intrinsic clearance of both drugs.

Thus, the rate of drug excretion is dependent upon all three renal clearance processes in the manner indicated below:

\[ \text{rate of excretion} = (1 - F_R) \cdot (\text{rate of filtration} + \text{rate of secretion}) \]
where $F_R$ is the fraction of drug reabsorbed, and the rate of filtration is the product of GFR and the concentration of drug in urine ($C_U$)

\[
\text{rate of filtration} = \text{GFR} \cdot C_U
\]

Or

\[
\text{rate of filtration} = \text{GFR} \cdot C \cdot f_U
\]

When the rate of excretion ($\text{CL}_{\text{REN}} \cdot C$) exceeds the rate of filtration ($f_U \cdot \text{GFR} \cdot C$) or when $\text{CL}_{\text{REN}} > f_U \cdot \text{GFR}$, it can be inferred that the drug is subject to secretion. When $\text{CL}_{\text{REN}} < f_U \cdot \text{GFR}$, it can be inferred that the primary mechanism for clearance of the drug is reabsorption.

**Example:** The following information was gathered upon administration of drugs X, Y and Z to a patient, and each drug were eliminated by the kidney only.

<table>
<thead>
<tr>
<th></th>
<th>$f_U$</th>
<th>$\text{CL}_{\text{REN}}$ (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug X</td>
<td>0.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Drug Y</td>
<td>0.05</td>
<td>11.5</td>
</tr>
<tr>
<td>Drug Z</td>
<td>0.2</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Assuming that the GFR is 115 mL/min, identify whether each drug is predominantly filtered, reabsorbed, or secreted.

<table>
<thead>
<tr>
<th>$f_U$</th>
<th>$\text{CL}_{\text{REN}}$ (mL/min)</th>
<th>$f_U \cdot \text{GFR}$ (mL/min)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug X</td>
<td>0.1</td>
<td>11.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Drug Y</td>
<td>0.05</td>
<td>11.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Drug Z</td>
<td>0.2</td>
<td>11.5</td>
<td>23</td>
</tr>
</tbody>
</table>

Renal clearance would equal $f_U \cdot \text{GFR}$ if filtration were the only process determining the rate of urinary excretion. If $\text{CL}_{\text{REN}}$ exceeds $f_U \cdot \text{GFR}$, secretion must contribute to flux of drug from blood into urine. If $\text{CL}_{\text{REN}}$ is less than $f_U \cdot \text{GFR}$, reabsorption of drug from the urine into blood must be occurring.

**Fun Fact:** Athletes use "masking agents" like probenicid to reduce the secretion of various organic anions, like steroid metabolites, thus reducing urine concentration and passing drug tests!
Based upon the following graphs, determine whether each drug is predominantly filtered, reabsorbed, or secreted.

**Graph 1: Impact of renal blood flow**

Based upon the above graph:

Drug A is filtered. As blood flow increases, renal clearance approaches the GFR (but will not exceed the GFR).

Drug B is secreted, as indicated by a rate of renal clearance that exceeds the GFR, and by the fact that as blood flow increases, renal clearance increases.

Drug C is reabsorbed, as indicated by a rate of renal clearance that is lower than the GFR and a lack of influence of renal blood flow.

Note: In this example, it is assumed that $f_U$ is 1 and $Q_U$ is constant.
Graph 2: Impact of urine flow

Based upon the above graph:

Drug A is filtered, because a change in urine flow does not impact the renal clearance.

Drug B is secreted, as indicated by a rate of renal clearance which exceeds the GFR, and the fact that renal clearance is unaffected by urine flow.

Drug C is reabsorbed, as indicated by a renal clearance rate below the GFR and by the increase in renal clearance with increasing urine flow.

Note: In this example, it is assumed that $f_U = 1$, and $Q_{REN}$ is constant.
Based upon the above graph:

Drug A is filtered because as the unbound fraction increases, renal clearance increases until it approaches the GFR (recall that only unbound drug can be filtered).

Drug B must be secreted, because its renal clearance can exceed the GFR and because a positive relationship exists between the fraction of unbound drug and renal clearance (recall that only unbound drug can interact with transporters).

Drug C is reabsorbed, as indicated by a renal clearance below the GFR.

The table below summarizes factors that indicate the major mechanism of renal elimination, in terms of the relationships between actual renal clearance (CL\textsubscript{DRUG}), the GFR and urine flow (Q\textsubscript{U}).
### Table 11-1: Summary of determining if a drug is predominantly filtered, reabsorbed or secreted.

<table>
<thead>
<tr>
<th>Clearance Ratio</th>
<th>Predominant Mechanism</th>
<th>Impacted by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\frac{C_l_{DRUG}}{f_u \cdot GFR}$ = 1</td>
<td>Filtration</td>
<td>1. Protein binding&lt;br&gt;2. Molecular size&lt;br&gt;3. Nephron function&lt;br&gt;4. Renal blood flow</td>
</tr>
<tr>
<td>$\frac{C_l_{DRUG}}{f_u \cdot GFR}$ &lt; 1</td>
<td>Reabsorption (partial)</td>
<td>1. Urine pH&lt;br&gt;2. Drug pKa&lt;br&gt;3. Urine flow&lt;br&gt;4. Drug lipophilicity</td>
</tr>
<tr>
<td>$\frac{C_l_{DRUG}}{f_u \cdot Q_u}$ = 1</td>
<td>Reabsorption (complete)</td>
<td>1. Renal blood flow&lt;br&gt;2. Protein binding&lt;br&gt;3. Intrinsic transporter activity</td>
</tr>
<tr>
<td>$\frac{C_l_{DRUG}}{f_u \cdot GFR}$ &gt; 1</td>
<td>Secretion</td>
<td></td>
</tr>
</tbody>
</table>

---

**Assessing Renal Function**

Typically, a patient’s GFR is assessed by determining the rate of creatinine clearance. This value is calculated based upon the Cockcroft-Gault equation:

\[
CL_{CR} = \frac{(140 - \text{Age}) \cdot \text{IBW}}{72 \cdot \text{SCr}} \text{ for males}
\]

\[
CL_{CR} = \left(\frac{(140 - \text{Age}) \cdot \text{IBW}}{72 \cdot \text{SCr}}\right) \cdot 0.85 \text{ for females}
\]

where age is the patient’s age (in years), IBW is ideal body weight (in kg) and SCr is serum creatinine (in mg/dL). Creatinine is used as an indicator of the filtration rate (and kidney function) because it does not bind to proteins ($f_u = 1$), it is not secreted (or minimally secreted), and is not reabsorbed by the kidney. Thus its elimination is reflective of filtration processes only. Creatinine is a degradation product of creatine. Nearly all of the creatine in the body is located in muscle where it used in energy metabolism. IBW is proportional to muscle mass, and hence, is also indicative of creatine reserves. Individuals with more muscle have larger stores of creatine, and thus produce more creatinine. With age, a decrease in renal function and an increase in the break down of

---

FYI: The Crockcroft-Gault equation was derived based upon data from 200 male patients. The female equation was based on theoretical and historical considerations rather than direct observation. Other equations exist for estimating GFR via serum creatinine (i.e., Mawer, Jellife, Wagner etc.).
muscles contribute to an increase in serum creatinine. Hence, age is incorporated into the above equation. One benefit of using creatinine clearance as an index of the GFR is that since creatinine is an endogenous compound, it is not necessary to administer any exogenous substrate in order to measure renal function. Renal function can also be determined by administration of an agent such as inulin, which is a non-degradable sugar that exhibits no protein binding, and is not reabsorbed or secreted by kidney (like creatinine). Below is a table that compares various methods for assessing renal function and GFR.

Renal blood flow can be assessed with p-aminohippurate (PAH) because this compound exhibits little protein binding and is actively secreted. PAH is essentially a high extraction drug for renal secretion, in that its clearance is dependent on renal blood flow ($Q_{REN}$).

**Gathering Information from Excretion Data**

Below are four mathematical methods that can be used to determine the renal clearance of a compound.

**Method 1: Urine Excretion Rate vs. Blood Concentration**

This first method relates the rate of excretion ($\Delta X_u/\Delta t$) to the plasma (or blood) concentrations. In the equation below, $X_U$ is the mass of drug that is excreted from the body, unchanged, in the urine, $CL_{REN}$ is the renal clearance and $C$ is the plasma drug concentration.

\[
\left( \frac{dX_U}{dt} \right) = CL_{REN} \cdot C \quad \text{Equation 11-6}
\]

Therefore, $CL_R$ can be approximated by:

\[
CL_{REN} = \frac{C_U \cdot Q_U}{C}
\]

or
where \( C_U \) is the drug concentration in urine, \( Q_U \) is urine flow and \( C \) is the concentration of drug in plasma. Drug concentration in the blood is the driving force for the rate of excretion (recall that this is a first-order process). Imagine that it is Halloween and your house is full of candy. Candy in your house (analogous to drug in the blood) is the driving force for the process of candy consumption (analogous to the process of excretion). The amount of candy inside your house, governs the amount of candy that you will consume. If you have no candy in the house, you would eat no candy. If you have a little bit of candy, you would eat a little bit of candy. If you have a lot of candy, you would eat a lot of candy.

In the following equations describing renal clearance, blood concentration (the driving force for renal excretion) is determined either by sampling at the mid-point of the urine collection period \( (C_{\text{MID}}) \) or by averaging the blood concentrations over the entire urine collection interval \( (C_{\text{SS}}) \). Typically, use of \( C_{\text{SS}} \) provides the best estimation of \( CL_{\text{REN}} \).

\[
CL_{\text{REN}} = \frac{\left( \frac{dX_U}{dt} \right)}{C} \quad \text{or} \quad CL_{\text{REN}} = \frac{\left( \frac{dX_U}{dt} \right)}{C_{\text{SS}}} \quad \text{Equation 11-7}
\]

\( C_{\text{SS}} \) is defined as the AUC in blood during the urine collection period, divided by the time of collection. This is, in essence, a way to average the drug concentrations over time.

\[
C_{\text{ss}} = \frac{\text{AUC}}{t}
\]

As illustrated in the graph below, the relationship between \( C_{\text{mid}} \) (or \( C_{\text{SS}} \)) and the urine excretion rate is linear, with a slope equal to \( CL_{\text{REN}} \). A change in \( CL_{\text{REN}} \), as might occur in the case of renal dysfunction, will alter the slope of the line.
The major limitation associated with this method is with respect to the collection interval. Ideally the urine collection interval should be $\leq t_{1/2}$. In clinical studies, a practical lower limit to the urinary collection interval is ~2 h. For drugs with a half-life less than 2 h, application of this method is problematic. In this case, an alternative method should be used to estimate $CL_{REN}$.

Example: To obtain a rough estimate of renal clearance, urine was collected over the course of hours 2 through 4 after an IV bolus dose. The urine collected contained 10 mg of drug. A blood sample collected at the midpoint of the urine collection interval (3 h) revealed a blood concentration of 1 mg/L. What is the renal clearance of this drug?

$$
Cl_{REN} = \frac{\frac{dX_U}{dt}}{C_{MID}} = \frac{10 \text{ mg}}{2 \text{ h} \times 1 \text{ mg/L}} = 5 \text{ L/h}
$$

Method 2: Amount Excreted in Urine vs. AUC

A second method for determining renal clearance is related to the above equation, and similar to the systemic clearance equation which is calculated based upon dose and AUC. This equation, presented below, relates the amount of drug excreted in the urine to the AUC in the blood.

$$
Cl_{REN} = \frac{X_U}{AUC} \quad \text{Equation 11-8}
$$

The graphical relationship between AUC and $X_U$ will be linear, with a slope equal to $CL_R$, as illustrated below.
Figure 11-7: Relationship between AUC and the amount of drug excreted unchanged in the urine. The slope of the line indicates renal clearance.

Note that with this method, the urine collection interval will not be problematic.

**Example:** To obtain a rough estimate of renal clearance, urine was collected over the course of hour 2 through 4 after an IV bolus dose. The mass of drug in the urine was 10 mg. Blood samples, collected at 2 h and again at 4 h, had concentrations of 2 and 1 mg/L, respectively. What is the renal clearance of this drug?

\[
Cl_{\text{REN}} = \frac{X_U}{AUC} = \frac{X_U}{(C_1 + C_2) \cdot 1/2 \cdot (t_2 - t_1)} = \frac{10\text{mg}}{(2 + 1) \cdot 1/2 \cdot (4 - 2)} = 3.3\text{ L/h}
\]

**Method 3: Fractional Clearance**

The next two methods for determining renal clearance also involve measurement of the amount of drug excreted in the urine, however, these methods require recovery of the entire amount of drug excreted. This requirement is potentially problematic for drugs with long half-lives. Recall that it takes ~5 half-lives for an entire (~98%) dose of drug to be eliminated.

This third method determines renal clearance based upon the fraction of the total systemic clearance that is contributed by renal elimination processes (\(F_{\text{REN}}\)).

\[
Cl_{\text{REN}} = F_{\text{REN}} \cdot Cl
\]

**Equation 11-9**
The fraction of the total systemic clearance contributed by renal elimination is, in turn, calculated as the ratio of the mass of drug eliminated unchanged in the urine \((X_u)\) to the mass of drug that was initially administered to the system \((X_0)\). Therefore:

\[
F_{\text{REN}} = \frac{X_u}{X_0}
\]

**Example:** A 100 mg dose of drug was administered as an IV bolus. 25 mg of drug was excreted unchanged in the urine and 75 mg of drug was excreted as metabolite in the urine. The AUC was 5 mg\(\cdot\)h/L. What is the renal clearance of this drug?

\[
\text{Cl} = \frac{X_0}{\text{AUC}} = \frac{100\text{mg}}{5\text{mg}\cdot\text{h}/\text{L}} = 20\text{L}/\text{h}
\]

\[
\text{Cl}_{\text{REN}} = F_{\text{REN}} \cdot \text{Cl} = \frac{X_u}{X_0} \cdot \text{Cl}
\]

\[
\text{Cl}_{\text{REN}} = \frac{25\text{mg}}{100\text{mg}} \cdot 20\text{L}/\text{h} = 5\text{L}/\text{h}
\]

**Method 4: Amount remaining to be excreted**

The fourth method for calculating renal clearance utilizes the concept of approach to steady-state (analogous to the estimation of \(K_f\) in association with steady-state infusions). In this case, calculations are based upon the amount of drug remaining to be excreted. For a drug which is eliminated by the kidney, at \(t=0\) there is no drug in the urine and at \(t = \infty\) some fraction of the dose will have been excreted into the urine (recall that \(F_{\text{REN}}X_0 = X_{U, \infty}\)). A graph of the cumulative amount of drug in the urine over time will look very similar to the concentration-time profile associated with an IV infusion, with an asymptotic approach to \(X_{U, \infty}\).
The equation describing the cumulative mass-time relationship is very similar to the equation describing the change in blood concentration associated with infusion administration.

\[ X_U = X_U^\infty \cdot \left(1 - e^{-kRt}\right) \]  

Equation 11-10

where \( X_U \) is the cumulative amount of drug which has been excreted into the urine at time = t, \( X_U^\infty \) is the total amount of drug that will eventually be excreted into urine, and \( k \) is the first-order rate constant for elimination (CLR/V = kR). The next step in this approach is to manipulate the above equation to invert the cumulative excretion profile (this will result in a profile similar to the concentration-time profile associated with an IV bolus dose). The rationale behind this inversion step is that on semi-log coordinates, this inverted profile will appear as a straight line from which half-life can easily be determined. To invert this profile, multiply the right side of the equation through by \( X_U^\infty \) and rearrange:

\[ (X_U^\infty - X_U) = X_U^\infty e^{-kRt} \]

On semilog coordinates, the graphical relationship between the mass of drug remaining to be excreted \( (X_U^\infty - X_U) \) and time is linear, and the slope of the line is equal to \( K_R \) (the renal contribution to K). K, like systemic clearance, reflects the sum of many individual processes. Thus, K = \( K_R + K_H \), where the R and H subscripts indicate renal and hepatic processes.
One limitation to this approach for calculating renal clearance is that it requires an accurate estimate of the mass of drug which will be eventually eliminated in the urine. If $X_{U,\infty}$ is estimated incorrectly, the resulting value of $CL_R$ will be erroneous. When the value of $X_{U,\infty}$ cannot be estimated accurately, an alternative method (e.g., the rate of excretion method) may be more useful.

Example: A 100 mg dose of drug was administered as an IV bolus. Urine was collected over the course of 24 h. What is the $K_{REN}$ of this drug?

