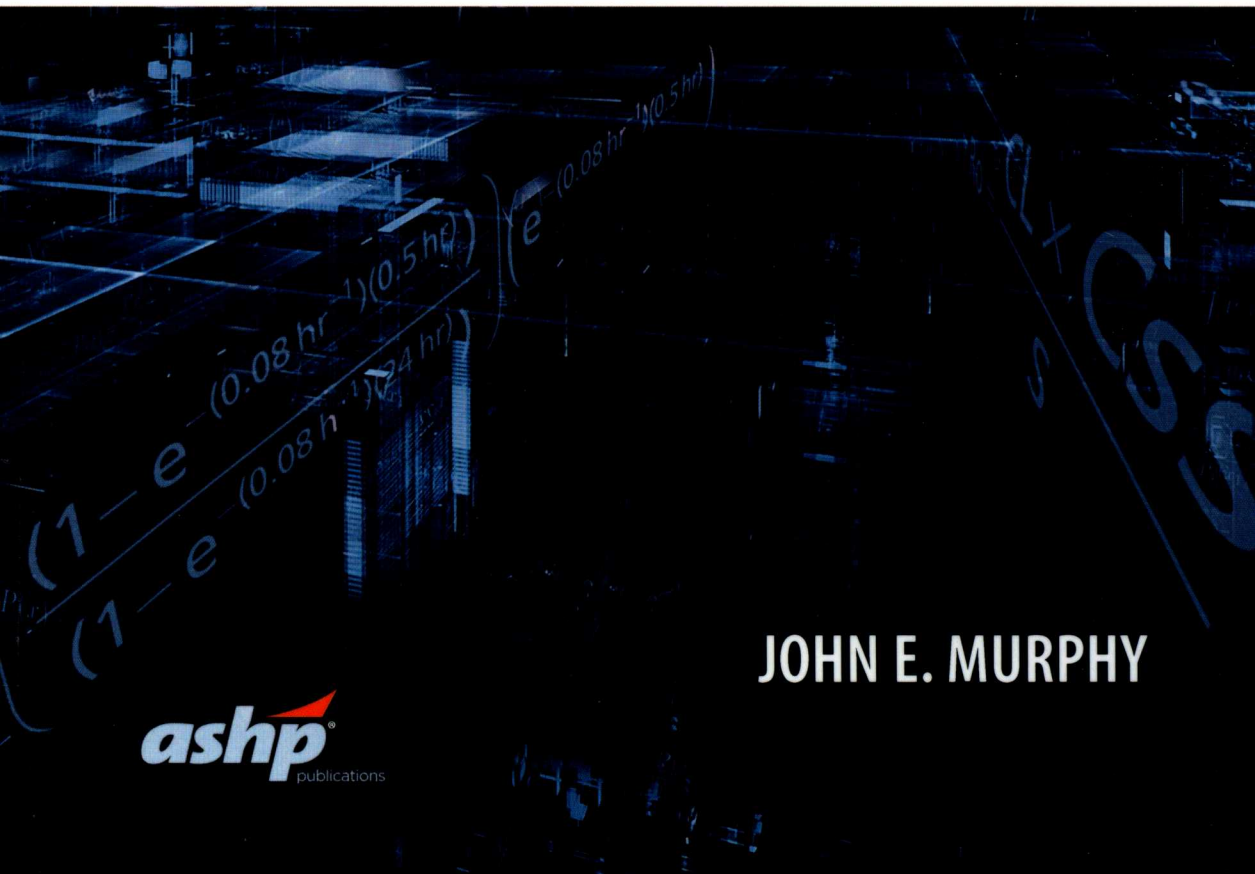
Clinical Pharmacokinetics

6th Edition



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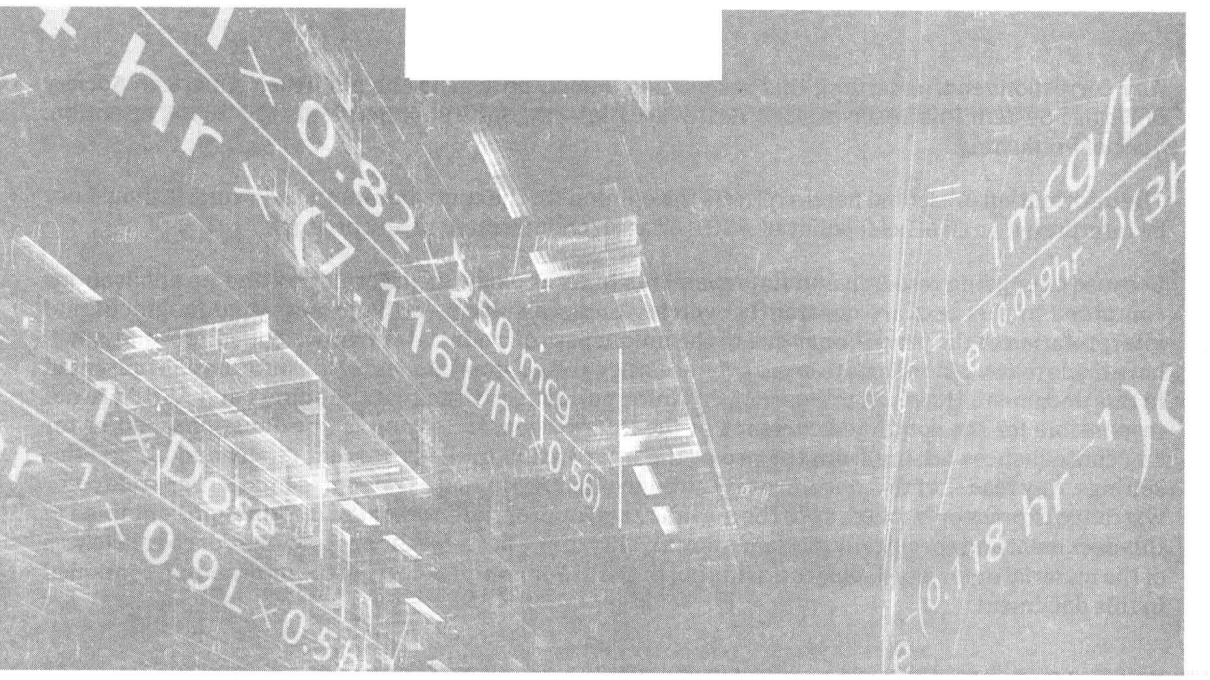

Clinical Pharmacokinetics

6th Edition

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Because of ongoing research and improvements in technology, the information and its applications contained in this text are constantly evolving and are subject to the professional judgment and interpretation of the practitioner due to the uniqueness of a clinical situation. The editors and ASHP have made reasonable efforts to ensure the accuracy and appropriateness of the information presented in this document. However, any user of this information is advised that the editors and ASHP are not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the document in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this document and specifically disclaims any liability to any party for the accuracy and/or completeness of the material or for any damages arising out of the use or non-use of any of the information contained in this document.

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DEDICATION

This sixth edition is again dedicated to:

Our patients, to whom we devote our professional lives; to my past and present students and residents who continue to inspire me;

My mother and father, for their nurturing; to my family (and my four grandchildren) for making life interesting and fun;

Mercer University and the University of Arizona for providing me the best jobs I could have ever hoped for; and

The pharmacy profession for giving me opportunities I never dreamed existed for a guy like me way back when it all started.

