SEVENTH EDITION

CONCEPTS IN CLINICAL PHARMACOKINETICS

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Virginia H. Fleming

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ashp publications

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Preface

The term *pharmacokinetics* can evoke a variety of responses. For some, it is the difficult course with complex equations. For others, it is the beautiful science of how the medications move though the human body. And for others, it is an opportunity to enhance patient care through patient-specific dosing. Still others see pharmacokinetics as an area of review for licensure or specialty exam content.

The seventh edition of *Concepts in Clinical Pharmacokinetics* is a combination of new and old. What remains fundamental in this edition is the successful strategy of presenting pharmacokinetic modeling principles in a step-by-step process utilizing defined lessons that explain concepts in straightforward terms and illustrate the concepts through examples within each lesson. Self-assessment opportunities are offered as via in-lesson examples and end-of-lesson practice problems with correct answers provided. The aim of this edition is to provide content in a manner that facilitates learning for students who are introduced to the pharmacokinetic concepts for the first time and/or as a review for practitioners moving from one practice specialty to another. In addition, the review of the concepts is useful for those preparing for board exams or specialty certification exams.

The following have been updated in the seventh edition:

- Assessment of renal function and dosing of aminoglycoside and vancomycin antibiotics
- Content in other chapters with new figures to demonstrate learning points
- All in-lesson and end-of-lesson questions

Pharmacokinetic concepts are further illustrated by application to clinical dosing cases, including aminoglycosides, vancomycin, theophylline, digoxin, and phenytoin. These cases are designed to show the easily understandable, step-by-step approach for performing appropriate clinical dosing calculations. All cases provide the complete mathematical solutions for each calculation, allowing readers to "check their math." Equations are explained in detail, and all similar equations used throughout the text are cross-referenced to the basic concept. There is also a valuable appendix containing basic and drug-specific pharmacokinetic equations.

The goal for this edition, as with the previous six editions, remains the same—to provide the student or practitioner with the concepts and clinical applications needed for a better understanding of this complicated, yet still vital, subject.

Robin L. Southwood
Virginia H. Fleming
Gary Huckaby
August 2018

Acknowledgments

We are indebted to our colleagues and mentors Bill Spruill, Joe DiPiro, and the late Bill Wade, for the opportunity to prepare the seventh edition of *Concepts in Clinical Pharmacokinetics.*

A Note from the Authors on Using This Edition

The seventh edition continues the strategy of teaching basic pharmacokinetic concepts, mathematical models, and clinical application principles needed to determine values such as dose, interval, steady-state concentration, half-life, etc. Specific conceptual and mathematical formulas are combined to solve more complex dosing situations. Eleven lessons contain a practice quiz to chart your progress, and there are three separate practice sets of questions with answers. The last four lessons are completely devoted to clinical cases that fully explain, step-by-step, how to dose multiple drugs that generally require serum drug concentration monitoring. This edition has all new problems in each lesson. Content in the aminoglycoside and vancomycin lessons have been updated.

We strongly encourage you to attempt to solve these cases without looking at the step-by-step explanations, and then when finished, check your answers against the key. We wish you much success in your endeavors and hope you enjoy the book!

Robin L. Southwood
Virginia H. Fleming
Gary Huckaby

Abbreviations

α : distribution rate constant for two-compartment model

AUC : area under plasma drug concentration versus time curve

AUMC : area under the (drug concentration × time) versus time (moment) curve

β : terminal elimination rate constant

C : concentration

$\overline{C}$	average steady-state concentration
C_0, C_1, C_2	initial (just after infusion), first, second concentrations
C_{in}	concentration in blood on entering organ
C_{last}	last measured concentration
C_{max}	maximum concentration
C_{max1}, C_{max2}	first, second maximum concentrations
C_{ssmax}	steady-state maximum concentration
C_{ssmin}	steady-state minimum concentration
C_{min}	minimum concentration
C_{out}	concentration in blood on leaving organ
C_{peak}	peak concentration
C_{ss}	steady-state concentration
C_t	concentration at time *t*
C_{trough}	trough concentration