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>$X_u$ (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>23.6</td>
</tr>
<tr>
<td>4</td>
<td>37.9</td>
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<td>6</td>
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</tr>
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<td>16</td>
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</tr>
<tr>
<td>24</td>
<td>59.8</td>
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</tbody>
</table>

Step 1) Graph the mass of drug excreted in the urine vs. time in order to estimate $X_{U,\infty}$.
In this case, $X_{U,\infty}$ is approximately 60 mg

**Step 2)** Calculate $X_{U,\infty} - X_U$

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>$X_u$ (mg)</th>
<th>$X_{U,\infty} - X_U$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>23.6</td>
<td>36.4</td>
</tr>
<tr>
<td>4</td>
<td>37.9</td>
<td>22.1</td>
</tr>
<tr>
<td>6</td>
<td>46.6</td>
<td>13.3</td>
</tr>
<tr>
<td>8</td>
<td>51.8</td>
<td>8.2</td>
</tr>
<tr>
<td>10</td>
<td>55.1</td>
<td>4.9</td>
</tr>
<tr>
<td>12</td>
<td>57.0</td>
<td>3.0</td>
</tr>
<tr>
<td>16</td>
<td>58.9</td>
<td>1.1</td>
</tr>
<tr>
<td>24</td>
<td>59.8</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Step 3)** Graph $X_{U,\infty} - X_U$ versus time

**Step 4)** Estimate $K$ from the graph:

Since $t_{1/2}$ is $\sim 2.5$ h, $K = 0.28$ h$^{-1}$

**Step 5)** Estimate $F_{REN}$
\[ F_{\text{REN}} = \frac{X_u}{X_0} = \frac{60\text{mg}}{100\text{mg}} = 0.60 \]

Step 6) Estimate \( K_{\text{REN}} \)

\[ K_{\text{REN}} = F_{\text{REN}} \cdot K = 0.17 \]

**Summary**

The kidney plays an important role in the elimination of drugs. Drugs can enter the kidney tubule by passive filtration or active secretion. Some drugs (depending on characteristics such as lipophilicity, charge, or the degree to which it is a substrate for active transport), can be reabsorbed back into the blood from the tubule. It is possible to determine which of these mechanisms predominates in the renal elimination of a given drug by comparing the actual renal clearance to a reference clearance value which reflects the contribution of the filtration process only. Renal clearance can be estimated via several different approaches, based upon a combination of urine and blood data. Most commonly, renal clearance is estimated based upon the mass of drug excreted and the AUC in blood, or based upon the rate of drug excretion into urine and blood concentration.

**Skills Obtained**

- Predicting the predominant mechanism of renal elimination based upon protein binding and renal clearance
  - Drug X has an \( f_u = 0.5 \) and \( CL_R = 125 \text{ ml/min} \), what is the predominant mechanism of renal elimination? (secretion)
- Describing the factors which impact mechanisms of renal elimination
  - See summary chart
- Estimating renal clearance from excretion rate data
  - Over a 2 h interval, the urinary excretion rate is 50 mg/h and the average blood concentration is 5 mg/L. What is the renal clearance? (10 L/h)
- Estimating renal clearance based upon the amount of drug excreted and blood concentrations or systemic clearance information
  - Following a dose of 100 mg, 25 mg of drug appear unchanged in the urine. If \( CL = 45 \text{ L/h} \), what is the \( CL_R \)? (11.3 L/h)
- Estimating renal clearance based upon the mass of drug remaining to be excreted
**Summary Equations**

Estimate renal clearance based on excretion rate

\[
CL_{\text{REN}} = \frac{\left( \frac{dT}{dX} \right)}{C_{\text{MID}}}
\]

Estimate renal clearance based on amount excreted

\[
CI_R = \frac{X_U}{AUC}
\]

Estimate renal clearance based on fractional clearance

\[
CI_{\text{REN}} = F_{\text{REN}} \cdot CI \quad \text{with} \quad F_{\text{REN}} = \frac{X_U}{X_0}
\]

Estimate renal clearance based on amount remaining to excrete

\[
\left( X^\infty_U - X_U \right) = X^\infty_U e^{-K_{\text{REN}}t}
\]

**New Symbols**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
<td>Volume of fluid filtered by the kidney over a given period of time (normal values range from 115 to 135 mL/min)</td>
<td>Volume per time (e.g., L/h)</td>
</tr>
<tr>
<td>CL_R</td>
<td>Renal clearance</td>
<td>Volume of blood completely and irreversibly cleared of drug by the kidney per unit time</td>
<td>Volume per time (e.g., L/h)</td>
</tr>
<tr>
<td>X_U</td>
<td>Mass of drug excreted unchanged in the urine</td>
<td>Amount of drug excreted unchanged in the urine</td>
<td>Mass (e.g., mg)</td>
</tr>
<tr>
<td>X^\infty_U</td>
<td>Total mass of drug excreted unchanged in the urine</td>
<td>Amount of drug excreted by the kidney unchanged over infinite time</td>
<td>Mass (e.g., mg)</td>
</tr>
</tbody>
</table>
12) Multi-Compartment Models

**Goal**

- To describe the principles underlying multi-compartment pharmacokinetic behavior, and to introduce terminology associated with multi-compartment models.

**Objective**

*By the end of this chapter, you should be able to:*

- Describe the components of a two-compartment model scheme
- Select appropriate data points and use them to calculate the terminal half-life of a drug which exhibits multi-compartment disposition
- Explain the consequences of using $V_C$ vs. $V_{SS}$ to calculate a loading dose.
- Define and properly use the following terms: alpha ($\alpha$) and beta ($\beta$) phase, $V_C$; $V_{SS}$, and distributional equilibrium

**In Brief**

Up to now we assumed drug instantaneously distributes throughout the body – that is, the one-compartment model. Now, we will violate that assumption and introduce the multi-compartment model where drug can distribution at different rates within the body. We will introduce two new volume terms, the volume of the central compartment and the steady-state volume of distribution and new rate constants for the distribution phase and the elimination phase. Finally, we will discuss how multi-compartment behavior affect drug dosing in a clinical setting and how we monitor these drugs with respect to blood sampling during therapeutic drug monitoring.

**Introduction**

All of the concepts introduced up to this point have been presented in the context of the one-compartment pharmacokinetic model. The fundamental assumption of this model is that the entire body behaves as a kinetically homogeneous unit, that is, that drug equilibrates instantaneously with all of the tissues of the body. This simplistic model provides a reasonably accurate description of the behavior of some drugs. For other drugs, however, the rates of drug distribution into various tissues spaces of the body are so different that a one-compartment model cannot accurately describe the behavior of the drug in the body.

**Reasons for Distributional Behavior**

- Tissue blood flow (highly vs. poorly perfused)
- Properties of the drug
- Protein Binding
- Cell membrane characteristics
Several factors can result in differential rates of drug distribution into various organs or tissue spaces. These include the rate of blood flow and the physicochemical composition of the organ or tissue, the physicochemical properties of the drug, the extent of protein binding in an organ or tissue, and the properties of various types of cell membranes (see the Distribution chapter). The shape of the blood concentration-time profile will reflect the influence of differential rates of drug distribution into various tissue spaces in the body. Thus, in order to describe this type of drug distribution behavior, it is necessary to represent the body with a multi-compartment model.

As with the one-compartment model, compartments do not necessarily correspond to specific organs or tissues. Instead, a given compartment represents all of the tissue spaces in which drug equilibrates at a similar rate, and to a similar extent. For example, drug generally equilibrates very rapidly and extensively in blood; thus, one compartment might include blood as well as any other well-perfused tissues with high rates of blood flow. Tissue spaces which are poorly-perfused (e.g., bone) would be represented as a distinct pharmacokinetic compartment. Note that if the fraction of drug distributing into a given tissue space is very low, the effect of this tissue space on overall disposition is generally ignored.

One- and two-compartment pharmacokinetic systems are contrasted below in terms of their structural representation and typical blood concentration-time profiles. As the equations associated with multiple compartment models can become somewhat complex, this chapter will focus on the conceptual, rather than the mathematical principles underlying multiple compartment behavior.
In the two-compartment model, one compartment, termed the central compartment, represents the blood (and any other tissues in which the drug equilibrates rapidly). The apparent volume of distribution for drug in this compartment is termed $V_C$. The second compartment, termed the peripheral compartment, represents other tissue spaces, distinct from the central compartment in terms of the rate and / or extent of drug equilibration. The apparent volume of distribution for drug in this compartment is symbolized as $V_P$. In the schematic above, drug, which is administered into the central compartment, can be eliminated from the central compartment (via a systemic clearance process, termed, CL) and it can distribute into the peripheral compartment (via a process governed by the first-order rate constant $k_{12}$). Whereas systemic clearance from the central compartment (CL) is irreversible, drug is free to distribute between the central and peripheral compartments. The first-order rate constant governing movement of drug from the peripheral to the central compartment is termed $k_{21}$. Note that the subscripts identify the direction of movement (with the central and peripheral compartments being numbered 1 and 2, respectively, $k_{12}$ indicates movement from the central to peripheral compartment).

**alpha ($\alpha$) = distribution phase**

**beta ($\beta$) = elimination phase**

$\alpha > \beta$
Drug will move out of the central compartment via systemic elimination as well as by distribution into the peripheral compartment. Since the driving force for drug movement out of the central compartment (i.e., central compartment concentration) is greatest immediately upon administration (in the case of an IV bolus dose), an initial, relatively rapid decline in plasma concentrations will be observed. As the driving force for movement out of the central compartment (the central compartment concentration) declines, and the driving force for movement of drug from the peripheral compartment into the central compartment (the peripheral compartment concentration) rises, the rate of decline of plasma concentrations will decrease.

These two portions of the blood concentration-time profile are termed the alpha ($\alpha$) phase (the steep initial decline in blood concentration) and the beta ($\beta$) phase (the slower subsequent decline in blood concentration). The alpha phase will always be faster than the elimination or beta ($\beta$) phase. During the alpha phase (also termed the distribution phase), both distribution (i.e., between the central and peripheral compartments) and elimination (i.e., systemic clearance from the central compartment) processes contribute to the overall rate of change in concentrations in the central compartment. During the beta phase, (also termed the elimination phase) the rates of movement of drug between the central and peripheral compartments will finally become equal (i.e., distributional equilibrium), so the only process contributing to net movement of drug out of the central compartment will be systemic clearance. Note that the net distribution of drug from the central into the peripheral compartment is sometimes described in terms of the half-life of this process (distributional half-life), which is simply calculated as $0.693/\alpha$.

Mathematically, the two-compartment model is described by:

$$C = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}$$  \hspace{1cm} \text{Equation 12-1}$$

where $A$, $B$, $\alpha$, and $\beta$ represent complex expressions that include $X_0$, $V_C$, CL, and the rate constants that govern distribution between the central and peripheral compartments ($k_{12}$ and $k_{21}$). As in the case of the one-compartment model, a key assumption is that all processes are first-order and the system exhibits only linear pharmacokinetics.

Recall that the Extravascular Administration chapter introduced a mathematical approach called the method of residuals which could be used to deconvolve the contributions of absorption and elimination processes to a given blood concentration-time profile. Similarly, this method can be useful for deconvolving the contribution of distribution and elimination
processes to the blood concentration-time profile associated with a two-compartment system.

Consider the $\beta$ phase (the elimination phase) of the above blood concentration-time profile. At late time points during this phase (when net distribution from the central compartment to the peripheral compartment is essentially complete), the above equation can be reduced to:

$$ C = B \cdot e^{-\beta \cdot t} $$

which is analogous to the equation for a one-compartment model after IV bolus administration. After subtracting this simplified equation from the complete concentration-time equation, the remainder represents only the contributions of the distribution process (the $\alpha$-phase), which is indicated by the dotted line in the graph above.

**Distributional Equilibrium**

In multiple-compartment systems such as illustrated above with IV bolus administration, at time zero, immediately after the dose is administered, the entire dose will be contained in the central compartment. Thus, the concentration in the peripheral compartment at time zero, is zero. Because of the substantial difference in concentrations between the two compartments, and because the movement of drug between the two compartments is a first-order process, initially, the rate of movement of drug from the central to the peripheral compartment will exceed the rate of movement in the reverse direction, (as described by LeChatlier’s principle). This will result in net distribution of drug out of the central and into the peripheral compartment (i.e., central compartment concentrations will fall and peripheral compartment concentrations will rise). Eventually, the rates of drug movement between the two compartments will become equal, and concentrations in both compartments will decline in parallel.
(i.e., at equal rates). At this point, the system is referred to as existing in a state of distributional equilibrium, because although drug continues to move between the central and peripheral compartments, there is no net movement of drug from one compartment to the other.

The processes that contribute to drug disposition after IV bolus administration in a two-compartment system are illustrated schematically in the figure below.

Phase 1) Upon administration to the central compartment, drug equilibrates instantly within the central compartment. The concentration in the peripheral compartment is zero.

Phase 2) Drug undergoes net movement out of the central compartment, via either distribution into the peripheral compartment or systemic elimination.

Phase 3) At the end of the distribution phase, the difference in the rate of drug movement from one compartment to the other decreases to zero. At this point, unbound drug in the central and peripheral compartments exists in a state of distributional equilibrium.

Phase 4) At this point, although there is no net movement of drug from the central to the peripheral compartment (i.e., distribution equilibrium), drug continues to be eliminated from the central compartment via systemic clearance, resulting in the $\beta$ phase of the blood concentration-time profile. During the $\beta$-phase, as drug is lost from the central compartment due to systemic clearance, driving-force principles dictate that some drug molecules will move from the peripheral to the central compartment, resulting in a net and parallel decrease in concentrations in both compartments. This replenishment of drug in the central compartment contributes to the smaller slope of the $\beta$ vs. the $\alpha$ phase (the reduced rate of drug loss from the central compartment) during the $\beta$ phase.
Please note that during the $\beta$ phase, the unbound drug concentration in the peripheral compartment is always higher than the unbound drug concentration in plasma, although the concentrations in both compartments decline in parallel.

Phase 1) The dose enters the central compartment

Phase 2) Drug is both eliminated (trash can) and enters the peripheral compartment (alpha phase)

Phase 3) Distribution equilibrium is attained

Phase 4) Drug elimination from the central compartment shifts the concentration gradient and drug moves back from the peripheral to the central compartment

At early points in time, as illustrated in the figure below, central compartment concentrations fall while peripheral compartment concentrations rise. Once equilibrium is attained (Phase 3 of the above diagram), central and peripheral compartment concentrations fall in parallel. During multiple dosing or long-term infusion administration regimens, when blood concentrations (i.e., central compartment concentrations) are at steady-state, concentrations in the peripheral compartment (which may include the site of drug action) will be at steady-state as well. Thus, if
blood concentrations change, peripheral compartment concentrations will change in parallel.

**Figure 12-4: Ratio of tissue to blood as a function of time.**
At distributional equilibrium, this ratio is constant.

The ratio of tissue concentration ($C_t$) to blood concentration ($C_b$) is sometimes referred to as a partition coefficient ($k_p$). The extent to which a drug partitions into a certain tissue will depend upon the degree of protein binding in blood vs. in tissue (recall that only unbound drug will equilibrate with unbound drug in tissue), the lipophilicity of the compound relative to the tissue (which may depend in part upon physicochemical properties of the drug, such as ionization), and the degree to which the drug may be a substrate for active, asymmetrical transport into or out of the tissue (e.g., via drug efflux transporters such as P-glycoprotein). The resulting tissue partition coefficient can serve as an index of the degree to which a drug can access a given tissue or organ.

**Volumes of Distribution**

Thus far, two new terms have been introduced in the context of multi-compartment pharmacokinetic systems: $\alpha$-phase, referring to the net distribution phase of drug disposition, and $\beta$-phase, referring to the net elimination phase. We will now discuss new terms which represent the volume of distribution in the central and peripheral compartments of a multi-compartment system.

**Volume of the Central Compartment ($V_C$)**

The first new volume term is similar to the apparent volume of distribution in a one-compartment model (recall that in a one-compartment system, the entire body, including the blood acts as a single, homogenous pharmacokinetic compartment). In multi-compartment systems, the ap-
parent volume of distribution of the central compartment, \( V_C \), is defined as:

\[
V_C = \frac{X_0}{C_0} \quad \text{Equation 12-2}
\]

where \( C_0 \) is the plasma concentration at time zero. At the moment at which drug is administered (if administered as a bolus), the entire dose of drug resides in this central compartment. So, the dose divided by the concentration produced at time zero yields the apparent volume of this compartment.