Pharmacokinetic studies have continued to be published since the first edition of the *Clinical Pharmacokinetics*. The second, third, fourth, fifth and now sixth edition authors have taken advantage of advances in understanding to update the chapters. In many cases more judicious monitoring of drug concentrations is suggested compared to the early editions. For some drugs, the dosing approaches are radically different now. For others, new prediction approaches are available that have been tested in larger numbers of patients or with more sophisticated data analysis. Because the impact of drug interactions and the determination of the appropriate dosing weight on pharmacokinetics and pharmacodynamics on obese patients can be important to dosing decisions, the authors include this information when available. Pharmacogenomic issues are increasingly essential in decisions about drug dosing or who should receive certain drugs; therefore, most of the relevant chapters are updated regarding the impact of pharmacogenetic studies on dosing. In addition, a specific chapter has been added to help interpret issues related to applying pharmacogenomics to drug dosing. All of these updates and additions should be helpful to users of pharmacogenomics to inform drug dosing.

This book was originally designed to help predict drug doses to achieve target drug concentrations from doses administered to patients. However, important chapters on rational use of drug concentration measurements; dosing in overweight and obese patients; pharmacogenomics; dosing considerations for a wider variety of drugs used in neonatal, pediatric and geriatric patients; drug dosing in renal disease (and dialysis); and creatinine clearance estimation (the precursor to dose and concentration estimates for a number of drugs) have been added over the years and round out the sixth edition. Tables on international and traditional units for drugs and laboratory tests are included as well as specific content on the use of both types of units, which should facilitate worldwide use of the textbook.

