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## APPLICATION OF PHARMACOKINETICS TO CLINICAL SITUATIONS: INTRODUCTION

The success of drug therapy is highly dependent on the choice of the drug and drug product and on the design of the dosage regimen. The choice of the drug and drug product, eg, immediate release versus modified release, is based on the patient's characteristics and the known pharmacokinetics of the drug as discussed in earlier chapters. A properly designed dosage regimen tries to achieve a specified concentration of the drug at a receptor site to produce an optimal therapeutic response with minimum adverse effects. Individual variation in pharmacokinetics and pharmacodynamics makes the design of dosage regimens difficult. Therefore, the application of pharmacokinetics to dosage regimen design must be coordinated with proper clinical evaluation of the patient and monitoring.

## INDIVIDUALIZATION OF DRUG DOSAGE REGIMENS

Not all drugs require rigid individualization of the dosage regimen. Many drugs have a large margin of safety (ie, exhibit a wide therapeutic window), and strict individualization of the dose is unnecessary. The U.S. Food and Drug Administration (FDA) has approved an *over-the-counter* (OTC) classification for drugs that the public may buy without prescription. In the past few years, many prescription drugs, such as ibuprofen, loratidine, omeprazole, naproxen, nicotine patches, and others, have been approved by the FDA for OTC status. These OTC drugs and certain prescription drugs, when taken as directed, are generally safe and effective for the labeled indications without medical supervision. For drugs that are relatively safe and have a broad safety-dose range, such as the penicillins, cephalosporins, and tetracyclines, the antibiotic dosage is not dose titrated precisely but is based rather on the clinical judgment of the physician to maintain an effective plasma antibiotic concentration above a minimum inhibitory concentration.

For drugs with a narrow therapeutic window, such as digoxin, aminoglycosides, antiarrhythmics, anticonvulsants, and some antiasthmatics, such as theophylline, individualization of the dosage regimen is very important. The objective of the dosage regimen design for these drugs is to produce a safe plasma drug concentration that does not exceed the minimum toxic concentration or fall below a critical minimum drug concentration below which the drug is not effective. For this reason, the dose of these drugs is carefully individualized to avoid plasma drug concentration fluctuations due to intersubject variation in drug absorption, distribution, or elimination processes. For drugs such as phenytoin that follow nonlinear pharmacokinetics at therapeutic plasma drug concentrations, a small change in the dose may cause a huge increase in the therapeutic response, leading to possible adverse effects.

The monitoring of plasma drug concentrations is valuable only if a relationship exists between the plasma drug concentration and the desired clinical effect or between the plasma drug concentration and an adverse effect. For those drugs in which plasma drug concentration and clinical effect are not related, other pharmacodynamic parameters may be monitored. For example, clotting time may be measured directly in patients on warfarin anticoagulant therapy. For asthmatic patients, the bronchodilator, albuterol, is given by inhalation via a metered-dose inhaler and the patient's FEV<sub>1</sub> (forced expiratory volume) may be used as a measure of drug efficacy. In cancer chemotherapy, dose adjustment for individual patients may depend on the severity of side effects and the patient's ability to tolerate the drug. For some drugs that have large inter- and intrasubject variability, clinical judgment and experience with the drug is needed to dose the patient properly.

## THERAPEUTIC DRUG MONITORING

The therapeutic range for a drug is an approximation of the average plasma drug concentrations that are safe and efficacious in most patients. When using published therapeutic drug concentration ranges, such as those in , the clinician must realize that the therapeutic range is essentially a probability concept and should never be considered as absolute values (; ). For example, the accepted therapeutic range for theophylline is 10–20 µg/mL. Some patients may exhibit signs of theophylline intoxication such as central nervous system excitation and insomnia at serum drug concentrations below 20 µg/mL (see , below) whereas other patients may show drug efficacy at serum drug concentrations below 10 µg/mL.

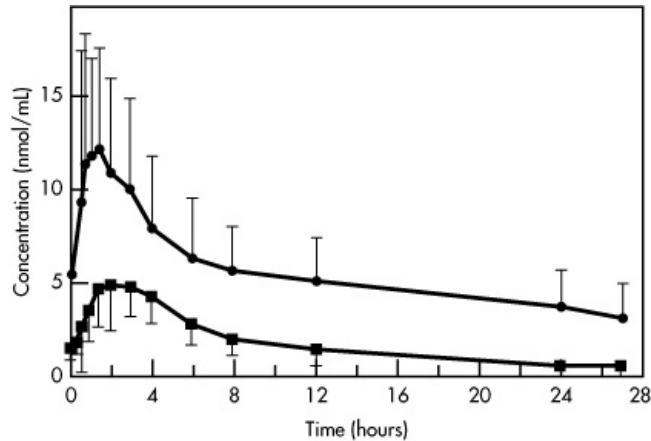
**Table 20.1 Therapeutic Range for Commonly Monitored Drugs**