Note that the corresponding volume term which applies to the peripheral compartment, \( V_P \), is generally not discussed in the context of clinical pharmacokinetics. This is primarily due to the difficulty or inconvenience of sampling drug concentrations in the appropriate reference tissue or fluid.

**Volume at Steady-State (\( V_{SS} \))**

The second new volume term, \( V_{ss} \), describes the steady-state volume of distribution, or the apparent volume of the entire system. This volume is defined mathematically as

\[
V_{ss} = V_C + V_P \quad \text{Equation 12-3}
\]

\( V_{SS} \) is the sum of the volumes of the central compartment, \( V_C \), and the peripheral compartment, \( V_P \). \( V_{SS} \) reflects the total distributional space of the system. The central volume (\( V_C \)) and the steady-state volume (\( V_{SS} \)) terms can be estimated from the blood concentration-time profile.

**Volume of the Elimination Phase (\( V_\beta \))**

An additional volume term, \( V_{area} \) or \( V_\beta \), is used occasionally in the literature. This parameter is calculated by dividing the systemic clearance by the terminal rate constant for a multi-compartment system. Although this calculation is simple, and results in a parameter which has units of volume, it is essentially meaningless; it provides no information about the intrinsic properties of the system. We will not mention this term further.

**Relationships Between Volume Terms**

Recall that one way in which the apparent volume of distribution can provide information about a pharmacokinetic system is by indicating
whether a drug distributes primarily into the blood or primarily into the peripheral tissues.

Why is it important to understand the definitions of and the relationships between these various volume terms? The target tissue for a given drug may behave as if it resides in the central compartment or in the peripheral compartment. If the target tissue is in the central compartment, the onset of pharmacologic response may be rapid, compared to a that for a drug with a target tissue in the peripheral compartment. The above-discussed volume terms will also be important in terms of designing an appropriate bolus loading dose for a multi-compartment system, as will be discussed later in the chapter.

**Clinical Implications of Drug Distribution**

For many drugs, the $\alpha$-phase is so short (on the order of minutes), that the system can essentially be treated as if it exhibits one-compartment behavior. When significant distributional behavior exists, it is imperative that blood samples collected for the purpose of monitoring drug concentrations be obtained during the $\beta$- rather than the $\alpha$-phase. This is par-
particularly important for drugs such as aminoglycosides, digoxin and lithium because they display distributional behavior and taking the wrong samples to estimate half-life can greatly effect your dose adjustments; these drugs have a low therapeutic index and a small mistake can have negative therapeutic results. The examples below illustrate the importance of ensuring that samples are collected during the elimination phase of drug disposition.

In the first example, the concentration-time profile associated with a two-compartment drug is illustrated. The two data points (filled circles) indicate drug concentrations in samples collected during both the $\alpha$ and $\beta$ phases of the profile. Assuming that the slope of the relationship between these two points is indicative of the elimination phase would lead to the conclusion that the half life (calculated based upon the slope of the elimination phase) is shorter than it actually is.

In the second example, both samples are collected during the elimination phase of the drug disposition profile, thus, calculation based upon these two points would yield an accurate estimation of half-life.

The potential for erroneous calculation of a drug’s half-life in part underlies the design of a given drug’s sampling scheme relative to its administration scheme. For example, blood samples for monitoring aminoglyco-
coside therapy are collected 30-45 minutes after the end of the infusion, while sampling to monitor oral lithium therapy begins 12 h after the dose is administered. How is it possible to determine the time at which the distribution process ends and the elimination process begins? Recall that five distributional half-lives ($\alpha$) will elapse before distribution is complete. For most drugs that require monitoring, the recommended sampling times take into account the average distributional time, thus, sampling schemes are drug-specific.

As discussed earlier, although many drugs exhibit multi-compartment behavior, from a clinical standpoint it is not always necessary to describe these systems with the more complicated equations of a multi-compartment model. In some cases it is possible to generate a reasonable approximation of the disposition of the drug (for clinical decision-making purposes) using one-compartment model equations. For example, in the case of oral administration, the absorption process may obscure the multi-compartment behavior of a drug, if the half-life for absorption is long, relative to the distribution half-life ($t_{1/2\alpha}$). This type of situation is particularly likely in the case of drugs which are formulated for sustained release.

Thus far, multi-compartment behavior has only been discussed in the context of two-compartment models. A pharmacokinetic model may, in theory include any number of compartments. A three-compartment model is used to describe the disposition of certain drugs such as aminoglycosides. Schematically, a three-compartment model may be constructed as illustrated below:

![Figure 12-8: Schematic of a three-compartment model.](image)

In the three-compartment model illustrated above, there are two peripheral compartments. In this particular example, the peripheral compart-
ments differ in depth (i.e., the rate of equilibration with the central compartment, which in turn, influences the apparent volume of each compartment). The shallow peripheral compartment ($V_{SP}$), equilibrates with the central compartment more rapidly than the deep peripheral compartment ($V_{DP}$) does. One example illustrating the importance of this concept concerns the potential for ototoxicity in association with aminoglycoside therapy. In this case, the ear (the site of toxicity) functions as a deep peripheral compartment (i.e., drug will enter this compartment slowly and will also exit the compartment slowly). As drug accumulates in this deep compartment, the risk for this particular toxicity increases. Therefore, when designing aminoglycoside dosing schedule, a low trough concentration is desired, to ensure that this deep compartment does not accumulate a toxic concentration of drug. As in the two-compartment model, the subscripts of the rate constants indicate the direction of drug movement.

Although other more complex models of drug disposition exist, these are generally not used in the clinical context.

**Multiple Dosing with a 2-Compartment System**

The same general rules for designing multiple dose regimens apply to both drugs with one-compartment behavior and drugs with multi-compartment behavior. As the number of pharmacokinetic compartments increases, however, the equations will become more cumbersome. Thus, it is desirable to use one-compartment model equations whenever they can provide a sufficiently accurate description of the system.

Sometimes a one-compartment model is used to predict the disposition behavior of a drug with multi-compartment properties. The potential errors associated with this approach include an underestimation of peak concentrations and/or an overestimation of trough concentrations. Recall that average steady-state concentrations are governed by the dosing rate and clearance; this parameter is model independent. Thus, when describing a multi-compartment system using a one-compartment model, the average steady-state concentrations will be same as if a multi-compartment model had been applied, however, the peaks and troughs will not necessarily be the same. Using Microsoft Excel to conduct simulations of the above-described situations will further illustrate the effects of substituting describing a multi-compartment system with a one-compartment model vs. the more complex multi-compartment model.
Loading Doses

In the context of clinical pharmacokinetics a major impact of multi-compartment behavior is on the design of loading doses. Recall from our previous discussion of loading dose design for one-compartment systems, that a bolus loading dose can be calculated based upon the volume of distribution:

\[ X_{0,L} = C_{\text{MAX,Desired}} \cdot V \]

Equation 12-4

In multiple-compartment models, however, more than one volume term can be calculated.

What happens if \( V_C \) is used to calculate a loading dose in a two-compartment system? We will use lidocaine, an antiarrhythmic, to demonstrate. Lidocaine has a CL of 10 mL/min/kg, a \( V_C \) of 0.5 L/kg, a \( V_{SS} \) of 1.5 L/kg, and a therapeutic range of 1 to 5 mg/L. If the target concentration is 5 mg/L and the patient weighs 70 kg, the infusion rate \( (k_0) \) will be 210 mg/h and the loading dose, as calculated based on \( V_C \), is 175 mg (for a 70 kg person).

\[
C_{SS} = \frac{k_0}{Cl} \\
k_0 = C_{ss} \cdot Cl = \\
k_0 = 5 \text{ mg/L} \cdot 10 \text{ mL/min/kg} \cdot \frac{1}{1000 \text{ mL}} \cdot \frac{60 \text{ min}}{1 \text{ h}} \cdot 70 \text{ kg} \\
k_0 = 210 \text{ mg/h}
\]

\[
X_{0,L} = C_{\text{MAX,Desired}} \cdot V \\
X_{0,L} = 5.0 \text{ mg/L} \cdot 0.5 \text{ L/kg} \cdot 70 \text{ kg} \\
X_{0,L} = 175 \text{ mg}
\]
Below is a graph of the concentration-time profile associated with the above example. The gray lines represent the individual contributions of the bolus loading dose and infusion doses to blood concentrations, and the black line represents the combined effect of both doses (bolus plus infusion) on blood concentrations.

![Figure 12-10: Impact of a bolus loading dose calculated using $V_C$. Gray lines represent the individual effects of the bolus loading dose and infusion on blood concentrations. The black line represents the influence of the combined doses (bolus+infusion) on blood concentration. Note the temporary drop in concentration resulting from the combined doses.](image)

Note the rapid drop and subsequent slow rise in blood concentration after administration of the combined bolus loading dose and infusion. This drop reflects the rapid distribution phase in this multi-compartment system. This phenomenon may be referred to as “undershooting”, because the loading dose results in concentrations that initially fall below the desired steady-state level. As a clinical note, lidocaine loading doses are usually administered over a few several-minute intervals, in order to minimize this large drop in concentration.

Returning again to the example of lidocaine, the bolus loading dose for this drug is calculated below, using $V_{SS}$ rather than $V_C$. In this case, the calculated loading dose is 525 mg. The graph below illustrates the resulting concentration-time profile. Again, the gray lines represent the individual contributions of the bolus loading dose and the infusion to blood concentrations, and the black line represents the effect of the combined doses on blood concentrations.

\[
X_{D,0L} = \frac{C_{MAX,Desired}}{V} \\
X_{D,0L} = 5.0 \text{ mg/L} \times 1.5 \text{ L/kg} \times 70 \text{ kg} \\
X_{D,0L} = 525 \text{ mg}
\]
In this example, the loading dose yields very high initial concentrations, thus “overshooting” the desired concentration. The concern in this case is with the potential for toxicity to result from these high initial concentrations. Because $V_{SS}$ is always greater than $V_C$, calculation of a bolus loading dose using $V_{SS}$ will always result in a larger dose.

Whether calculating a bolus loading dose based upon $V_C$ or upon $V_{SS}$, the desired target concentrations will not be achieved immediately. Generally, these types of calculations will be made based upon $V_C$, because the risks associated with undershooting the desired $C_{SS}$ are usually lower than the risks associated with overshooting the desired $C_{SS}$. Ideally, a loading infusion could be used to avoid either of these problems, however, calculation of the rate of infusion is complicated, as it would be necessary to modify the infusion rate over time to compensate for distributional behavior.

**Summary**

Many drugs exhibit distributional, or multi-compartment, behavior. Mathematically, representation of this distributional behavior can be complex. For this reason, it is common in clinical situations to use the simpler one-compartment model to predict drug concentrations, whenever this substitution will provide a reasonable approximation of drug distributional behavior. Some important points to remember about drugs with multiple-compartment behavior are: 1) that the target tissue for a given drug may reside in a peripheral compartment, thus the onset of pharmacologic effect may be slow, 2) that it is necessary to consider distributional behavior when selecting sampling times for estimation of drug half-life during therapeutic drug monitoring, and 3) that calculation of a loading dose for a drug with multi-compartment behavior is complicated by distributional behavior.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>Alpha phase – represents distribution of drug</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Beta phase – represents elimination of drug</td>
</tr>
<tr>
<td>$V_C$</td>
<td>Volume of the central compartment</td>
</tr>
<tr>
<td>$V_{ss}$</td>
<td>Volume of distribution at steady-state. Represents total distributional space</td>
</tr>
</tbody>
</table>

**Skills Obtained**

- Describing the components of a two-compartment model
- The ability to discuss the implications of sampling during the distribution phase when determining a drug’s half-life, and the implications of designing therapeutic regimens based upon this erroneously-calculated parameter.

**Summary Equations**

General equation to describe a two-compartment model after IV bolus administration

$$C = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}$$
### New Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
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<tr>
<td>A</td>
<td></td>
<td>The intercept of the slope associated with the distributional phase ( (\alpha) )</td>
<td>Volume per time (e.g., L/h)</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>The intercept of the slope associated with the elimination phase ( (\beta) )</td>
<td>Volume per time (e.g., L/h)</td>
</tr>
<tr>
<td>( \alpha )</td>
<td></td>
<td>The rate constant governing distribution in a two-compartment system</td>
<td>Inverse hours (e.g., 1/h)</td>
</tr>
<tr>
<td>( \beta )</td>
<td></td>
<td>The rate constant governing elimination in a two-compartment system</td>
<td>Inverse hours (e.g., 1/h)</td>
</tr>
<tr>
<td>( V_C )</td>
<td>Central compartment volume</td>
<td>The volume of distribution for the central compartment in a multi-compartment system</td>
<td>Volume (e.g., L)</td>
</tr>
<tr>
<td>( V_P )</td>
<td>Peripheral compartment volume</td>
<td>The volume of distribution for a peripheral compartment in a multi-compartment system</td>
<td>Volume (e.g., L)</td>
</tr>
<tr>
<td>( V_{SS} )</td>
<td>Steady-state volume</td>
<td>The volume of distribution at steady-state, where ( V_{SS} ) is the sum of ( V_C ) and ( V_P )</td>
<td>Volume (e.g., L)</td>
</tr>
</tbody>
</table>
13) Nonlinear Pharmacokinetics

Goal

To discuss the principles behind dose- and time-dependent pharmacokinetic behavior, as well as the impact on drug concentration-time profiles.

Objectives

By the end of this chapter, you should be able to

- Describe several factors which might result in dose- or time-dependency
- Define nonlinear pharmacokinetics and non-stationary pharmacokinetics, and determine whether a drug demonstrates these behaviors
- Define, calculate, and correctly use the terms $V_{\text{MAX}}$ and $K_m$
- Graphically depict nonlinear behavior in terms of the relationships between dose and AUC, or between dosing rate and average steady-state concentrations.
- Calculate the appropriate dosing rate to achieve a given steady-state concentration in a nonlinear system, when the nonlinearity is due to saturable metabolism.

In Brief

In linear kinetics we assume that if you double the dose, the concentrations within the body will also double because clearance and volume of distribution is independent of drug concentration and time. Some drugs do not behave this way. In a nonlinear system drug concentrations will change disproportionally to the administered dose and whether this is higher or lower will depend on the mechanisms causing the nonlinearity. Throughout this chapter we will take a look at the different variables that affect the outcomes of a nonlinear system, how Michaelis-Menten kinetics fits into the nonlinear system, and how the equations that we derive from Michaelis-Menten kinetics helps us determine clearance, AUC, and other important variables to administer a correct dose in the clinical setting. We also will discuss non-stationary kinetics where parameters like clearance or volume change with respect to time, versus change with respect to concentration as seen with nonlinear kinetics.
Introduction

All of the concepts covered thus far have been presented in the context of linear pharmacokinetic systems. All of the pharmacokinetic models were based upon assumptions of linear or "dose proportional" pharmacokinetics. As an illustration of dose-proportional behavior, consider the case of digoxin, a cardiac glycoside used to treat congestive heart failure. If a patient’s blood concentration is 2 μg/L but the desired concentration is 1 μg/L, how should the dose be adjusted? One might intuitively assume that reducing the dose by half would reduce the blood concentrations by half. In this particular situation, this assumption would be correct, because under the conditions described, digoxin exhibits linear pharmacokinetics. Thus, altering dose (or clearance) would result in the same fold change in AUC (i.e., half the dose = half the AUC).

As you may recall, in a linear, one-compartment pharmacokinetic system with IV bolus input and first-order clearance from the central compartment, the rate of change in drug concentration (dX/dt) is a product of CL and drug concentration:

\[ V \cdot \frac{dX}{dt} = -CL \cdot C \]  
Equation 13-1

In this case, CL is independent of concentration and the route of administration, thus, CL is a constant. This assumption is fundamental in linear pharmacokinetic systems. The figure below depicts the linear relationship between dose and AUC, and between dose and C_{SS}.

Figure 13-1: Dose-AUC and dose-C_{SS} relationships in a linear pharmacokinetic system.

In nonlinear pharmacokinetic systems, the relationship between dose and AUC is not necessarily linear. In this case, the values of parameters such as clearance can change in with time, and / or with changes in concentration. The dose-AUC relationship may deviate from linearity, as
illustrated in the figure below (the solid line represents a linear pharmacokinetic situation).