Cl : clearance

Cl_b	biliary clearance
Cl_h	hepatic (liver) clearance
Cl_i	intrinsic clearance
Cl_m	clearance by metabolism (mainly liver)
$Cl_{other\ organs}$	clearance by other organs
$Cl_{P\rightarrow mX}$	formation clearance for a given metabolite *X*
$Cl_{P\rightarrow m1}$	fractional clearance of parent drug (*P*) to form metabolite 1 (m_1)
Cl_r	renal clearance
Cl_t	total body clearance

conc : concentration

Δ : change in

E : extraction ratio

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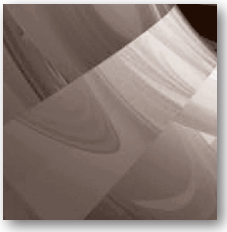

- e : base of natural logarithm
- F : fraction of drug absorbed that reaches systemic circulation (bioavailability)
  - F_{m1} fraction of m_1 formed from a single dose of the parent drug
  - F_p fraction of unbound drug in plasma
  - F_t fraction of unbound drug in tissue
- GFR : glomerular filtration rate
- GI : gastrointestinal
- K : elimination rate constant
  - K_0 rate of drug infusion
  - K_{12} rate constant for transfer of drug from compartment 1 to compartment 2
  - K_{21} rate constant for transfer of drug from compartment 2 to compartment 1
  - K_a absorption rate constant
  - K_m Michaelis–Menten constant (drug concentration at which elimination rate = ½ Vmax)
- λ : terminal elimination rate constant
- m_1, m_2, m_3 : metabolites 1, 2, and 3
- $m_{1,u}, m_{2,u}, m_{3,u}$: amount of m_1, m_2, or m_3 excreted in the urine
- MRT: mean residence time
- n : number of doses
- Q : bloodflow
  - Q_h hepatic bloodflow
- S : salt form of drug
- SST : serum separator tube
- τ : dosing interval
- t : time (after dose)
  - t' time after end of infusion ($t' = \tau - t$ for trough concentration)
  - t'' time (duration) of loading infusion
  - t_0 time zero
  - $T½$ half-life
  - $t_{90\%}$ time required to reach 90% of steady-state concentration
- V : volume; volume of distribution
  - V_{area} volume of distribution by area
  - V_c volume of central compartment
  - V_{extrap} extrapolated volume of distribution
  - V_p plasma volume
  - V_{ss} steady-state volume of distribution
  - V_t tissue volume
  - V_{max} maximum rate of the elimination process
- X : amount of drug
  - X_0 dose (or initial dose) of drug
  - X_1, X_2 amount of drug at different times
  - X_c amount of drug in central compartment
  - X_d daily dose of drug
  - X_p amount of drug in peripheral compartment

LESSON 1

Introduction to Pharmacokinetics and Pharmacodynamics

OBJECTIVES

After completing Lesson 1, you should be able to:

1. Define and differentiate between *pharmacokinetics* and *clinical pharmacokinetics*.
2. Define *pharmacodynamics* and relate it to pharmacokinetics.
3. Describe the concept of the *therapeutic concentration range*.
4. Identify factors that cause interpatient variability in drug disposition and drug response.
5. Describe situations in which routine clinical pharmacokinetic monitoring would be advantageous.
6. List the assumptions made about drug distribution patterns in both one- and two-compartment models.
7. Represent graphically the typical natural log of plasma drug concentration versus time curve for a one-compartment model after an intravenous (IV) dose.

Pharmacokinetics is currently defined as the study of the time course of drug absorption, distribution, metabolism, and excretion. *Clinical pharmacokinetics* is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.

Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient's drug therapy. Other uses include assessment of adherence and indirect assessment of organ function. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations.