As with every edition, I gratefully acknowledge the chapter authors who volunteered a portion of their lives to this book's creation and to the authors' support staff for their assistance. Finally, without a doubt, many thanks are due to the best collaborators in the world—the ASHP staff. I would particularly like to thank the staff editors—Michael Soares (1st edition), Con Ann Ling (2nd edition), Dana Battaglia (3rd to 5th editions), and Ruth Bloom (6th edition) for their outstanding dedication to making these editions happen. They all did much work and receive little of the credit, but I know their value and it is tremendous. Thanks.

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GENERAL PHARMACOKINETIC PRINCIPLES

John E. Murphy

INITIATING THERAPY

When therapy is initiated in a patient, a standard dose and interval may be used, or the dose and interval may be individualized by use of population means of clearance or volume of distribution and half-life. These population pharmacokinetic parameters are useful for estimating drug concentrations based on an administered or planned dose and dosing schedule. To adjust therapy, these values then may be compared to actual drug concentration measurements (DCMs) and integrated with the patient's therapeutic outcome.

Using population mean values

Unfortunately, not all patients fit closely to the population means, and some of these means were developed on small samples that may not represent the general population or the patient being monitored. However, for a number of drugs, population means with standard deviations can provide useful information on reasonable ranges of the concentration values to expect.

In any case, a patient's actual pharmacokinetic values (i.e., clearance, volume of distribution, and half-life) may need to be determined to adjust therapy for a desired outcome.

Considering other factors in pharmacokinetic monitoring[1]

In addition to the problems with population pharmacokinetic means, unexpected drug concentration measurements can occur for various reasons. Some patients may not be adherent with drug therapy, taking either more or less than was prescribed for them. In the institutional setting, administration errors can account for unexpected results; a patient may be given the wrong dose of a drug, may be given the drug at the wrong time, or may not receive the scheduled drug at all.

Errors on medication administration records also can occur. For example, it might be indicated that a drug was given at a time other than the actual time it was received by the patient. Furthermore, incomplete drug delivery due to patient problems (e.g., infiltration of an IV fluid or clogging of a nasal cannula) can influence drug concentration measurements.

Problems in sample collection can lead to unexpected drug concentration measurements. A blood sample may be drawn at the wrong time, or the time the sample was collected may be reported incorrectly. Samples can be taken from the wrong patient or obtained incorrectly (e.g., through a drug administration line that was inadequately flushed prior to sample withdrawal). In addition, samples may be improperly stored. The drug concentration sampling strategy may also impact the ability to best design a new dosing schedule to target desired concentrations.[2]

Other things to consider include drug or disease state interactions that may influence the prediction of drug concentration measurements and the use of inaccurate assays.

Some reasons drug concentration measurements may fall outside of the range predicted by population estimates:

- Patient truly does not well fit the population average values (i.e., falls outside of one standard deviation of the mean).

- Population values used for the predictions were determined in patients unlike the patient being monitored.
- Patient has not been adherent with therapy (may have taken either more or less than prescribed).
- Nurse did not give the dose at the time prescribed (whether it has been signed off as given on time or not).
- Dose not given at all (whether it is signed off as given or not). Also doses are occasionally administered but not signed off as being given.
- Wrong dose is given (either once or more often).
- Error made in dosing schedule on medication administration record (e.g., every 18-hr schedule is put on record such that patient is given doses 18 and 30 hr apart).
- Complete dose was not administered prior to sample withdrawal because of patient problems (e.g., infiltration of an intravenous (IV) line, clogging of nasal cannula).
- Phlebotomist drew blood at a time other than requested and:
  (1) reported that it was collected on time, or (2) or inaccurately reported, and it is incorrectly assumed to have been drawn at the scheduled time.
- Sample was taken from the wrong patient.
- Sample was obtained incorrectly (e.g., through a drug administration line which has been improperly flushed prior to sample withdrawal).
- Sample was not stored properly, leading to artifactual results.
- Assay or assay instrument quality is not satisfactory, or the reported result is not accurate.
- Pharmacokinetic drug interaction has occurred, which was not accounted for correctly in estimation of DCMs.
- In vitro drug interaction occurred, resulting in artifactual results.
- Disease interaction occurred that was not considered, such as reduced absorption rate due to poor blood flow.
- Patient has reduced plasma binding proteins or a drug–drug interaction has displaced the drug from protein (see Protein binding issues, below).