**Figure 13-2: Potential relationships between dose and AUC in a nonlinear system (dashed lines). The solid line represents the dose-AUC relationship in a linear system.**

As illustrated by the red dashed line above, in a nonlinear system, an increase in dose may result in a disproportionately large increase in AUC (upward-curved relationship). This relationship might reflect, for example, saturation of the ability of the system to metabolize drug, so that as drug concentrations increase, the ability to clear the dose from the system declines. In the second case, as illustrated by the blue dashed line above, an increase in dose in a nonlinear system may result in a disproportionately small increase in the AUC. This relationship may reflect a process such as, for example, saturation of the mechanisms that allow for absorption of an administered dose. Thus, as the dose becomes very large, a smaller fraction of the total dose will be absorbed. For this reason, increases in systemic drug concentrations cannot always be achieved simply by administration of larger doses. Note that at low doses of drug, all three systems appear to exhibit a linear relationship between dose and AUC (i.e., nonlinear behavior is not apparent).

As discussed above, all drugs exhibit nonlinear behavior when the administered dose is large enough to saturate fundamental processes such as metabolism or absorption, however, this behavior is not typically apparent within the standard range of therapeutic concentrations. Only a few drugs exhibit nonlinear behavior within a concentration range typically encountered in clinical settings. In a dose-dependent nonlinear pharmacokinetic system, the following three pharmacokinetic parameters: CL, V and F, will depend upon the dose of the drug.

**Mechanisms of Nonlinearity**

Following a brief explanation of the physiological mechanisms underlying nonlinearity, mathematical descriptors of the system will be discussed. Each of the four major categories of pharmacokinetic processes can be subject to nonlinear behavior, as illustrated in the table below.
Nonlinearity (i.e., dose- or time-dependency) in drug absorption is usually a function of nonlinear bioavailability (F). Factors that can impact the linearity of the absorption process include drug transport across the gut wall (e.g., amoxicillin), solubility limitations (e.g., griseofulvin), and/or gut wall or first-pass metabolism (e.g., nicardipine). All active drug transport processes (whether in the gut, liver, kidney, etc.) are capacity-limited, and exhibit Michaelis-Menten kinetics (see below). Solubility limitations are common, as many drugs are lipophilic and do not dissolve easily in aqueous environments. Increases in dose will result in an increased fraction of the dose which remains undissolved, thus, the fraction of the dose which is bioavailable (F) will decrease with increasing dose.

The figure below illustrates the dose-AUC relationship when F is capacity-limited.

In the case of distribution processes, binding to proteins in the plasma or even in tissue may be saturable. For example, molecules such as albumin and α1-acid glycoprotein (two of the primary drug-binding proteins in the blood) possess a fixed number of binding sites. The concentrations of each of these proteins in the blood are $600 \, \mu\text{M}$ and $15 \, \mu\text{M}$, respectively. Assuming 1 binding site per protein (which is an underesti-
mate) high plasma concentrations of drug (e.g., > 600 μM for a drug that binds to albumin) will saturate these proteins. Most drugs, however, are administered at doses so low that saturation of binding to plasma proteins would not occur. Changes in the fraction of unbound drug could impact both CL and V. If only V was impacted, dose proportionality would still exist because AUC is determined by the dose and CL.

The linearity of excretion processes could be impacted by changes in protein binding as discussed above. Recall that in the case of renal excretion, only unbound drug can be filtered or secreted, thus, the unbound fraction will impact the total amount of reabsorption. In addition, secretion (e.g., of digoxin, glucuronides) is a capacity-limited process, because it depends upon active transport (a capacity-limited process which obeys Michaelis-Menten kinetics). Some drugs are actively reabsorbed by transporters (e.g., lithium), thus reabsorption can also be capacity-limited. Drugs that cause diuresis (e.g., theophylline) or change urine pH (e.g., salicylic acid) may induce changes in their own excretion. Below is an example of the impact on the dose-AUC relationship when tubular reabsorption is saturated (left) and when secretion is saturated (right).

Before considering the mechanisms responsible for nonlinearity in the fourth type of pharmacokinetic process, metabolism, we will more closely examine two types of relationships pertinent to capacity-limited renal secretion or reabsorption. The graphs below illustrate the relationships between renal excretion rate and drug concentration (left) and between renal clearance and drug concentration (right). Beginning with the figure on the left, note that for a drug that is secreted and filtered (solid black
line), at low drug concentrations, the relationship between excretion rate and drug concentration is curved. However, as drug concentrations increase, the relationship becomes increasingly linear, reflecting saturation of the secretion process. The black dashed line, representing the contribution of secretion alone, depicts a curved relationship, illustrative of the Michaelis-Menten kinetics of the secretion process. The red line represents a drug which undergoes filtration only (the middle line in the two graphs). As dose increases, the excretion rate increases but the renal clearance remains constant. The blue line (lowest line in the two graphs) represents a drug that undergoes active reabsorption as well as filtration. At high drug concentrations, the system becomes saturated, and the rate of renal clearance approaches the rate of clearance for a drug that undergoes filtration alone (indicating that at high drug concentrations, reabsorption is a minor contributor to the overall rate of renal clearance).

Figure 13-5: Depiction of excretion rate-drug concentration profile (left) and renal clearance-drug concentration profile (right). Black lines are for drugs that are secreted and filtered; red are for drugs that are filtered only and blue lines are for drugs that are filtered and actively reabsorbed. Black dash line represents the contribution of secretion alone.

Finally, we will consider the mechanisms that can be responsible for capacity-limited metabolism. The most common examples of metabolism capacity-limited drugs are phenytoin and ethanol. Ethanol saturates the relevant enzymes such that this drug appears to obey zero-order kinetics (we will discuss this further below, in the context of explaining why $V_{\text{MAX}}$ is a zero-order parameter). Phenytoin is another drug that exhibits capacity-limited metabolism (although not to the same degree as ethanol). While many drugs exhibit capacity-limited metabolism, other drugs can induce their own metabolism (carbamazepine is a classical example). Because carbamazepine induces the expression of the enzymes that metabolize it (recall that the process of synthesizing new proteins takes time), its clearance increases over time, reflecting the increase in

Ethanol follows zero-order kinetics because it saturates metabolic enzymes in recreational doses.
the number of enzymes. This referred to as non-stationary behavior. The term non-stationary behavior means that pharmacokinetic parameters change over time (contrast this with nonlinear behavior, which refers to pharmacokinetic parameters changing with dose or concentration). Another example of a potentially non-stationary drug is propranolol. Propranolol is known to decrease $Q_H$, which will substantially impact the clearance of this drug, since it is a high-extraction compound. Finally, in some cases (e.g., lidocaine) the same enzymes may be responsible for metabolizing both parent and metabolite. Thus, as the concentration of metabolites increases, metabolism of the parent is inhibited. Below is an example of the dose-AUC relationship that would result from saturation of a metabolic process.

![Figure 13-6: Dose-AUC relationship associated with capacity-limited metabolism. As enzymes become saturated, clearance decreases and AUC increases.](image)

**Overview of Michaelis-Menten Kinetics**

Nonlinear processes obey Michaelis-Menten kinetics. Michaelis-Menten kinetics are defined by the following relationship between the concentrations of enzyme (E) (or transporter), substrate (C; e.g., drug) and the product (P):

\[
[E] + [C] \xrightleftharpoons{\kappa_a}{\kappa_p} [EC] \xrightarrow{\kappa_p} [P] + [E]
\]

where $k_a$ is the equilibrium rate constant that governs the formation of EC (the enzyme-substrate complex) and $k_p$ is the rate constant that governs the formation of the product.

This schematic can be used to describe the rate at which substrate is converted to product. The velocity (or speed) at which substrate is converted to product ($dC/dt$) is determined by:

\[
\text{velocity} = \frac{dC}{dT} = -\frac{V_{\text{MAX}} \cdot C}{(K_M + C)}
\]

Equation 13-2
where $V_{MAX}$ is the maximal velocity of the reaction in terms of mass per unit time (or concentration per unit time), $K_M$ is the Michaelis-Menten constant (the concentration that elicits 50% of $V_{MAX}$), and $C$ is the concentration of substrate. The negative sign indicates a loss of substrate. It is important to note that $V_{MAX}$ and $K_M$ will vary between drugs, and between patients.

The figure below illustrates a Michaelis-Menten relationship between reaction velocity and drug concentration. Note the similarity of the above equation to both the well-stirred model that appeared in the chapter on hepatic clearance, and the $E_{MAX}$ model that will be presented in the upcoming chapter on pharmacodynamics.

![Figure 13-7: The relationship between substrate concentration and rate of reaction. $V_{MAX}$ is the maximal reaction rate, $K_m$ is the concentration which results in a reaction rate which is 50% of $V_{MAX}$](image)

### Table 13-2

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michaelis-Menten</td>
<td>$\text{reaction rate} = -\frac{V_{MAX} \cdot C}{(K_M + C)}$</td>
</tr>
<tr>
<td>“Well-Stirred Model”</td>
<td>$\text{Cl}<em>H = -\frac{Q_H \cdot f \cdot C</em>{l_i}}{Q_H + f \cdot C_{l_i}}$</td>
</tr>
<tr>
<td>$E_{MAX}$ Equation</td>
<td>$E = -\frac{E_{MAX} \cdot C}{(EC_{50} + C)}$</td>
</tr>
</tbody>
</table>

As drug concentration increases, reaction velocity (e.g., the rate of elimination, excretion, uptake, etc.) increases, eventually approaching the maximal velocity in an asymptotic manner.

The remainder of the discussion will focus on capacity-limited clearance processes, because these occur more frequently than other types of nonlinear processes. When drug concentrations are much lower than $K_M$ ($C \ll K_M$), the system will appear to exhibit linear kinetics. However, in

Most clinical drug concentrations are well below the $K_M$ of enzymes (within the linear range of enzyme activity).
the case where \( K_M \) is much larger than the drug concentration (e.g., \( K_M = 1000 \) and \( C = 0.01 \)) the influence of concentration can be ignored (recall that the effect of adding a very small number to a very large number is negligible). Thus, in the following equation, the \( C \) term can be removed from the denominator and the equation can be reduced as shown below.

\[
\frac{dC}{dT} = - \left( \frac{V_{MAX}(C)}{(K_M + C)} \right) = - \left( \frac{V_{MAX}}{K_M + C} \right) \cdot C
\]

\[
\frac{dC}{dT} = - \left( \frac{V_{MAX}}{K_M} \right) \cdot C
\]

\[
\frac{dC}{dT} = -CL \cdot C
\]

Note that in the final substitution above, \( CL \) is expressed in terms of \( V_{MAX} \) and \( K_M \). Since both \( V_{MAX} \) and \( K_M \) are constant, clearance is constant and independent of concentration.

When concentration is much greater than the \( K_M \) (\( C >> K_M \)) the \( K_M \) value can be eliminated from the denominator (by the rationale discussed above) and concentrations will cancel out:

\[
\frac{dC}{dT} = - \left( \frac{V_{MAX}(C)}{(K_M + C)} \right) = - \left( \frac{V_{MAX}}{K_M + C} \right) \cdot C
\]

\[
\frac{dC}{dT} = - \left( \frac{V_{MAX}}{C} \right) \cdot C
\]

\[
\frac{dC}{dT} = -V_{MAX}
\]

So at high concentrations, the system will appear to obey zero-order kinetics. In this case, \( V_{MAX} \) is the mass of drug removed per unit time.
**Example:** Drug X has a $V_{\text{MAX}}$ of 600 mg/d and a $K_M$ of 12 mg/L. What is the clearance for Drug X when $C = 0.1$ mg/L? What is the clearance of Drug X when $C = 100$ mg/L?

$$\text{Cl} = \frac{V_{\text{MAX}}}{K_M + C} = \frac{600}{12 + 0.1} = 49.6 \text{ L/d}$$

$$\text{Cl} = \frac{V_{\text{MAX}}}{K_M + C} = \frac{600}{12 + 100} = 5.4 \text{ L/d}$$

As illustrated in the above example, as dose (and thus, concentrations) increase, clearance decreases, therefore clearance is concentration-dependent. When drug concentrations are low as in the low-dose example above, the system will appear to obey linear kinetics. In this case, clearance is simply $V_{\text{MAX}}/K_M$ (CL = 600 / 12) or ~50 L/d. In the high-dose case, clearance is low at early time points (when concentrations are highest). The rate of clearance increases as concentrations fall. Because clearance is dependent on concentration, doubling the dose will not result in a doubling of drug concentration, as would occur in a linear system. This is further illustrated in the graph below.

![Graph showing the relationship between dosing rate and average steady-state concentration.](image)

**Figure 13-8:** The relationship between dosing rate and average steady-state concentration. In the case of capacity-limited metabolism (solid line), doubling the dose causes an increase in $C_{SS}$ which is larger than would be expected if the kinetics were linear (dashed line). The gray box indicates the therapeutic range.
Phenytoin is an example of a drug that exhibits concentration-dependent clearance. As illustrated above, when the dosing rate increases \( (X_0/\tau) \), the average steady-state concentration \( (C_{SS}) \) increases disproportionately, relative to the increase that would be anticipated under linear pharmacokinetic conditions. In this case, if it is necessary to increase \( C_{SS} \) from 10 mg/L to 20 mg/L, doubling the dose would not be the appropriate strategy.

Another pharmacokinetic parameter that is impacted by concentration-dependent clearance is the half-life of a drug.

In the figure above, note that as dose increases, half-life increases because higher concentrations result in lower clearance (and thus, a longer half-life). There are at least two clinically important implications of this relationship. The first is that in a nonlinear system it is inappropriate to calculate dosing regimens based upon clearance or half-life values, because in a nonlinear system, these parameters may be dose-dependent (whereas in a linear pharmacokinetic system, these parameters were constant regardless of drug concentration). The second clinical implication relates to the time it takes for a system to reach steady-state conditions. How might a variable half-life impact the time it takes to reach steady-state? Recall that the amount of time required to reach steady-state is related to half-life. Although half-life changes with concentration, steady-state conditions will eventually be attained as the changes in half-life become smaller in association with the decline in drug concentrations.

Thus far, we have discussed the effects of concentration-dependency in clearance processes. The same principles, however, can be applied to absorption or any other process that may change with concentration. Also, thus far we have primarily discussed ways in which systems may
change with respect to concentration, however, certain changes may occur in a time-dependent manner.

For example, carbamazepine induces its own metabolism. Thus, the CL calculated after the first dose will be lower than the CL calculated after subsequent doses, because metabolic clearance increases with time. A second example is valproate. Valproate demonstrates chronopharmacokinetics, that is, pharmacokinetics changes that occur based upon the time of day. This within-day variation is due to time-dependent fluctuations in protein binding. Blood levels of free fatty acids vary throughout the day (e.g., in association with eating). These fatty acids can displace valproate from the proteins to which it is bound. Inconsequently, the unbound fraction changes, causing changes in both clearance and volume.

How to determine nonlinear pharmacokinetics.

The mathematic expressions required to describe the behavior of nonlinear pharmacokinetic systems are more complicated that those which describe linear pharmacokinetic systems. Clinically, the major concern is how to select the correct dose, when the system in question changes as a function of concentration or time. In the subsequent discussion, only the case of nonlinear behavior due to concentration-dependent clearance will be considered. Phenytoin that exhibits nonlinear behavior at clinical concentrations, is an example of nonlinearity due to concentration-dependent clearance.

It is important to understand how to recognize nonlinear behavior. In some cases, this may be fairly straightforward. For instance, a report from a clinical trial might indicate that a dose of 100 mg was associated with an AUC of 10 mg*h/L, and a dose of 200 mg was associated with an AUC of 50 mg*hr/L. The fact that a two-fold increase in dose produced a five-fold change in AUC should indicate that this particular drug exhibits nonlinear behavior.

There are several approaches to identify nonlinear behavior. As discussed earlier, under linear conditions, plotting X₀ vs. AUC results in a straight line with a slope approximating 1/CL. Recall the equation below, which describes a fundamental property of linear pharmacokinetic systems:

\[
AUC = \frac{F \cdot X_0}{Cl}
\]

Equation 13-3

Divide AUC by the dose to see if you have linear pharmacokinetics!

Auto-induction will cause an increase in clearance over time, thus requiring upward titration of dose to maintain steady-state concentrations.
Thus, if the relationship between $X_0$ vs. AUC deviates from a straight line, this indicates that the system exhibits nonlinear pharmacokinetics.

Another method for identifying nonlinearity, which is analogous to the graphical method presented above, is to dose-normalizing AUC values. That is, to divide AUC by the $X_0$. If the system is linear, this relationship should be constant regardless of $X_0$ and AUC as seen in the example below. Changes in the value of $AUC/X_0$ would thus indicate nonlinearity.