A drug's effect is often related to its concentration at the site of action, so it would be useful to monitor this concentration. Receptor sites of drugs are generally inaccessible to our observations or are widely distributed in the body; therefore, direct measurement of drug concentrations at these sites is not practical. For example, the receptor sites for digoxin are thought to be within the myocardium. Obviously we cannot directly sample drug concentration in this tissue. However, we can measure drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids (**Figure 1-1**). *Kinetic homogeneity* describes the predictable relationship between plasma drug concentration and concentration at the receptor site where a given drug produces its therapeutic effect (**Figure 1-2**). Changes in the plasma drug concentration reflect changes in drug concentrations

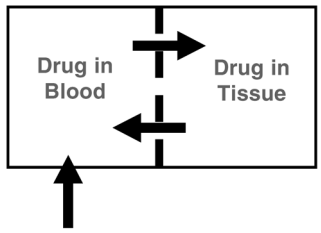

FIGURE 1-1.
Blood is the fluid most often sampled for drug concentration determination.

at the receptor site, as well as in other tissues. As the concentration of drug in plasma increases, the concentration of drug in most tissues will increase proportionally.

Similarly, if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease. **Figure 1-3** is a simplified plot of the drug concentration versus time profile after an IV drug dose and illustrates this concept.

The property of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics. It is the foundation on which all therapeutic and toxic plasma drug concentrations are established. That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues where the disease process is to be modified by the drug (e.g., the central nervous system in Parkinson's disease or bone in osteomyelitis). This assumption, however, may not be true for all drugs.

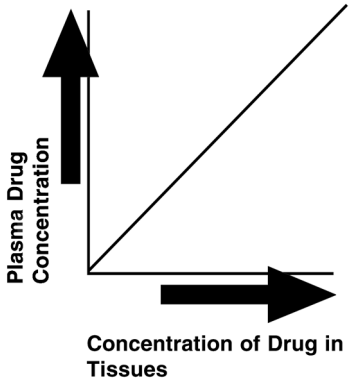

FIGURE 1-2.
Relationship of plasma to tissue drug concentrations.

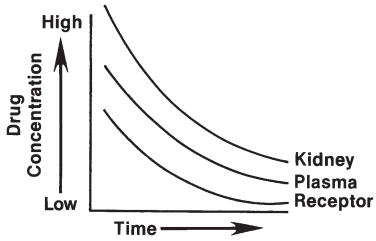

FIGURE 1-3.
Drug concentration versus time.

Clinical Correlate

Drugs concentrate in some tissues because of physical (such as molecular size or weight) or chemical (such as lipophilicity/hydrophilicity or ionization) properties. Examples include digoxin, which concentrates in the myocardium, and lipid-soluble drugs, such as benzodiazepines, which concentrate in fat.

Basic Pharmacodynamic Concepts

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. The effect of a drug present at the site of action is determined by that drug's binding with a receptor. Receptors may be present on neurons in the central nervous system (i.e., opiate receptors) to depress pain sensation, on cardiac muscle to affect the intensity of contraction, or even within bacteria to disrupt maintenance of the bacterial cell wall.

For most drugs, the concentration at the site of the receptor determines the intensity of a drug's effect (**Figure 1-4**). However, other factors affect drug response as well. The density of receptors on the cell surface, the mechanism by which a signal is transmitted into the cell by second messengers (substances within the cell), or the regulatory factors that control gene translation and protein production may influence drug effect. This multilevel regulation results in variation of sensitivity to drug effect from one individual to another and also determines enhancement of, or tolerance to, drug effects that can result in intrapatient variation.

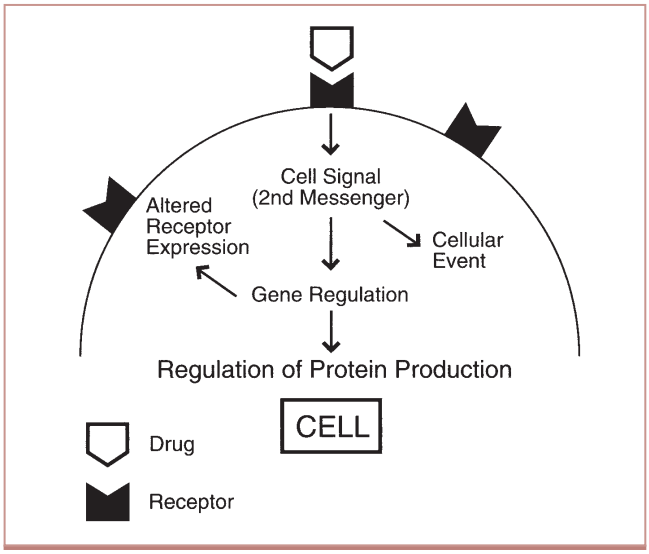

FIGURE 1-4.
Relationship of drug concentration to drug effect at the receptor site.