Protein binding issues

When patients have reduced plasma proteins or highly bound drugs are displaced from plasma proteins by drug or endogenous compound interactions, there may be increased free fraction (unbound concentration/total concentration) and movement of drug out of the bloodstream into tissue. Movement of drug out of the bloodstream can lead to decreases in total (bound and unbound) plasma or serum drug concentrations even when the unbound concentration remains unchanged. Since total concentration is what is usually reported when drug concentration measurements are ordered, this can lead to incorrect assumptions that a dose may need to be increased. Increased unbound fraction can also lead to increased elimination, which will also decrease total concentration. If there is no increase in elimination, the unbound concentration may remain the same as when plasma proteins are normal or no interaction exists, even though the total concentration is decreased. In some cases of highly bound drugs (e.g., phenytoin), an unbound concentration measurement may be warranted if the total concentration is low, to ensure that adequate unbound concentrations exist.

Verifying drug concentration measurements

If measured values fall outside the range estimated using ± one standard deviation of the predicted clearance, volume of distribution, and/or half-life, concentrations should generally be re-checked before the initially measured concentration(s) are accepted as valid. This step does not preclude changing

the dose or interval if such a change would have been made empirically at the start of therapy. If the measured concentrations are far from those predicted, a determination must be made as to whether the measured drug concentrations are reasonable (i.e., within reasonable expectation based on the range of population values) or whether one or more of the problems noted above occurred.

The occurrence of certain problems can be determined with detective work. For example, a patient can be questioned about compliance, past outpatient pharmacy records can be checked, and the nurse administering the drug or the phlebotomist drawing the blood sample can be interviewed. Unfortunately, the validity of the information gathered after the fact may be questionable.

Because of these potential problems, measured drug concentrations may not be a true reflection of the patient's actual drug distribution and clearance. Therefore, an erroneous decision about the dosing needs of the patient can be made. Accurate information is essential to quality therapeutic drug monitoring.

A well-coordinated system of communication is needed between those administering or taking a medication and those collecting blood (or other body fluid or tissue) for analysis. Such a system can prevent many of the problems associated with assessing the validity of reported drug concentrations and dose/sample collection timing. It also can reduce erroneous decision-making based on faulty data as well as the expense of repeating questionable drug concentration measurements. The lack of such a system is a waste of resources and provides the potential for harming patients secondary to a high incidence of debatable data.

After as many causes of discrepancy as possible are eliminated, a decision must be made as to whether the difference between predicted and actual values is due to patient variability from population averages or to erroneous values. If the values are judged to be erroneous, drug concentrations probably should be re-measured, although the need for further evaluation should be as carefully considered as the original decision to monitor (see Chapter 1, Rational Use of Drug Concentration Measurements).

Determining need for dosage adjustments

Once the drug concentration measurement and dosing information is determined to be as accurate as possible, the need for dosage adjustments are determined based on pharmacodynamic response and patient outcome. The need for dosage adjustment or the continuation of therapy should be based on patient response relative to measured drug concentration rather than on drug concentration alone.

This approach may not be proper, however, when the disease or symptoms are not continuous or easy to quantify. For example, keeping an anticonvulsant drug within the therapeutic range can be important when seizure activity is infrequent. Without an adequate seizure history, the maintenance of a dosing schedule that produces drug concentration measurements above or below the normal accepted therapeutic range may not be prudent.

Deciding on monitoring frequency and sample timing

How frequently a patient should be monitored for efficacy or side effects related to drug therapy varies with the drug, the intensity of the disease, the stability of body functions, and other factors. In general, the more severely compromised the patient, the more frequently the patient should be monitored. This is essentially the same as would be recommended for most laboratory tests and monitoring schemes.

Clinicians should be aware of the many factors that can alter a drug's pharmacokinetic and pharmacodynamic activities. Addition or deletion of other drug therapy (or diet) that may interact with the drug being monitored should signal the need for closer inspection. Changes in the function of the primary organs of drug elimination (e.g., liver and kidneys) or in cardiac function also should signal the need for closer monitoring.

Patient (or caregiver) adherence to the treatment regimen must be assessed whenever a decision is based on a drug concentration measurement. Simply assuming appropriate adherence to the prescribed regimen can lead to grave errors in the worst case and a waste of resources in others.