<table>
<thead>
<tr>
<th>$X_0$ (mg)</th>
<th>AUC (mg*h/L)</th>
<th>$AUC/X_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>100</td>
<td>2</td>
<td>0.02</td>
</tr>
<tr>
<td>500</td>
<td>10</td>
<td>0.02</td>
</tr>
</tbody>
</table>

An additional approach is to administer several different doses of a drug, and to plot dose-normalized concentrations ($C/X_0$) vs. time, as illustrated in the figures below. This approach will result in concentration-time profiles which are superimposeable if the system is linear (right panel) and non-superimposable if the system is nonlinear, (left panel). Note that in this case, as with all of the approaches described, if these methods are applied to data collected after very low doses of drug (i.e., within the linear range of behavior), it will not be possible to determine whether nonlinearity would occur at any dose higher than those tested.
In order to determine whether a system exhibits nonlinearity due to time-dependency in the clearance process, recall that if a system is stationary, (that is, clearance does not depend on time or dose number), the AUC through infinity after a single dose is equal to the AUC over a single dosing interval at steady-state \((\text{AUC} = \text{AUC}_\tau)\). Thus, it is possible to identify nonlinearity by simply comparing the AUC calculated after a single dose to the AUC calculated over one dosing interval at steady-state \((\text{AUC}_\tau)\).

Several methods have been presented for identifying systems with linear vs. nonlinear behavior. The next section will present methods for determining the appropriate dose to administer in a system that has been identified as exhibiting nonlinear pharmacokinetics. Several methods for calculating doses in nonlinear systems, however, all require an estimate of \(K_M\) and \(V_{\text{MAX}}\). Note that the following examples will be limited to drugs that are eliminated by Michaelis-Menten kinetics through a single pathway.

**Estimating Doses in Nonlinear Pharmacokinetics**

Two approaches for designing an appropriate dosing regimen for a nonlinear system will be discussed. Each approach will be illustrated using the example of a phenytoin dosing regimen. In this example, the drug is administered at two different dosing rates \((X_0/\tau)\), 150 and 300 mg/day. The steady-state drug concentrations are 8.6 mg/L and 25.1 mg/L, re-
spectively. Find the $K_m$ and $V_{MAX}$ and recommend a dosing rate to produce a steady-state concentration of 11.3 mg/L.

**Graphical Approach**

One approach is to begin by estimating $K_m$ and $V_{MAX}$ graphically. The equations below are simply rearrangements of the Michaelis-Menten equation that facilitate graphing of the data. Beginning with the Michaelis-Menten equation, modify the expression to reflect steady-state conditions by replacing $v$ (the velocity of the reaction) with $X_0/\tau$. (because at steady-state, the rate in, $X_0/\tau$, equals the rate out, $v$) and replace $C$ with $C_{SS}$.

$$
\frac{X_0}{\tau} = \frac{(V_{MAX})(C_{SS})}{(K_M + C_{SS})} \quad \text{Equation 13-4}
$$

Simply rearrange this equation by first multiplying both sides by $(K_M + C_{SS})$:

$$
\frac{X_0}{\tau} \cdot K_M + \frac{X_0}{\tau} \cdot C_{SS} = (V_{MAX})(C_{SS})
$$

Then rearranging:

$$
\frac{X_0}{\tau} = \frac{(V_{MAX})}{C_{SS}} \cdot \frac{X_0}{\tau} - \frac{X_0}{\tau} \cdot K_M \quad \text{Equation 13-5}
$$

Finally, plotting dosing rate ($X_0/\tau$) vs. the dosing rate normalized for the steady-state concentration will yield a straight line with the slope $-K_m$ and the intercept $V_{MAX}$. This graphical approach is known as the Ludden method.
Figure 13-12: The Ludden method. Plotting dose rate normalized for $C_{SS}$ vs. dose rate yields a straight line with the y-intercept equal to $V_{MAX}$ and the slope equal to $-K_M$.

Returning to the phenytoin example above, the Ludden method would be applied to the following data:

Table 13-3: Example of dosing rates and resulting average steady-state concentrations

<table>
<thead>
<tr>
<th>Dosing Rate (mg/d)</th>
<th>$C_{SS}$ (mg/L)</th>
<th>Dosing Rate/$C_{SS}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>8.6</td>
<td>17.4</td>
</tr>
<tr>
<td>300</td>
<td>25.1</td>
<td>12.0</td>
</tr>
</tbody>
</table>

Based upon the graph above, $V_{MAX}$ (as determined by the y-intercept) is 650 mg/d and $K_M$ (as determined by the slope of the line) is 27.8 mg/L (slope = $\Delta y/\Delta x$). In order to calculate the dosing rate which will result in a $C_{SS}$ of 11.3 mg/L, insert the values of $V_{MAX}$, $K_M$ and the desired $C_{SS}$ into the previously derived equation:

$$X_0/\tau = \frac{(V_{MAX})(C_{SS})}{(K_M + C_{SS})}$$
Thus, to achieve a steady-state concentration of 11.3 mg/L, it will be necessary to administer a dose of 200 mg/d (rounding up from 188 mg/d). An important caveat is that this method will not result in accurate values if the blood concentrations are not determined at steady-state. In addition, at least two steady-state concentrations must be used, and these concentrations must be obtained under two different dosing rates.

**Calculation Approach**

A second, mathematical approach for estimating $V_{\text{MAX}}$ and $K_m$ involves solving two equations simultaneously. This approach also requires the determination of steady-state blood concentrations under two different dosing rates. Beginning with one Michaelis-Menten equation for each dosing rate, (subscripts indicate which equation corresponds to which dose rate), insert the steady-state concentration values and dose rate values as illustrated below. $V_{\text{MAX}}$ and $K_m$ will be the same regardless of dose rate, because although these parameters are patient-specific and drug-specific, they are not concentration-specific.

\[
\frac{X_0}{\tau} = \frac{(650)(11.3)}{(27.8 + 11.3)} = 188 \text{mg/d}
\]

Solve one equation for $V_{\text{MAX}}$, and insert the resulting expression into the second equation in order to solve for $K_m$.

\[
\frac{X_0}{\tau} = \frac{(V_{\text{MAX}})(C_{SS,1})}{(K_M + C_{SS,1})} \Rightarrow V_{\text{MAX}} = \frac{X_{0,1}}{\tau} \cdot \frac{(K_{M2} + C_{SS,1})}{(C_{SS,1})}
\]

\[
\frac{X_0}{\tau} = \frac{(K_M + C_{SS,1})}{(C_{SS,1})} \Rightarrow \frac{X_{0,1}}{\tau} \cdot \frac{(K_M + C_{SS,1})}{(C_{SS,1})} = \frac{X_{0,2}}{\tau} \cdot \frac{(K_M + C_{SS,2})}{(C_{SS,2})}
\]

\[V_{\text{MAX}} \text{ and } K_m \text{ are dependent on the patient, not the concentrations.}\]
Finally, insert the values specified in the initial example ($X_0/\tau = 150 \text{ mg/l}$ and $C_{SS} = 8.6$; $X_0/\tau = 300 \text{ mg/l}$ and $C_{SS} = 25.1$) and solve for $K_M$.

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

The resulting value of $K_M$ is 27.3 mg/L, which closely approximates the value determined using the Ludden Method ($K_M = 27.8 \text{ mg/L}$). This $K_M$ value can subsequently be inserted into the Michaelis-Menten equation in order to calculate $V_{MAX}$.

$$X_{0,1}/\tau = \frac{(V_{MAX})(C_{SS,1})}{(K_M + C_{SS,1})}$$

$$150 \text{ mg/d} = \frac{(V_{MAX})(8.6)}{(27.3 + 8.6)}$$

$$V_{MAX} = 663 \text{ mg/d}$$

The resulting $V_{MAX}$ value, 663 mg/d, also closely approximates the value of 650 mg/d which was calculated using the Ludden Method.

In order to determine the appropriate dosing rate, simply insert the values of $V_{MAX}$ and $K_M$, and our the desired $C_{SS}$ value (11.3 mg/L) and solve as indicated below.

$$X_0/\tau = \frac{(V_{MAX})(C_{SS})}{(K_M + C_{SS})}$$

$$X_0/\tau = \frac{(663)(11.3)}{(27.3 + 11.3)} = 194 \text{ mg/d}$$

The appropriate dosing rate is again determined to be 200 mg/d (this time, rounding up from 194 mg/d).

Various other methods exist for calculation of $V_{MAX}$ and $K_M$, however, they are beyond the scope of this text. These alternative methods gen-
erally involve graphical analyses and rearrangements of the Michaelis-Menten equation.

**Summary**

The pharmacokinetic concepts introduced prior to this chapter involved assumption of linear pharmacokinetic behavior, that is, disposition characterized by proportional changes in drug concentrations resulting from changes in dose. The current chapter illustrated numerous conditions under which linear pharmacokinetics are not observed. Capacity-limited processes (e.g., transport, metabolism) can cause disproportionate changes in drug concentrations with respect to dose. These capacity-limited systems may influence the linearity of absorption, distribution, elimination or metabolism processes. The primary impact of nonlinear behavior on clinical pharmacokinetics is increased complexity in the design and / or adjustment of a dosing regimen. Some drug disposition characteristics may change over time, such as in the case of auto-induction. Time-dependent pharmacokinetic behavior may necessitate adjustment in the dosing regimen (e.g., dose increases to compensate for the effects of pharmacokinetic tolerance). Overall, it is important to remember that systems that exhibit nonlinear pharmacokinetics cannot be treated as linear systems, e.g., simply doubling the dose will not necessarily result in double the concentrations or AUC.

<table>
<thead>
<tr>
<th>Linear Kinetics</th>
<th>Nonlinear Kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assumption</strong></td>
<td>C &lt;&lt; KM</td>
</tr>
<tr>
<td>CL</td>
<td>Constant, independent of concentration</td>
</tr>
<tr>
<td>AUC</td>
<td>AUC changes proportionally to dose</td>
</tr>
<tr>
<td>t½</td>
<td>Constant, independent of concentration</td>
</tr>
<tr>
<td>C SS</td>
<td>C SS changes proportionally with dose</td>
</tr>
<tr>
<td>Time to steady-state (tss)</td>
<td>tss is constant since t½ is constant</td>
</tr>
</tbody>
</table>

**Useful Equations**

To determine the clearance of a drug in a concentration-dependent system.
\[
CL = \left( \frac{V_{MAX}}{K_M + C} \right)
\]

To determine \( V_{MAX} \) and \( K_M \) if dosing rate and steady-state concentrations are known. This equation is also used for the Ludden Method – graphical analysis to determine \( V_{MAX} \) and \( K_M \).

\[
\frac{X_0}{\tau} = \left( V_{MAX} \right) - \frac{X_0}{C_{SS}} \cdot K_M
\]

To determine \( K_M \) based upon steady-state concentrations obtained under two different dosing rates.

\[
K_M = \left( \frac{X_{0,2}/\tau - X_{0,1}/\tau}{X_{0,1}/\tau - X_{0,2}/\tau} \right) \left( \frac{C_{SS,1}}{C_{SS,2}} \right)
\]

**New Symbols**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{MAX} )</td>
<td>Maximal reaction velocity</td>
<td>The maximal rate of the reaction (in terms of metabolism, the maximal metabolic rate)</td>
<td>Mass per time (e.g., mg/h)</td>
</tr>
<tr>
<td>( K_M )</td>
<td>Affinity</td>
<td>The concentration that elicits 50% of the maximal reaction (or metabolic) rate</td>
<td>Mass per volume per time (e.g., mg/L)</td>
</tr>
</tbody>
</table>
14) Pharmacodynamic Basics

Goals

To introduce the discipline of pharmacodynamics and to discuss how it relates to pharmacokinetics and to clinical pharmacy practice.

Objectives

*By the end of this chapter, you should be able to:*

- Define and correctly use pharmacodynamic terminology, including: reversible response, irreversible response, biophase, direct response and indirect response
- Describe the relationship generally expected between response and concentration at the site of action and correctly use the terminology associated with the equations that describe this relationship
- Estimate from a graph metrics that are related to drug potency ($TD_{50}$, $LD_{50}$, $ED_{50}$, $EC_{50}$) and maximal response ($E_{MAX}$) as well as identify from graphical depiction differences in the sigmoidicity factor $N$
- List the factors that determine the rate of onset and offset of action for drugs with reversible or irreversible binding and direct or indirect effects
- Estimate the duration of action of drug administered as an IV bolus when the concentrations encountered are confined to the log-linear range of the concentration-response relationship
- Explain the significance of $N$ with respect to drug titration

In Brief

Pharmacodynamics is the time course of drug action, often we associate this with ability to see the response of a drug we have administered to a patient. We will assume that the pharmacologic effect is driven by a receptor-mediated process and have theoretical sigmoid relationship between drug dose or concentration and the responses. We will differentiate between examining the dose-response relationship and the concentration-response relationship. Terms like EC50 or ED50 and Emax will be introduced to describe the relationship between drug amount and effect. Drugs will behave in various sections of the theoretical sigmoid relationship (the lower linear part, the middle log-linear part, or the upper curvilinear part). We discuss hysteresis behavior and differentiate between clockwise and counterclockwise hysteresis. Finally, we discuss how to estimate the duration of effect.
**Introduction**

The ultimate goal of drug therapy is to produce the desired pharmacologic response. Thus, it is difficult to discuss the true impact of pharmacokinetics on drug therapy without also discussing pharmacodynamics. Pharmacodynamics is the relationship between drug concentration at the site of action and the resulting pharmacologic response. Pharmacokinetics and pharmacodynamics must both be considered when trying to understand or predict the factors that will determine drug response. Pharmacokinetics will determine the relationship between concentrations at the site of action and the administered dose or dose rate. Pharmacodynamics will determine the relationship between pharmacologic response and the drug concentration at the site of action. When taken together, pharmacokinetics and pharmacodynamics allow the clinician to understand the relationship between pharmacologic response and the administered dose or dose rate.

Consider aminoglycoside antibiotics, which can produce ototoxicity at high concentrations in the ear. In a previous chapter the concept of a deep pharmacokinetic compartment was presented, and the ear as a distributional locale for aminoglycosides was used as example of such a deep compartment. Drug will enter into and egress from a deep compartments at a slower rate than shallow compartments. To ensure that the ear does not accumulate high concentrations, aminoglycoside dosing regimens are designed to produce low trough plasma concentrations. In the presence of low plasma trough concentrations, the equilibrium between drug concentrations in the ear and drug concentrations in the plasma are shifted to favor drug exiting the ear back into plasma. When trough aminoglycoside concentrations are too high, drug will accumulate in the deep compartment, resulting in an increase in the incidence of adverse events.

**Drug Receptor Interaction**

Discussion of the kinetics of pharmacologic response (i.e., pharmacodynamics) requires several assumptions. The first assumption is that the biologic effect is receptor-mediated. Receptors can mean hormone or neurotransmitter receptors, enzymes, nucleic acids or glycoproteins. Note that not all responses are receptor-mediated (e.g., anesthetics, ethanol). The second assumption is that binding of drug to the receptor is readily reversible and saturable. For many drugs, pharmacologic effects are governed by receptors, and the density of receptors of the target organ may ultimately determine the magnitude of drug response at a given drug concentration. The theory that drug effect is proportional to the fraction of activated receptors is called the receptor occupancy theo-
The final assumption is that the effect is stationary (that is, it is time-independent at a fixed concentration).

Figure 14-1: Depiction of a drug molecule interacting with a receptor. Drug binds reversibly to the receptor. When bound, the drug can elicit a response from that receptor.

Unbound vs. Bound vs. Total Drug

When we talk about drug concentrations we have several points of reference: unbound, bound, and total drug concentration. The total drug concentration is as it seems, the total concentration of drug within the blood. It is comprised of the unbound drug concentration and the bound drug concentration. Most drugs have some affinity for proteins within the blood such as albumin. As such, at any one time, some fraction of drug is bound to proteins, and some fraction is unbound. The extent of binding is dependent on many factors and is discussed elsewhere in this book. The important part to note is that it is the unbound drug concentration that is free to interact with drug receptors. Thus if you want to describe the best possible relationship between drug concentration and its effect, the unbound concentration is clinically the most important.