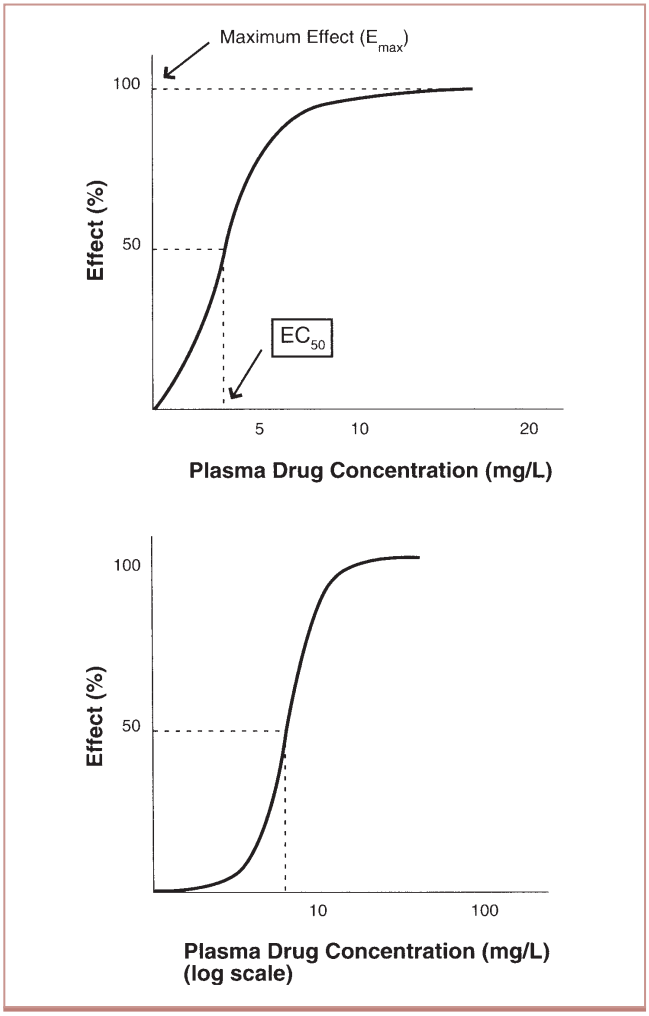

FIGURE 1-5.
Relationship of drug concentration at the receptor site to effect (as a percentage of maximal effect).

In the simplest examples of drug effect, there is a relationship between the concentration of drug at the receptor site and the pharmacologic effect. If enough concentrations are tested, a maximum effect (E_{max}) can be determined (**Figure 1-5**). When the logarithm of concentration is plotted versus effect (Figure 1-5), one can see that there is a concentration below which no effect is observed and a concentration above which no greater effect is achieved.

One way of comparing *drug potency* is by the concentration at which 50% of the maximum effect is achieved. This is referred to as the *50% effective concentration* or EC_{50}. When two drugs are tested in the same individual, the drug with a lower EC_{50} would be considered more potent. This means that a lesser amount of a more potent drug is needed to achieve the same effect as a less potent drug.

The EC_{50} does not, however, indicate other important determinants of drug response, such as the duration of effect. Duration of effect is determined by a complex set of factors, including the time that a drug is engaged on the receptor as well as intracellular signaling and gene regulation.

For some drugs, the effectiveness can decrease with continued use. This is referred to as *tolerance*. Tolerance may be caused by pharmacokinetic factors, such as increased drug metabolism, that decrease the concentrations achieved with a given dose. There can also be pharmacodynamic tolerance, which occurs when the same concentration at the receptor site results in a reduced effect with repeated exposure. An example of drug tolerance is the use of opiates in the management of chronic pain. It is not uncommon to find these patients requiring increased doses of the opiate over time. Tolerance can be described in terms of the dose-response curve, as shown in **Figure 1-6**. When tolerance occurs, efficacy may be regained by increasing drug dose. Drug-free intervals do not usually restore efficacy. Tachyphylaxis is a form of tolerance that occurs rapidly and is unique because loss of efficacy does not respond to dose increases but does return with drug-free intervals.