Single samples provide useful feedback from the patient as to clearance of the drug, but at least one sample is necessary to calculate each pharmacokinetic parameter. For example, if knowledge of a patient's V and CL or V and k are desired for dosing adjustment, two samples are necessary. The time of sampling can also be optimized to determine the pharmacokinetic behavior of a drug and provide the best future predictions.[2] Trough samples are not optimum DCM collection times, but they are often used by clinicians when desired concentrations have been based on the trough (e.g., current approaches to vancomycin dosing). Trough concentrations are also least impacted when errors occur in the time a dose is given or sample collected.[2] Thus, even though more robust pharmacokinetic information may be obtained by other sampling times, approaches such as drawing an aminoglycoside "peak" 30 min after the end of a dosing infusion rather than the true peak and measuring troughs instead of earlier concentrations are often used for therapeutic drug monitoring.

A BASIC PHARMACOKINETIC GLOSSARY

As the science of pharmacokinetic evaluation of drug therapy has progressed, the terminology used has grown as well. Although terms such as *half-life* and *volume of distribution* are standardized in most pharmacokinetic texts, a wide variety of terminology is used to describe other basic concepts.

For this reason, an attempt was made to standardize the terminology used throughout this book. The wide collection of studies used to reference the chapters somewhat hindered this effort.

With that understanding, the following terminology is offered as a guideline to interpreting the values and terms in this book.

Selected pharmacokinetic terminology

Actual body weight (ABW)—Patient's measured body weight; equivalent to total body weight.

Average steady state concentration (Css_{av})—Concentration measured approximately halfway between the peak and trough (except for some sustained-release preparations) for a drug administered long enough to be at steady state. Hence, for an IV bolus regimen on an every 6-hr interval, the Css_{av} would be at 3 hr after a dose. For a dose requiring absorption that peaks 2 hr after administration, the average would occur at approximately 4 hr on a 6-hr interval.

Ideal body weight (IBW)—Ideal weight for a patient based on his or her height and sex according to insurance actuarial tables for longevity.

Lean body weight (LBW)—Patient's body weight plus some but not all fat weight. It is often used interchangeably with IBW, but LBW increases as patients increase in weight, while IBW is constant.

Peak concentration (C_{peak})—Peak concentration is the highest or maximum concentration after any type of dosing method. It is the concentration of drug that occurs immediately after an IV bolus dose, at the end of a dose infusion, or at a particular time (t_{peak} or t_{max}) after dose administration for a drug requiring absorption. It may also be called C_{max} or Css_{max}. Occasionally, the "peak" is considered the concentration measured within 30–60 minutes after the true peak time (e.g., 30 min after the end of a dose infusion for aminoglycosides); this peak might be considered a "therapeutic peak" for assessment of patient response rather than the actual peak. This time lag before collection in part acknowledges the reality that doses are not always given precisely on time and that blood samples are not always drawn precisely when scheduled for a true peak.

Steady state—Point in time reached after a drug has been given for approximately five elimination half-lives (97% of steady state has been achieved after five half-lives). At steady state, the rate of drug administration equals the rate of elimination, and drug concentration-time curves found after each dose on an even schedule (e.g., every 8 hr) should be approximately superimposable (i.e., if one graph of a drug concentration–time curve were laid on the next dose graph, they would be the same).

Administration of a loading dose can affect the time to steady state if the loading and maintenance doses are matched correctly. If the loading dose provides exactly the amount needed to achieve the steady state concentration that will be achieved by the maintenance dose, then steady state is achieved immediately. If the loading dose is too small or too large relative to attainment of the concentrations that will occur with maintenance doses, five half-lives will be required to achieve 97% of the *difference* between the loading dose concentrations and the final steady state concentrations.

Therapeutic range—Range of concentrations where optimum outcome is expected, based on results of groups of individuals taking the drug. In reality, each person has his or her own therapeutic range for each drug. As concentrations rise to the upper limit of the therapeutic range and beyond, the probability of drug toxicity increases. As concentrations fall to or below the lower limit of the range, the probability of inadequate response increases. This range should be viewed only as an initial target, because patients may respond when below it and may not be toxic when above it. Furthermore, minor toxicity above a therapeutic range might be acceptable to a patient if efficacy increases. Serious toxicity is a definite upper limit to any individual's therapeutic range.