Direct vs. Indirect Responses

A general scheme for pharmacologic response is shown above. The drug (the circle), binds reversibly to the receptor to form a drug-receptor complex. Formation of the complex elicits a response. Unbound drug and unbound receptor are in equilibrium with the drug-receptor complex and this equilibrium will impact the degree of response. Once drug interacts with receptor, a response is elicited; in the present example, the response is considered to be direct (a response that has little to no time delay between complex formation and effect). If the drug is removed, the equilibrium will be shifted to the left, and the pharmacologic effect will be reduced. For direct responses, drug pharmacokinetics drives onset and offset of action. An example of direct response is neuromuscular blockade. As drug concentration (in the biophase) increases, you obtain an immediate increase in the magnitude of neuromuscular blockade is observed.

Not all drugs produce responses that can be considered to be direct. In fact, most drugs produce an indirect response. Indirect responses re-
quire a biochemical cascade of events to occur after the drug-receptor complex is formed, but before the desired therapeutic response is observed. These steps result in a time delay between drug concentration in the biophase and effect. These events are represented by arrows in the figure below.

![Figure 14-2: A drug binds to a receptor, eliciting an indirect response: in this case drug binding to a receptor causes a cascade of events that eventually leads to a response](image)

As mentioned, an indirect response is typical for most drugs. For example, antidepressants generally must be administered for several weeks before their pharmacologic effect becomes apparent, because it takes time for the necessary biochemical changes to occur. Correspondingly, cessation of drug administration removes the stimulus for the pharmacologic response, but the pharmacologic effect may persist for a period of time even after drug is cleared from the body. Thus, drug disposition and/or a cascade of biochemical events downstream from the activated receptor will drive the onset and offset of an indirect pharmacologic response. The onset of effect is slow because it takes time for the cascade of effects to occur; offset of effect is slow because it takes time to reverse the numerous downstream effects.

**Reversible vs. Irreversible Binding**

The discussion to this point has been based upon the assumption that binding between the drug and receptor is a reversible process. When the pharmacologic effect is reversible, loss of drug drives the loss of effect because the equilibrium shifts toward dissociation of bound drug from the receptor.

![Reversible Binding Diagram](image)

Some drugs (e.g., chemotherapeutic agents), however, may bind irreversibly to a receptor. In the case of irreversible binding, the loss of receptor and the drug-receptor complex drives the loss of effect.
Drugs such as chemotherapeutic agents and antibiotics/antivirals evidence irreversible binding. The receptors, in the case of these agents, are cells or organisms, and the binding of drug results in the death of the cell or organism; an irreversible event. So not only can binding be irreversible, but pharmacologic responses can be also irreversible. In the case of irreversible binding, the rate of receptor turnover (i.e., the rate at which new receptors or cells are produced) is a very important factor in determining the offset of drug action.

The table below summarizes different types of binding (reversible vs. irreversible) and responses (direct vs. indirect).

**Table 14-1: Summary of Types of Binding and the nature of the response**

<table>
<thead>
<tr>
<th>Nature of Response</th>
<th>Type of Binding</th>
<th>Reversible</th>
<th>Irreversible</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct</strong></td>
<td>Rapid Onset / Offset</td>
<td>Rapid Onset / Slow Offset</td>
<td>Response kinetics determined predominantly by <em>drug disposition</em>&lt;br&gt;e.g. neuromuscular blockers</td>
</tr>
<tr>
<td></td>
<td>Slow Onset / Offset</td>
<td>Slow Onset / Slow Offset</td>
<td>Response kinetics determined by <em>drug disposition</em> and/or <em>post-receptor events</em> (onset) and <em>receptor turnover</em> (offset)&lt;br&gt;e.g., chemotherapeutics, antibiotics</td>
</tr>
<tr>
<td><strong>Indirect</strong></td>
<td>Slow Onset / Offset</td>
<td>Slow Onset / Slow Offset</td>
<td></td>
</tr>
</tbody>
</table>

**Agonists and Antagonists**

As mentioned above, receptor number can impact pharmacologic response. For example, beta-blocker drugs bear a warning that cessation of therapy should be accomplished via gradual titration of the dose in order to avoid possible cardiac events. During beta-blocker therapy, an increase in the expression of beta receptors on the heart occurs as a
compensatory mechanism in response to the pharmacologic blockade of these receptors. If drug therapy is abruptly stopped, endogenous beta receptor ligands (e.g., epinephrine) will regain access to receptors. Due to the compensatory response to the drug, many more receptors will be present. This rapid increase in the number of activated receptors will result in a rapid increase in pharmacologic response, thus elevating the risk of adverse cardiac events.

Beta-blockers are antagonists of endogenous sympathetic compounds. *Antagonists* do not elicit a response from the receptor but rather inhibit the receptor interaction of a second agent (epinephrine or norepinephrine in this case). Inhibition of binding can be competitive, noncompetitive or uncompetitive in nature. However, competitive inhibition is the most common. Competitive inhibitors compete with the agonist for binding to the same receptor site. Examples of competitive antagonists are propranolol (β-receptors), naloxone (opioid receptors) and cimetidine (histamine H₂-receptors). Noncompetitive inhibitors (e.g., insecticides and phenylcyclidine for acetylcholine receptors) inactivate the receptor or enzyme without altering the binding of substrate to the receptor; these types of inhibitors inactivate the receptor whether or not substrate is bound.

An *agonist* interacts with the receptor and elicits a maximal pharmacologic effect (in this example, epinephrine is an agonist at beta receptors). A *partial agonist* elicits a partial or submaximal response when it interacts with the receptor (e.g., ephedrine binding to β-receptors, buprenorphine binding to μ-receptors).

**Concentration-Response Relationships**

In order to discuss the relationship between the concentration of drug and the resulting pharmacologic response, first consider the two extremes of this relationship. At one extreme, when no drug is present the effect is zero, or at least at a baseline level, as indicated by point A in the figure below. Note that most drugs modulate a given physiologic function, so in many cases, pharmacologic response must be determined relative to a baseline value which is typically not zero (e.g., blood pressure, heart rate). At the opposite extreme of this relationship, when all the receptors are occupied a maximal pharmacologic effect is approached, as indicated by point B on the figure below. According to theory, the maximal response will occur in association with activation of all receptors in the system. This maximal response is denoted as $E_{\text{MAX}}$, (effect maximum).
The portion of the relationship between these two extremes (points A and B) is not linear, because according to receptor theory, pharmacologic response asymptotically approaches a maximal level ($E_{\text{MAX}}$). This relationship is illustrated graphically below. Effect is always plotted on a linear scale; concentration typically is plotted on a log scale. Note the difference in the shape of the concentration-effect relationship resulting from plotting drug concentration on a linear (left) vs. a log (right) scale. Thus, concentration-effect relationships are generally described as being sigmoidal (or ‘S’-shaped).

Analogous to the concept of $K_m$ in an enzyme-substrate reaction, the term $EC_{50}$ denotes the concentration of drug which is required to elicit 50% of the maximal response (the $E_{\text{MAX}}$) as depicted in the figure below.
Figure 14-5: Concentration-effect relationship: $E_{\text{MAX}}$ is the maximal effect, $EC_{50}$ is the concentration that elicits 50% the maximal response. Gray lines represent concentration-effect relationships with various $EC_{50}$ values.

The $EC_{50}$ is commonly used to compare drug potency. As the $EC_{50}$ denotes a concentration that is required to elicit a given response, the lower the $EC_{50}$ is, the higher the potency of the drug (i.e., the lower the drug concentration required to elicit 50% of the maximal response). In the figure above, the concept of $EC_{50}$ is illustrated graphically in terms of its relationship to the concentration-effect profile. Note that the shape of the relationship does not change with $EC_{50}$; only the location of the profile along the x-axis changes. The profiles shifted toward the left (gray dotted, gray dashed) represent more potent drugs (lower $EC_{50}$). The profiles shifted toward the right (gray solid) represent less potent drugs (higher $EC_{50}$).

An additional term, $ED_{50}$, is similar to $EC_{50}$ but refers to the relationship between dose and therapeutic response (D for dose, C for concentration). Other analogous terms are $LD_{50}$, which refers to the dose that is lethal to 50% of the organisms to which it is administered, and $TD_{50}$, which refers to the dose that produces a specific toxicity in 50% of the organisms to which it is administered (e.g., tumor growth). Both of these latter metrics indicate a relationship between dose and toxicity rather than therapeutic effect.

The ratio of $TD_{50}/ED_{50}$ is referred to as the therapeutic ratio or therapeutic index. A large value indicates that the dose that elicits a therapeutic response is substantially smaller than the dose which elicits a toxic response. Thus, it is desirable for this ratio to be large (> 2, but the larger the better). Therapeutic drug monitoring, as discussed in the first chapter, is particularly important for drugs with a narrow therapeutic window (that is, the concentrations required to produce therapeutic responses are very close to the concentrations which elicit toxic responses). Essentially, the therapeutic ratio indicates the magnitude of the difference between the doses that produce a given level of therapeutic (e.g., 50% of $E_{\text{MAX}}$) vs. toxic (e.g., 50% of the maximum toxic response) response, as illustrated in the figure below. Drugs that require therapeutic monitoring (e.g., digoxin, lithium) have low therapeutic ratios (~2).
Figure 14-6: Therapeutic index is defined by the ratio of the TD_{50} (dose that elicits toxicity in 50% of the subjects) to the ED_{50} (dose that elicits therapeutic effect in 50% of the subjects)

The equation below describes effect (E) as a function of drug concentration (C). Note that dose can be substituted for concentration (in that case, ED_{50} substitutes for EC_{50}).

\[
E = \frac{E_{MAX} \cdot C}{EC_{50} + C}
\]

Equation 14-1

In this equation, \(E_{MAX}\) is the maximum possible effect, \(C\) is concentration at the site of action and \(EC_{50}\) is the concentration that elicits 50% of the maximal response. In clinical settings, blood concentrations (rather than concentrations at the site of drug action) are typically measured due to practical limitations associated with sampling from, for example, tissues or organs. Blood concentration is therefore a surrogate for concentration at the site of drug action (e.g., heart tissue, brain, etc.).

The equation above describes the response to drug as saturable (i.e., as concentration increases, pharmacologic effect approaches \(E_{MAX}\) asymptotically). This graded nature of pharmacologic responses (as opposed to a binary “on or off” type of response) is very important because it allows a desired level of therapeutic effect to be achieved by titrating, or adjusting the size of, a dose of drug. Although the relationships between pharmacologic response and dose (or concentration) are always sigmoidal, the slope of the effect vs. the natural log of the dose (or concentration) may vary. A factor known as the Hill coefficient (N) accounts for this difference, which is drug-specific.

\[
E = \frac{E_{MAX} \cdot C^N}{EC_{50}^N + C^N}
\]

Equation 14-2
Generally, the minimum value of N is assumed to be 1. As this value increases, the slope of the relationship between effect and the log of the drug concentration becomes very steep. As N becomes very large, the response becomes essentially binary instead of graded (i.e., with a very small increase in concentration, the response abruptly changes from 0 to 100%). Pharmacologic responses tend, however, to be graded. Clinically, a small slope in this relationship is desirable, because it allows for doses to be titrated more easily.

Figure 14-7: Impact of increasing the Hill coefficient, N, on the shape of the log-concentration vs. response relationship

In some (but not all) cases, value of the Hill coefficient may represent some physiological event which impacts the log-concentration vs. effect relationship. For example, in terms of the sigmoidal relationship between oxygen concentration and hemoglobin saturation, the Hill coefficient reflects the stoichiometry of the hemoglobin-oxygen binding reaction (i.e., one molecule of hemoglobin binds 4 oxygen molecules, thus, N=4). In the case of a drug concentration vs. response relationship, N could reflect the stoichiometry of drug-receptor binding, (i.e., the Hill coefficient would reflect the number of molecules which are required to bind to each receptor in order to yield a given quantal pharmacologic response). Most frequently, the Hill coefficient is an empirical parameter that describes the steepness of the slope; it does not correspond to any particular physiologic process.
Regions of the Concentration-Response Profile

The discussion of concentration-response relationships, up to this point has focused upon the entire theoretical range of the relationship between drug concentration and effect. In practice, however, the concentration-effect relationship observed for most drugs administered within their therapeutic range does not appear sigmoidal, because this range of therapeutic concentrations and observed effects constitutes only a small portion of the entire theoretical relationship Therefore, it often is necessary to consider which region of the theoretical concentration-effect profile the observed concentration-effect values occupy.

First, consider the area at the foot of the curve, far below the EC\textsubscript{50} ([Drug] \ll EC\textsubscript{50}). Within this region, the relationship between concentration and response is essentially linear; an increase in concentration will result in a proportional increase in effect. Antihypertensives are examples of drugs that act in this area of the concentration-response curve. Note that this relationship does not appear linear in the graph below; the log scale of the x-axis causes this linear relationship to appear curved.

Consider the above example, in which EC\textsubscript{50} is 8 and the E\textsubscript{MAX} is 100. In order to increase the effect by 50% (e.g., from 5 to 7.5) it would be necessary to increase the concentration by 50%. Again, within this portion of the relationship, a linear increase in concentration results in a linear increase in effect.

Next, consider the region surrounding the EC\textsubscript{50}. The concentration-effect relationship within this region is log-linear, i.e., a log-change in concentration results in a linear increase in effect. This log-linear region typically exists between 20 and 80% of the maximal effect. Neuromuscular blockers, propranolol and theophylline are examples of drugs that exert
their therapeutic effects within in this range of the theoretical concentration-response relationship.

**Figure 14-9: Theoretical concentration-response relationship where the gray region indicates the log-linear portion of the relationship ([Drug] \approx EC_{50})**

In the above example, the EC$_{50}$ is 8 and the E$_{MAX}$ is 100. In order to increase the effect by 50% (e.g., from 50 to 75), it would be necessary to increase the concentration by 3-fold. Again, within this portion of the theoretical concentration-response profile a log-linear relationship exists between concentration and response.

Finally, consider the upper portion of the curve, closest to the maximal effect (where [Drug] >> EC$_{50}$). Within this region, large changes in drug concentration will result in only minimal changes in effect. This range of the theoretical concentration-response profile will not be relevant for most clinically useful drugs. Some SSRIs are administered in this region of the profile. In such cases, increasing dose will not necessarily translate to an increase in effect (or at least therapeutic effect). The “law of diminishing returns” applies to responses within this portion of the sigmoidal curve (i.e., as the value of x increases, the corresponding increase in the y value will become vanishingly small).
As an example, the EC$_{50}$ in the above graph is 8 and the E$_{MAX}$ is 100. To increase the effect by 10% (e.g., from 85 to 94), it would be necessary to increase the concentration by 2.5-fold. Note that within this portion of the theoretical concentration-effect relationship, a large increase in concentration yields a small increase in effect.

The table below summarizes the properties of the different regions of the concentration-effect relationship.

**Table 14-2: Examples of how different regions of the concentration-response relationship behave**

<table>
<thead>
<tr>
<th>Region</th>
<th>[Drug]</th>
<th>Drug vs. Effect Relationship</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>$&lt;&lt;$ EC$_{50}$</td>
<td>Linear</td>
<td>antihypertensives</td>
</tr>
<tr>
<td>II</td>
<td>$\approx$ EC$_{50}$</td>
<td>Log-linear</td>
<td>neuromuscular blockers</td>
</tr>
<tr>
<td>III</td>
<td>$&gt;&gt;$ EC$_{50}$</td>
<td>Curved</td>
<td>SSRIs</td>
</tr>
</tbody>
</table>

**Hysteresis Effects: Impact of Time and Tolerance**

Recall that blood concentrations often are used clinically as a surrogate for concentrations at the site of drug action because of the difficulty associated with sampling concentrations at the site of drug action. Although typically, a plasma drug concentration vs. effect profile will exhibit a sigmoidal shape, this is not always the case. Due to that fact that the time course of the change in plasma drug concentrations will not necessarily parallel the time course of the change in concentrations at the site of drug action (the receptor site), a direct relationship between effect and plasma drug concentrations is not always observed. Some drugs may exhibit concentration-response profiles that appear as loops (i.e., hysteresis), such that at a given plasma concentration can be associat-
ed with two significantly different response levels. This disparity between the responses associated with a given plasma drug concentration reflects a time-dependent relationship between effect and plasma concentrations. Thus, a hysteresis loop can be considered to be either clockwise or counterclockwise, depending upon the region of the loop which corresponds to early vs. late sampling times, as will be discussed below.