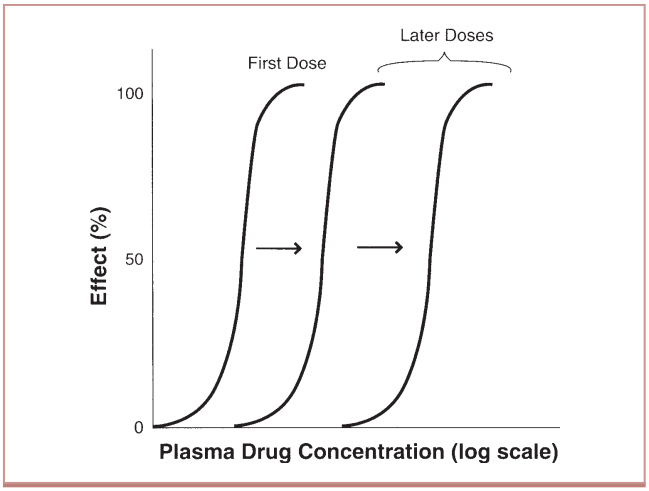

FIGURE 1-6.
Demonstration of tolerance to drug effect with repeated dosing.

To assess the effect that a drug regimen is likely to have, the clinician should consider pharmacokinetic and pharmacodynamic factors. Both are important in determining a drug's effect.

Clinical Correlate

Tolerance can occur with many commonly used drugs. One example is the hemodynamic tolerance that occurs with continued use of organic nitrates, such as nitroglycerin. With continued uninterrupted use, the effect of this drug is reduced. Nitrates exhibit tachyphylaxis, a tolerance that can be reversed by interspersing drug-free intervals during chronic drug use. Another example of tolerance occurs with narcotic analgesics. With chronic continual use, receptors are downgraded so that higher doses of the drugs are required to achieve the same level of analgesia. Tolerance may also occur with side effects of certain drugs so that when titrated slowly over time, the patient is able to tolerate higher doses of the drug without being limited by unpleasant or burdensome side effects. These types of tolerance are referred to as *physiologic tolerance,* which should be differentiated from *psychological dependence* in which the patient believes strongly that they need a drug and feel anxiety when separated from the drug.

Clinical Correlate

One way to compare potency between two drugs that are in the same pharmacologic class is to compare EC_{50}. The drug with a lower EC_{50} is considered more potent. The potency of a drug, however, does not necessarily determine which drug is "better" than another. It correlates to the amount of drug (dose) needed to achieve a desired effect, which may be larger than one drug than for another, but as long as equipotent doses of the two agents are given, a similar effect should be seen.

Therapeutic Drug Monitoring

Therapeutic drug monitoring is defined as the use of assay procedures for determination of drug concentrations in plasma, and the interpretation and application of the resulting concentration data to develop safe and effective drug regimens. If performed properly, this process allows for the achievement of therapeutic concentrations of a drug more rapidly and safely than can be attained with empiric dose changes. Together with observations of the drug's clinical effects, it should provide the safest approach to optimal drug therapy.

The usefulness of plasma drug concentration data is based on the concept that pharmacologic response is closely related to drug concentration at the site of action. For certain drugs, studies in patients have provided information on the plasma concentration range that is safe and effective in treating specific diseases: the therapeutic range (**Figure 1-7**). Within this therapeutic range, the desired effects of the drug are observed. Below it, there is greater probability that the therapeutic benefits are not realized; above it, toxic effects may occur.

No absolute boundaries divide subtherapeutic, therapeutic, and toxic drug concentrations. A gray area usually exists for most drugs in which these concentrations overlap due to variability in individual patient response. Numerous pharmacokinetic characteristics of a drug may result in variability in the plasma concentration achieved with a given dose when administered to various patients