Trough concentration (C_{trough})— Lowest or minimum concentration after a dose given intermittently (also called C_{min} or Css_{min}). It is the concentration that occurs immediately before the next dose for drugs given intermittently in a multiple-dose fashion. However, quite often the "trough" is the concentration measured within 30–60 minutes of the next dose. This trough might be considered a "therapeutic trough" related to this time in pharmacokinetic and pharmacodynamic studies of the drug. This time period in advance of the true trough also acknowledges variance in compliance with precise dose administration time and phlebotomist arrival time.

Selected pharmacokinetic symbols used in this text

These symbols generally follow the nomenclature suggested by the Committee for Pharmacokinetic Nomenclature of the American College of Clinical Pharmacology.[3] An exception is volume of distribution (V versus V_z).

C = concentration of drug (plasma, serum, blood, urine, saliva, etc.).

C_i = initial concentration. The larger of two measured concentrations in an elimination portion of a concentration-time curve. For example, in Equation 1 (see "General Pharmacokinetic Equations," below), C_i is the largest of two concentrations, Ci and C. Some authors designate the two concentrations as C_1 and C_2.

C_{max} = maximum drug concentration after a dose (also C_{peak}).

C_{min} = minimum drug concentration after a dose (also C_{trough}).

Css = concentration at steady state.

Css_{max} = maximum drug concentration after a dose at steady state (also Css_{peak}).

Css_{min} = minimum drug concentration after a dose at steady state (also Css_{trough}).

Css_{avg} = average steady state concentration. The concentration approximately halfway between Css_{max} and Css_{min} at steady state.

CL = apparent total body clearance (either in units of volume per time, such as liters per hour, or in units of volume per time per body weight, such as liters per hour per kilogram). $CL = k \times V$.

CrCl = creatinine clearance; the clearance of creatinine (in units of milliliters per minute or liters per hour).

D = dose (in amount, such as milligrams, or amount per patient body weight, such as milligrams per kilogram).

F = bioavailability fraction of a dose (no units). It is the fraction or percent of an administered dose that reaches the systemic circulation.

k = first-order elimination rate constant (in units of 1/time or time^{-1}). $k = 0.693/t_{1/2}$.

k_a = first-order absorption rate constant (in units of 1/time or time^{-1}). $k_a = 0.693/t_{1/2a}$.

K_m = Michaelis-Menten constant (in units of concentration such as milligrams per liter). It is the concentration at which the metabolic system is one-half saturated.

R_0 = zero-order infusion rate (in amount per time such as milligrams per hour).

S = fraction of a dose that is parent drug (i.e., the drug that is measured in plasma or serum). For example, phenytoin sodium is 92% phenytoin. Thus, S = 0.92 for phenytoin sodium products. No units.

S_{Cr} = serum creatinine (in mg/dL or µmol/L).

t = elapsed time. For example, it is the time between two concentrations, known or estimated, in the elimination phase of a drug following first-order elimination.

t' = time of an infusion (i.e., duration of infusion, usually in hours).

t_{peak} = time to peak (maximum concentration) of a drug that requires absorption (e.g., oral, intramuscular, inhaled, rectal, or buccal). Also called t_{max}.

$t_{1/2}$ = half-life of a drug (in units of time). It is the time needed to reduce the drug concentration or amount of drug in the body by one-half. $t_{1/2} = 0.693/k$.

$t_{1/2a}$ = absorption half-life of a drug product administered in a dosage form requiring absorption (in units of time). $t_{1/2a} = 0.693/k_a$.

T = time elapsed after the *end* of an infusion.

Δt = change in time (usually the time between two measured concentrations).

τ = dosage interval (in units of time, usually hours or days).

V = apparent volume of distribution (either in units of volume, such as liters, or in units of volume per body weight, such as liters per kilogram).

V_{max} = (V_m) maximum velocity of drug elimination for a drug following Michaelis-Menten (enzyme saturable) elimination. It is the amount of drug that can be biotransformed per unit of time (in units of amount per time, such as milligrams per day or in mg/kg/day).

GENERAL ESTIMATING EQUATIONS

Like the above terms and symbols, several equations are frequently used in pharmacokinetic calculations and are considered to be standards. Frequently used equations for calculating ideal or lean body weight and body surface area are as follows. Additional information is provided in Chapter 4, Medication Dosing in Overweight and Obese Patients. Creatinine clearance estimations are provided in Chapter 2, Estimating Creatinine Clearance.