For cases in which the target site for pharmacologic effect is in a peripheral compartment, the rate of drug equilibration between the plasma and the peripheral compartment is slow (recall that pharmacokinetic compartments are distinguished, in part, by their lack of instantaneous equilibration with drug in the central compartment). For example, the time-dependent change of concentrations in the brain will lag behind the corresponding changes of concentrations in the blood. Due, in part, to the existence of a physiologic and biochemical barrier between the two tissues (i.e., the blood-brain barrier), equilibration between the brain and plasma compartments will be relatively slow.

In order to illustrate the complexity of the relationship between effect, plasma concentration, and concentration at the site of action, the figure below depicts all three time-dependent profiles on the same time scale. The lines represent effect (gray), drug concentrations in the blood (solid black) and drug concentrations in the brain (dotted). Assume that concentrations in the brain drive pharmacologic effect, and that the relationship between brain drug concentration and effect is sigmoidal.

![Figure 14-11: Time-dependent changes in blood concentration (solid black), brain concentration (dotted) and effect (gray), where the site of action, the brain, is in a peripheral pharmacokinetic compartment](image)

Note that in the above example, brain concentrations increase more slowly and peak later, relative to blood concentrations. This temporal delay results in a counterclockwise hysteresis (loop effect) in the blood concentration-effect profile, as illustrated below.
In the figure above, arrows indicate the direction of time along the blood concentration-effect hysteresis loop. Time is the link between the concentration-time relationship and the effect-time relationship illustrated in Figure 0-11. For example, consider a single blood concentration value (e.g., 1) in the figure above. At an early time after extravascular drug administration, the blood concentration will be low (since it takes time for the drug to be absorbed into the blood) and the effect corresponding to this blood concentration of 1 will also be low (e.g., 10%). As blood concentrations reach their C\text{MAX} and subsequently decline, the blood concentration will again reach a value of 1. However, at this point in time, the corresponding effect is very high (e.g., 80%). This reflects the fact that when blood concentrations are at their peak, concentrations at the site of action in the peripheral compartment will still be rising (thus, the level of effect will still be rising), and when concentrations at the site of action in the peripheral compartment are at their peak (thus, the effect will be at its peak), blood concentrations will have already begun to decline.

Several types of mechanisms can potentially underlie counterclockwise hysteresis behavior. As discussed above, if the site of action lies in a peripheral pharmacokinetic compartment, hysteresis will be apparent in the blood concentration vs. effect relationship, reflecting a slow equilibration of drug in the blood with the effect site.

Indirect pharmacokinetic response is another mechanism that can underlie counterclockwise hysteresis behavior. Indirect effects result from a cascade of biochemical events. For example, when a drug activates a receptor, the receptor may, in turn activate a second messenger molecule, and the second messenger acts to increases protein synthesis. The sequence of events between receptor activation and the development of pharmacologic effect will take time, thus, a temporal dissociation between blood concentration and effect will be observed.
A third mechanism that may result in hysteresis in the blood concentration-effect relationship is the metabolism of parent drug to a pharmacologically active metabolite. Since the process of metabolism takes time, the pharmacologic effect (which arises from production of the metabolite) will be delayed relative to the time course of the concentration of parent drug in the blood. Note that the graphical relationship between metabolite concentration and effect would be sigmoidal

**Drug → Metabolite → Effect**

The relationship between blood concentration and effect also can exhibit clockwise hysteresis. A clockwise hysteresis is indicative of acute tolerance, because as blood concentrations increase, effect will initially increase but then as blood concentrations continue to increase, the corresponding level of effect declines. This situation is illustrated in the figure below. Consider, for example, a single concentration (e.g., 150). At early points (prior to the development of tolerance), blood concentrations are rising (as would be the case following oral administration), and the effect corresponding to a concentration of 150 is approximately 40. As blood concentrations begin to fall, the development of tolerance causes the pharmacologic effect to begin to decrease, even though blood concentrations are still rising. Thus, when concentrations decline to a value of 150, the corresponding effect is only 20. This type of behavior is common in the case of drugs that exert their pharmacologic effects on highly regulated physiologic parameters such as blood pressure. For example, cocaine, caffeine, nitroglycerin and ephedrine will increase blood pressure. However, since numerous homeostatic mechanisms work to regulate blood pressure, the effect of a given concentration of drug decreases with time as the body re-adjusts to keep blood pressure at its “biologic set-point”.

![Figure 14-13: Blood concentration vs. effect: note the clockwise hysteresis which is indicative of acute tolerance](image-url)
**Concentration-Response versus Dose-Response**

The previous section focused primarily on the concentration-response relationship, that is, the relationship between drug concentration and the pharmacologic response. The relationship can take many forms from linear, log-linear, sigmoidal or hysteresis. The dose-response relationship also can take many forms but because the dose-response relationship does not take into account time, you generally do not see hysteresis effects. Thus the concentration-response and dose-response for the same drug and same response can look different. For example, a drug might have dose-response relationship that follows the \( E_{\text{MAX}} \) (sigmoidal) relationship but when you look at the concentration-response relationship it may show counter-clockwise hysteresis.

In dose-response relationship you may also see different relations such as U-shaped (or J shaped) or inverted U-shaped (or inverted J-shaped)

![Example of an inverted J-shape response curve](image)

What these relationships tell us is that there is some optimal dose and that if we go too low we are sub-therapeutic but if we go to high it might worsen the condition we are trying to treat.

It is important to keep in mind that not all drugs have established concentration-response relationships or even dose-response relationships, though it is more likely a drug will have a defined dose-response relationship than a concentration-response relationship by the nature of clinical research and drug development.

**Estimating Duration and Magnitude of Action**

The discussion thus far has centered on conceptual aspects of pharmacodynamic behavior. The goal of pharmacodynamics (and fun-
dramatically, also of pharmacokinetics) is to predict pharmacologic effect. Pharmacokinetics is meaningless unless some sort of pharmacologic outcome is involved. The integration of pharmacokinetic and pharmacodynamic principles to describe and predict drug effects can, however, become somewhat complicated mathematically. For this reason, our discussion will be restricted to a very simple practical application: estimation of duration of drug action. For example, consider a drug that is administered via IV bolus. The observed pharmacological effects fall within the log-linear portion of the theoretical concentration-effect curve (the portion of the curve surrounding the EC_{50}; i.e., between 20 and 80% of the E_{MAX}). Based upon the equations for effect and concentration, equations describing effect vs. time can be developed as indicated below.

\[ E = m \cdot \ln(C) + e \]  
Equation 14-3

Where E is the effect (dependent variable), C is the blood concentration (the independent variable), m is the slope of the line and e is the y-intercept. This equation is simply the equation for a straight line (y=mx+b). The effect at time = 0 (termed E₀) corresponds to the concentration at time=0 (C₀).

\[ E_0 = m \cdot \ln(C_0) + e \]  
Equation 14-4

The e term may be eliminated by subtracting:

\[ E_0 = m \cdot \ln(C_0) + e \]

- (E = m \cdot \ln(C) + e )
\[ E_0 - E = m \cdot (\ln(C_0) - \ln(C)) \]

The resulting equation relates the effect at time = 0 (and thus, \( C_0 \)) to the effect at some concentration, \( C \). The equation for the change in concentration with respect to time after an IV bolus dose then can be inserted. Recall that:

\[ \ln(C_0) - \ln(C) = kt \]

Effect can thus be expressed as a function of \( k \)

\[ E_0 - E = m \cdot (kt) \quad \text{Equation 14-5} \]

and finally, the equation can be rearranged to solve for \( E \)

\[ E = E_0 - m \cdot (kt) \quad \text{Equation 14-6} \]

The graphical relationship between effect (\( E \)) and time (\( t \)) is linear, with a slope of \(-mk\) and a y-intercept of \( E_0 \). The slope of the line is thus reflective of the magnitude of the effect (\( m \), the slope from the log-linear profile) and the half-life (\( K \)) of the drug.

Pharmacologic effect can be prolonged by changing either the input (e.g., dose), the output (e.g., the half-life) or the concentration-effect relationship (e.g., change “\( m \)” by choosing a different drug). Note that “\( m \)” is related to the sigmoidicity factor “\( N \)”. For example, a drug with a long half-life will elicit a more sustained pharmacologic effect. A drug with a high value of \( N \) will exhibit very rapid increases or decreases in effect (the steeper the slope, the shorter the duration of action). Short-acting
Anesthetics have short half-lives but short-acting opioids tend to have large N values (i.e., steep slopes in the log concentration-response relationship).

Using the relationships described above, it is possible to estimate the duration of action for a drug as illustrated below. Note that this example applies only to a system with IV bolus input, 1-compartment pharmacokinetic behavior, and a range of pharmacologic effects that fall within the log-linear portion of the theoretical concentration-effect range. By considering the situation in which \( E = E_{\text{MIN}} \) (the minimum effect) and then solving for \( t \), the duration of action \( (t_d) \) can be calculated as:

\[
 t_d = \frac{E_0 - E_{\text{MIN}}}{m \cdot k} \quad \text{Equation 14-7}
\]

or in terms of concentrations:

\[
 t_d = \frac{\ln \left( \frac{X_0 / V \cdot C_{\text{MEC}}}{K} \right)}{K} \quad \text{Equation 14-8}
\]

where \( C_{\text{MEC}} \) is the minimum effective concentration, \( X_0 \) is the dose, \( V \) is volume and \( k \) is the elimination rate constant (realize that \( X_0 / V \) is equal to \( C_0 \)). The \( C_{\text{MEC}} \) can be relevant in clinical situations with drugs such as neuromuscular blockers or antibiotics. In the case of these types of drugs, a minimum concentration is required in order to elicit a desired pharmacologic response. This equation is useful, for example, in the context of neuromuscular blocker administration during surgery. In this situation, it is necessary to determine the drug’s half-life as well as the minimum concentration necessary to maintain neuromuscular blockade. Using the equations presented above, it is possible to select a dose that will elicit the desired duration of effect (e.g., the effect should last during the entire surgery but disappear soon after the surgery is complete).
Example: A patient is administered tubocurarine prior to surgery for the purpose of establishing neuromuscular blockade. The half-life of tubocurarine is 150 min, V is 20 L/kg and the minimum effective concentration is 0.5 mg/L. Calculate a dose which will maintain blockade for 60 min.

\[ t_d = \frac{\ln \left( \frac{X_0}{V \cdot C_{MEC}} \right)}{K} \]

\[ X_0 = e^{t_d \cdot K} \cdot V \cdot C_{MEC} \]

\[ X_0 = e^{60 \cdot 0.0046} \cdot 20 \cdot 0.5 \]

\[ X_0 = 13 \text{ mg/kg} \]

Integration of pharmacokinetics and pharmacodynamics allows clinicians to make good decisions about questions such as “what is the best dose?” “what is the best dosing regimen?” “what is the best route of administration?” and “what is the best dosage form?”.

Summary

The discipline of pharmacodynamics deals with the relationships between drug concentration and pharmacologic effect, as well as the time course of pharmacologic response. The steepness of the relationship between concentration and effect is governed by a slope factor. This slope factor is important in determining how to titrate doses to achieve a desired effect, and also may influence the duration of action of the drug. By combining the equations which describe pharmacodynamic behavior (concentration-effect relationships) with equations which describe pharmacokinetic behavior (concentration-time relationships) it is possible to predict pharmacologic effect in relation to time and ultimately, to design dosage regimens that will produce desirable therapeutic outcomes.
**Skills Obtained**

- Defining the relationship of concentrations to pharmacologic response using descriptors such as $E_{\text{MAX}}$, $EC_{50}$ and $N$
- Estimating the duration of action of a drug administered as a IV bolus, assuming 1-compartment behavior and a range of observed responses which lies within the log-linear portion of the theoretical concentration-response curve
  - How long will neuromuscular blockade last for an agent with a half-life of 20 min, when $X_0 = 5 \text{ mg}$, $V = 100 \text{ L}$ and the minimum effective concentration is 15 $\mu\text{g}/\text{L}$?
- Predicting the magnitude of pharmacologic response
  - What will be the effect on heart rate of a sympathetic stimulant with an $E_{\text{MAX}} = 130 \text{ bpm}$, $EC_{50} = 10 \text{ mg}/\text{L}$ and a concentration at the site of action of 25 $\text{mg}/\text{L}$?
- Describing the factors which could cause a counterclockwise hysteresis in the concentration-effect profile
- Defining the term *clockwise hysteresis*

**Summary Equations**

Estimate response from concentration data:

$$E = \frac{E_{\text{MAX}} \cdot C^N}{EC_{50}^N + C^N}$$

Estimate response at a specific point in time in the log-linear phase of the concentration-effect profile.

$$E = E_0 - m \cdot (kt)$$

Estimate the duration of action for a 1-compartment system after IV bolus administration in the log-linear portion of the concentration-response profile: in terms of effect.

$$t_d = \frac{E_0 - E_{\text{min}}}{m \cdot k}$$

Estimate the duration of action for a 1-compartment system after IV bolus administration in the log-linear portion of the concentration-response profile: in terms of concentration.
$$t_d = \frac{\ln \left( \frac{X_0}{V \cdot C_{MEC}} \right)}{k}$$

New Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Represents</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Drug affinity for receptor</td>
<td>The concentration of drug that elicits 50% of the maximal pharmacologic response</td>
<td>Mass per volume (e.g., mg/L)</td>
</tr>
<tr>
<td>E&lt;sub&gt;MAX&lt;/sub&gt;</td>
<td>Maximal effect</td>
<td>The maximal pharmacologic response of the system</td>
<td>Varies (e.g., % change, heart rate)</td>
</tr>
<tr>
<td>N</td>
<td>Hill coefficient</td>
<td>Sigmoidicity factor that determines the log-linear slope of the relationship between drug concentration and response</td>
<td>Unitless</td>
</tr>
<tr>
<td>E</td>
<td>Effect</td>
<td>The measured pharmacologic effect</td>
<td>Varies</td>
</tr>
</tbody>
</table>
Dealing with Functions of a Line

Often in pharmacokinetics, pairs of parameters can be related to each other by a straight line. The equation for a line can be expressed as:

\[ Y = mx + b \]

where \( m \) is the slope of the line, and \( b \) is the \( y \)-intercept.

The following examples present various lines both graphically and in the form of an equation. In particular, note the difference between the steepness as well as the orientation of the slopes (positive and negative \( x \) values indicate whether the slope is positive or negative relative to the \( x \) axis).

Above is a positive slope (i.e., oriented such that higher \( y \) values correspond to higher \( x \) values). The orientation of the slope is indicated in the equation by a positive value of the \( x \) term.
In the case above, there is no relationship between the two variables (i.e., $y$ is independent of $x$).

The above line evidences a negative slope in relation to the $x$ axis (i.e., oriented such that smaller $y$ values correspond to larger $x$ values), again in the equation by a negative value of the $x$ term.

**Determination of slope**

\[
\text{Slope (m)} = \frac{\text{rise}}{\text{run}} = \frac{\Delta y}{\Delta x} = \frac{y_2 - y_1}{x_2 - x_1}
\]
For example: \[ m = \frac{y_2 - y_1}{x_2 - x_1} = \frac{1-3}{3-1} = -1 \]

**Determining the Intercept**

For the above example, \( y = -1x + b \):

Consider a single point on the line \((1, 3)\)

\[ 3 = (-1)(1) + b \]

\[ b = 4 \]

the equation for this line may be written as:

\[ Y = -1x + 4 \]

In some cases, data plotted on rectilinear (Cartesian) coordinates appears curved and cannot be described by a straight line. For example:
Calculating the natural logarithm of the y-axis values and re-plotting the resulting coordinates will result in a straight line:

A simpler approach, which does not require log-transformation of the data, is to plot the data on semi-log coordinates

**Determination of Slope on Semi-log Coordinates**

In many situations in pharmacokinetics, data plotted on semi-log coordinates will produce a straight line. A simple method to determine the slope of this line is as follows:

1) Plot the data and draw the best-fitting line through them
2) Read the y-intercept (b) from the graph

3) Determine the x-value at which y is equal to one-half of the y-intercept (x_{1/2})

4) The slope of the line is \( 0.693/x_{1/2} \)

![Graph showing y vs. x with t_{1/2} indicated]  

The slope also may be calculated based upon any two points on a straight line:

\[
m = \frac{\ln y_2 - \ln y_1}{x_2 - x_1} = \frac{\ln \left( \frac{y_2}{y_1} \right)}{x_2 - x_1}
\]

**Dealing with Exponents and Logarithms**

Many pharmacokinetic processes can be described by an exponential function. The following sections review the concepts of exponents and logarithms.

**Exponents**

An exponent is expressed as follows:

\[ N = b^x \]

Where:

\[ x \] represents the exponent
b represents the base

\[ b^x \] is the \( x \)th power of the base \( b \)

For example: \( 1000 = 10^3 \) where 3 is exponent and \( 10^3 \) is the third power of the base 10

<table>
<thead>
<tr>
<th>Law of Exponents</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>((a^x)(a^y) = a^{x+y})</td>
<td>((10^4)(10^3) = 10^7)</td>
</tr>
<tr>
<td>((a^x)^y = a^{x \cdot y})</td>
<td>((10^4)^3 = 10^{12})</td>
</tr>
<tr>
<td>(\frac{a^x}{a^y} = a^{x-y})</td>
<td>(\frac{10^2}{10^3} = 10^{-1})</td>
</tr>
<tr>
<td>(\frac{1}{a^y} = a^{-y})</td>
<td>(\frac{1}{10^3} = 10^{-3})</td>
</tr>
<tr>
<td>(y^a = a^{1/y})</td>
<td>(10^1 = 10^{1/2})</td>
</tr>
<tr>
<td>(a^0 = 1)</td>
<td>(10^0 = 1)</td>
</tr>
</tbody>
</table>

Note: \(10^3 = 1000\) whereas \(10^{-3} = 0.001\)

**Logarithms**

The log of a number is the exponent to which a given base must be raised in order to equal that number. For example:

If \( N = b^x \) then \( \log_b N = x \)

For example: \(1000 = 10^3\) or \( \log_{10}1000 = 3 \)

If no base is specified, it is assumed that the base is 10

<table>
<thead>
<tr>
<th>Law of Logarithms</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \log (a \cdot b) = \log a + \log b )</td>
<td>( \log (2 \cdot 3) = \log 2 + \log 3 = 0.778 )</td>
</tr>
<tr>
<td>( \log (a/b) = \log a - \log b )</td>
<td>( \log (2/3) = \log 2 - \log 3 = -0.176 )</td>
</tr>
<tr>
<td>( \log a^x = x \log a )</td>
<td>( \log 2^4 = 4 \cdot \log 2 = 1.204 )</td>
</tr>
<tr>
<td>( -\log (a/b) = \log (b/a) )</td>
<td>( -\log (2/3) = \log 3 - \log 2 = 0.176 )</td>
</tr>
</tbody>
</table>
Ten (10) is one of the two base numbers used for logarithms. It is called the common logarithm and is generally expressed as “log”

The other base number used for logarithms is 2.718281828…, which is called ‘e’. Logarithms to the base “e” are called natural logarithms and are generally expressed as “ln”.

Examples:
\[ e^x = y \quad e^2 = 7.39 \]
\[ x = \ln y \quad 2 = \ln 7.39 \]

<table>
<thead>
<tr>
<th>Law of Natural Logarithms</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \ln (a\cdot b) = \ln a + \ln b )</td>
<td>( \ln (2\cdot 3) = \ln 2 + \ln 3 = 1.792 )</td>
</tr>
<tr>
<td>( \ln (a/b) = \ln a - \ln b )</td>
<td>( \ln (2/3) = \ln 2 - \ln 3 = -0.405 )</td>
</tr>
<tr>
<td>( \ln a^x = x \ln a )</td>
<td>( \ln 2^3 = 3\ln 2 = 2.079 )</td>
</tr>
<tr>
<td>-\ln (a/b) = \ln (b/a)</td>
<td>-\ln (2/3) = \ln 3 - \ln 2 = 0.405</td>
</tr>
<tr>
<td>( \ln (e) = 1 )</td>
<td>( e^{\ln (2)} = 2 )</td>
</tr>
<tr>
<td>( e^{\ln (a)} = a )</td>
<td></td>
</tr>
<tr>
<td>( \ln 1 = 0 )</td>
<td></td>
</tr>
</tbody>
</table>

Common mistakes: \( \ln (a+b) = \ln a + \ln b \)
\[ \ln (a-b) = \ln a - \ln b \]

Natural logarithms are related to common logarithms by a factor of 2.303
\[ \ln x = 2.303 \log x \]
For example: \( \ln 8 = 2.303 \log 8 \)

**Practice Problems**

1) Solve for \( x \) in the following equation

   \[ \text{Step 1)} \quad 10 = 30e^{-5x} \]
Step 2) \( \frac{1}{3} = e^{-5x} \)
Step 3) \( \ln \left( \frac{1}{3} \right) = \ln e^{-5x} \)
Step 4) \(-1.099 = -5x\)
Step 5) \(x = 0.220\)

2) Solve for \(x\) in the following equation

Step 1) \(x = 25e^{-0.40}\)
Step 2) \(\ln(x) = \ln(25) + \ln(e^{-0.40})\)
Step 3) \(\ln(x) = 3.22 - 0.40\)
Step 4) \(\ln(x) = 2.82\)
Step 5) \(x = 16.76\)

3) Solve for \(t\) (time in h) in the following equation

Step 1) \(0.3 = 1 - e^{-0.2t}\)
Step 2) \(0.7 = e^{-0.2t}\)
Step 3) \(\ln(0.7) = -0.2t\)
Step 4) \(t = 1.78\) h
## Appendix B: Common Pharmacokinetic Terms and Their Units

Symbols and units for various pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbols</th>
<th>Units</th>
<th>Example</th>
<th>Alternate a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>$X_0$</td>
<td>Mass</td>
<td>mg</td>
<td>D</td>
</tr>
<tr>
<td>Concentration</td>
<td>$C$</td>
<td>Mass/volume</td>
<td>mg/L</td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>$dx/dt$</td>
<td>Mass/time</td>
<td>mg/hr</td>
<td></td>
</tr>
<tr>
<td>Zero-order Rate Constant</td>
<td>$k_0$</td>
<td>Mass/time</td>
<td>mg/hr</td>
<td></td>
</tr>
<tr>
<td>First-order Rate Constant b</td>
<td>$k$</td>
<td>Time$^{-1}$</td>
<td>hr$^{-1}$</td>
<td>$\lambda$, $k_e$</td>
</tr>
<tr>
<td>Volume of distribution c</td>
<td>$V$</td>
<td>Volume</td>
<td>L</td>
<td>$V_D$</td>
</tr>
<tr>
<td>Area-under-the-curve d</td>
<td>AUC</td>
<td>Concentration$\cdot$time</td>
<td>mg$\cdot$h/L</td>
<td></td>
</tr>
<tr>
<td>Bioavailability</td>
<td>$F$</td>
<td>No units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance</td>
<td>$CL$</td>
<td>Volume/Time</td>
<td>mL/hr</td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>$t_{1/2}$</td>
<td>Time</td>
<td>hr</td>
<td></td>
</tr>
<tr>
<td>Amount f</td>
<td>$X$</td>
<td>mass</td>
<td>mg</td>
<td>A</td>
</tr>
<tr>
<td>Time</td>
<td>$t$</td>
<td>time</td>
<td>hours</td>
<td></td>
</tr>
<tr>
<td>Infusion Time</td>
<td>$T$</td>
<td>time</td>
<td>hours</td>
<td></td>
</tr>
<tr>
<td>Extraction ratio</td>
<td>$E$</td>
<td>No units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood flow</td>
<td>$Q$</td>
<td>Volume/time</td>
<td>mL/min</td>
<td></td>
</tr>
<tr>
<td>Fraction unbound</td>
<td>$f_U$</td>
<td>No units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing Interval</td>
<td>$\tau$</td>
<td>time</td>
<td>h</td>
<td></td>
</tr>
</tbody>
</table>

a symbols used by other textbooks

b a subscript ‘a’ represents rate constant of absorption, no subscript represents elimination rate constant (a subscript of ‘e’ also represents elimination rate constant)

c a subscript ‘c’ indicates central compartment volume, ‘p’ is peripheral compartment, ‘ss’ is steady-state, ‘$\beta$’ volume of the terminal phase

d with no subscript represents AUC from time = 0 through time = infinity, a subscript ‘t’ or any number (e.g., AUC$_{24}$) represents the AUC from time = 0 through time = t (or whatever number the subscript is)

e a subscript “I” represents intrinsic clearance, a subscript ‘R’ represents a renal clearance, a subscript ‘H’ represents hepatic clearance

f a subscript ‘U’ represents amount excreted in the urine
Appendix C: Useful Equations

Please note that the right-hand side assumes steady-state conditions. Equations for conditions approaching steady-state are slightly different.

Eq 1: \[ C = \frac{X_0}{V} e^{-kt} \]

Eq 2: \[ C = \frac{k_0}{Cl} (1 - e^{-kt}) \]

Eq 3: \[ C = \frac{k_0}{Cl} (1 - e^{-kt}) \cdot e^{-k(T-t)} \]

Eq 4: \[ C = \frac{k_a X_0 F}{V \cdot (k_a - K)} (e^{-kt} - e^{-k_at}) \]
Eq 5: \[ C = \frac{X_0 e^{-Kt}}{V (1 - e^{-Kt})} \]

Eq 6: \[ C = \frac{k_0 (1 - e^{-Kt})}{Cl (1 - e^{-Kt})} \]

Eq 7: \[ C = \frac{k_0 (1 - e^{-KT})}{Cl (1 - e^{-Kt})} \]

Eq 8: \[ C = \frac{k_a X_0 F}{V (k_a - K)} \left( \frac{e^{-Kt}}{(1 - e^{-Kt})} - \frac{e^{-K_{st}}}{(1 - e^{-K_{st}})} \right) \]
Appendix D: Method of Residuals

In the extravascular dosing chapter we discussed using the method of residuals to obtain an estimate of the absorption rate constant, $k_a$. The method of residuals is a way to tease apart absorption rate from a concentration-time profile after extravascular administration in a 1-compartment system OR to tease apart the distribution and elimination phases for a 2-compartment IV bolus model.

Below, this method will be discussed in the context of extravascular administration. In the concentration-time profile, the beginning part of the profile is determined by both absorption and elimination. In general, absorption occurs much faster than elimination, therefore absorption will end and the terminal portion of the profile is determined solely by elimination (assuming $k_a >> k$).

To tease the absorption rate out from the beginning part of the profile follow the steps below, given the data presented in the following table:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.25</td>
<td>2.8</td>
</tr>
<tr>
<td>0.5</td>
<td>4.1</td>
</tr>
<tr>
<td>0.75</td>
<td>4.6</td>
</tr>
<tr>
<td>1</td>
<td>4.7</td>
</tr>
<tr>
<td>1.5</td>
<td>4.4</td>
</tr>
<tr>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
</tr>
<tr>
<td>8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Step 1)** Plot the data on semi-log coordinates. Find the terminal
Step 2) Extend the terminal slope so that it intersects the y-axis as shown by the dashed line. This will serve as a reference line.

![Graph showing terminal slope and dashed line]

Step 3) It is necessary to calculate the difference in y values (i.e., the residual values) between the points on the dashed line (solid circle) and the points on the concentration-time profile (open circles).

![Graph with dashed line and concentraion-time profile]

Values for the data represented by closed circles can be estimated from the graph, and the values of the open circles are known (from the data set). NOTE: exact values can be calculated based upon the equation for the dashed.

Calculate only want the points preceding the $C_{MAX}$

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] (mg/L)</th>
<th>Dashed-Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>7.0</td>
</tr>
<tr>
<td>0.25</td>
<td>2.8</td>
<td>6.5</td>
</tr>
<tr>
<td>0.5</td>
<td>4.1</td>
<td>6.1</td>
</tr>
<tr>
<td>0.75</td>
<td>4.6</td>
<td>5.7</td>
</tr>
<tr>
<td>1</td>
<td>4.7</td>
<td>---</td>
</tr>
<tr>
<td>1.5</td>
<td>4.4</td>
<td>---</td>
</tr>
</tbody>
</table>
Step 4) Subtract the dashed-line values from the actual data points. Remember, the dashed line represents the contribution of elimination processes while the solid line represents the combined contributions of absorption plus elimination. By subtracting the influence of elimination, the values of the differences will indicate the contribution of absorption processes to the concentration-time profile.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>[Drug] (mg/L)</th>
<th>B Dashed-Line</th>
<th>C Difference (B-A)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
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<td>2.8</td>
<td>6.5</td>
<td>3.7</td>
</tr>
<tr>
<td>0.5</td>
<td>4.1</td>
<td>6.1</td>
<td>2.0</td>
</tr>
<tr>
<td>0.75</td>
<td>4.6</td>
<td>5.7</td>
<td>1.1</td>
</tr>
<tr>
<td>1</td>
<td>4.7</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1.5</td>
<td>4.4</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>3.9</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Step 5) Finally, plot the residuals (column C) and calculate the slope of the residual line, illustrated as the dotted line with gray circles, below (or the time required for the value in column C to fall by 50%) to determine $k_a$. Here the absorption half-life ($t_{1/2 \text{ abs}}$) is around 0.25 h so $k_a=0.693/t_{1/2 \text{ abs}}$ or 2.5 h$^{-1}$. Check this value by confirming that it takes 0.25 h for concentrations to decrease by 50% (e.g., from 7 to 3.5).

Summary

The method of residuals is a approach which can be applied to concentration-time data in order to feather apart the influence of two difference processes on the shape of the profile. The first step is to define the elim-
ination phase. The contribution of elimination can then be subtracted from the rest of the profile. The resulting “residual” line will be representative of the second contributing factor (e.g., absorption).
Index

‘flip-flop, 69
1-compartment, 50, 53, 188, 232, 234, 247
1-compartment model, 53
absolute bioavailability, 66
accumulation factor, 98
agonist, 218
alpha (α) phase., 178
Antagonists, 218
apparent volume of distribution, 25
beta (β) phase, 175, 178
biliary clearance, 44, 145
Bioavailability, 61
bioequivalence, 71
Biopharmaceutics, 7, 8
Clinical pharmacokinetics, 7, 8
clockwise hysteresis, 226, 227, 228, 234
C\text{MAX}, 57, 59, 60, 71, 72, 73, 74, 75, 76, 78, 96, 97, 98, 105, 107, 108, 109, 111, 112, 113, 114, 116, 117, 118, 120, 121, 123, 227, 248
C\text{MAX,SS}, 105, 107, 109, 111, 113, 114, 117, 121, 123
C\text{MIN,SS}, 105, 107, 109, 113, 117
Competitive inhibitors, 218
counter-clockwise hysteresis, 229
distributional equilibrium, 180
ED\text{50}, 213, 220, 221
\text{E}_{\text{MAX}}, 200, 213, 218, 219, 220, 221, 223, 224, 225, 229, 230, 234, 235
enterohepatic recycling, 146
extraction ratio, 43, 45, 131, 132, 133, 147
extravascular, 57, 58, 60, 61, 65, 66, 67, 68, 69, 75, 78, 79, 107, 111, 115, 116, 120, 125, 142, 144, 150, 227, 247
first-pass effect, 64
formation clearance, 150
formation limited disposition, 151
gastrointestinal transit time, 63
Hill coefficient, 221, 222, 235
hysteresis, 225, 227, 228, 229
Hysteresis, 225
infusion rate, 15, 81, 83, 86, 87, 88, 89, 92, 93, 94, 188, 190
linear pharmacokinetics, 39
linearity, 48
loading dose, 80, 82, 84, 85, 86, 87, 93, 94, 111, 175, 184, 188, 189, 190
Ludden Method, 207
Noncompetitive inhibitors, 218
non-stationary behavior, 199
one-compartment model, 40, 47, 48, 58, 81, 93, 175,
176, 178, 179, 182, 186, 187, 190
Open, 48
*partial agonist*, 218
*perfusion-limited distribution*, 29
permeability limited
distribution, 30
*pharmacodynamics*, 8
Pharmacodynamics, 8, 214
Pharmacokinetics, 1, 6, 8, 10, 11, 193, 206, 230
*principle of superposition*, 97
Ra, 98, 99, 100, 108, 110, 112, 115, 117, 126, See
Accumulation Ratio
rate limiting steps, 68
receptor occupancy theory, 215
*relative bioavailability*, 66
steady-state, 19, 70, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 93, 95, 98, 99, 100, 101, 102, 103, 104, 105, 106, 109, 111, 112, 113, 118, 120, 121, 124, 125, 137, 143, 147, 169, 181, 183, 184, 187, 191, 193, 202, 203, 206, 207, 209, 211, 212, 244, 245
t_{MAX}, 57, 59, 72, 73, 74, 75, 76
tolerance, 211, 228
trapezoidal method, 20