Calculating ideal body weight (IBW) in adults[4]

males = 50 kg + [(2.3)(Ht – 60)] kg

females = 45.5 kg + [(2.3)(Ht – 60)] kg

where Ht is a patient's height in inches.

Or,

males = 50 kg + [(0.9)(Ht – 152)] kg

females = 45.5 kg + [(0.9)(Ht – 152)] kg

where Ht is a patient's height in centimeters.

Note: For patients who are less than 60 inches tall (152 cm), the weight should be decreased more conservatively than 2.3 kg/inch (2.3 kg/2.54 cm).

Calculating ideal body weight in children aged 1–18 years[5]

For children **less than 5 feet (152 cm)** tall

$IBW = 2.05e^{(0.02)(Ht)}$

where Ht is height in centimeters (2.54 cm/inch) and IBW is ideal weight in kg.

For children **5 feet (152 cm) or taller**

IBW (males) = 39 + [2.27 (Ht – 60)]

IBW (females) = 42.2 + [2.27 (Ht – 60)]

where Ht is height in inches and IBW is ideal weight in kg.

Or,

IBW (males) = 39 + [0.9 (Ht – 152)]

IBW (females) = 42.2 + [0.9 (Ht – 152)]

where Ht is height in centimeters and IBW is ideal weight in kg.

Calculating surface area (SA) in meters² (m²)

For adults, children, and infants[6]

$SA = W^{0.5378} \times Ht^{0.3964} \times 0.024265$

where W is weight in kg and Ht is height in centimeters.

Another simpler approach to determining BSA uses the following formula[7]:

$$BSA = \sqrt{\frac{height \times weight}{3600}}$$

where height is in cm and weight is in kg.

Calculating Body Mass Index (BMI) for men and women[8,9,a]

METRIC

BMI = weight (kg) / [height (m)]² or [weight (kg) / height (m) / height (m)]

POUNDS AND INCHES

BMI = weight (lb) / [height (in)]² × 703 or [weight (lb) / height (in) / height (in)] × 703

[a] *BMI is an indicator of body fat and body fat content is related to the risk of disease and death. People are considered underweight if their BMI is <18.5, normal weight if 18.5 to 24.9, overweight if 25 to 29.9, and obese if ≥ 30. There are limits to the use of BMI, including the potential to overestimate body fat in athletes and others who have a muscular build and to underestimate body fat in the elderly and in those who have lost muscle mass.*

GENERAL PHARMACOKINETIC EQUATIONS

The following equations are used to determine or estimate concentration and other pharmacokinetic parameters. These equations may be manipulated to determine other parameters in the equation when the remaining parameters are known or can be estimated. For example, a dose may be calculated from known or estimated CL, V, or k values by manipulating the applicable equations to solve for dose (D).

1. Concentration at any time t after some initial concentration (C_i):

$$C = C_i \times e^{-kt}$$

2. k from two known drug concentration-time points in the elimination phase:

$$k = \frac{\ln(C_i/C)}{\Delta t}$$

3. Concentration at any time t after a single IV bolus dose:

$$C = \left(\frac{S \times D}{V}\right) e^{-kt}$$

4. Concentration at any time t after an IV bolus dose given every τ hours (at steady state):

$$C = \left(\frac{S \times D}{V}\right)\left(\frac{\left(e^{-kt}\right)}{\left(1 - e^{-k\tau}\right)}\right)$$

5. Concentration at any time t after the start of an IV infusion at rate R_0:

$$C = \left(\frac{(S \times R_0)}{CL}\right)(1 - e^{-kt})$$

6. Concentration at steady state of an IV infusion at rate R_0:

$$Css = \left(\frac{S \times R_0}{CL}\right)$$

7. Average steady state concentration of a dose given intermittently (by all dosing methods):

$$Css_{avg} = \left(\frac{S \times F \times D}{CL \times \tau}\right)$$

or

$$Css_{avg} = \left(\frac{S \times F \times D}{k \times V \times \tau}\right)$$

8. Concentration at any time t after a single dose requiring absorption:

$$C = \left(\frac{S \times F \times D \times k_a}{V \times (k_a - k)}\right)(e^{-kt} - e^{-k_a t})$$

9. Time to peak (maximum concentration) of a dose requiring absorption after a single dose:

$$t_{peak} = \frac{\ln(k_a/k)}{(k_a - k)}$$