Amikacin	20–30 µg/mL
Carbamazepine	4–12 µg/mL
Digoxin	1–2 ng/mL
Gentamicin	5–10 µg/mL
Lidocaine	1–5 µg/mL
Lithium	0.6–1.2 mEq/L
Phenytoin	10–20 µg/mL
Procainamide	4–10 µg/mL

Quinidine	1–4 $\mu\text{g}/\text{mL}$
Theophylline	10–20 $\mu\text{g}/\text{mL}$
Tobramycin	5–10 $\mu\text{g}/\text{mL}$
Valproic acid	50–100 $\mu\text{g}/\text{mL}$
Vancomycin	20–40 $\mu\text{g}/\text{mL}$

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**Figure 20-1.**



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>

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Correlation between the frequency and severity of adverse effects and plasma concentration of theophylline (mean  $\pm$  SD) in 50 adult patients. Mild symptoms of toxicity included nausea, vomiting, headache, and insomnia: a potentially serious effect was sinus tachycardia, and severe toxicity was defined as the occurrence of life-threatening cardiac arrhythmias and seizures.

( )

In administering potent drugs to patients, the physician must maintain the plasma drug level within a narrow range of therapeutic concentrations ( ). Various pharmacokinetic methods may be used to calculate the initial dose or dosage regimen. Usually, the initial dosage regimen is calculated based on body weight or body surface after a careful consideration of the known pharmacokinetics of the drug, the pathophysiologic condition of the patient, and the patient's drug history.

Because of interpatient variability in drug absorption, distribution, and elimination as well as changing pathophysiologic conditions in the patient, *therapeutic drug monitoring* (TDM) or clinical pharmacokinetic (laboratory) services (CPKS) have been established in many hospitals to evaluate the response of the patient to the recommended dosage regimen. The improvement in the clinical effectiveness of the drug by therapeutic drug monitoring may decrease the cost of medical care by preventing untoward adverse drug effects. The functions of a TDM service are listed below.

- Select drug.
- Design dosage regimen.
- Evaluate patient response.
- Determine need for measuring serum drug concentrations.
- Assay for drug concentration in biological fluids.
- Perform pharmacokinetic evaluation of drug concentrations.
- Readjust dosage regimen, if necessary.
- Monitor serum drug concentrations.
- Recommend special requirements.

## Drug Selection

The choice of drug and drug therapy is usually made by the physician. However, many practitioners consult with the clinical pharmacist in drug product selection and dosage regimen design. Increasingly, clinical pharmacists in hospitals and nursing care facilities are closely involved in prescribing, monitoring, and substitution of medications. The choice of drug and the drug product is made not only on the basis of therapeutic consideration, but also based on cost and therapeutic equivalency. Pharmacokinetics and pharmacodynamics are part of the overall considerations in the selection of a drug for inclusion into the drug formulary (DF). New pharmacokinetic and pharmacodynamic data are periodically reviewed and updated by Institutional Pharmacy and Therapeutic Committees (IPTCs).

Drugs with similar therapeutic indications may differ in dose and pharmacokinetics. The pharmacist may choose one drug over another based on cost, therapeutic, and pharmacokinetic considerations. Other factors include patient-specific information such as medical history, pathophysiologic states, concurrent drug therapy, known allergies, drug sensitivities, and drug interactions; all are important considerations in drug selection ().

<b>Table 20.2 Factors Producing Variability in Drug Response</b>	
<b>Patent Factors</b>	<b>Drug Factors</b>
Age	Bioavailability and biopharmaceutics
Weight	Pharmacokinetics (including absorption, distribution, and elimination)
Pathophysiology	Drug interactions
Nutritional status	Receptor sensitivity
Genetic variability	Rapid or slow metabolism
Gender	

## Dosage Regimen Design

The overall objective of dosage regimen design is to achieve a *target* drug concentration at the receptor site. Once the proper drug is selected for the patient, a number of factors must be considered when designing a therapeutic dosage regimen. First, the usual pharmacokinetics of the drug—including its absorption, distribution, and elimination profile—are considered in the patient. Some patients have unusual first-pass metabolism and bioavailability may be reduced. Second, the physiology of the patient, age, weight, gender, and nutritional status will affect the disposition of the drug and should be considered. Third, any pathophysiologic conditions, such as renal dysfunction, hepatic disease, or congestive heart failure, may change the normal pharmacokinetic profile of the drug, and the dose must be carefully adjusted. For some patients, the hidden effect of exposure to long-term medication or drug abuse are important. Personal lifestyle factors, such as cigarette smoking, alcohol abuse, and obesity are known to alter the pharmacokinetics of drugs.

Optimal dosing design can greatly improve the safety and efficacy of the drug, including reduced side effects and a decrease in frequency of therapeutic drug monitoring and its associated costs. For some drugs, TDM will be necessary because of the unpredictable nature of their pharmacodynamics and pharmacokinetics. Changes in drug or drug dose may be required after careful assessment by the pharmacist of the patient, including changes in the drug's pharmacokinetics, drug tolerance, cross sensitivity, or history of unusual reactions to related drugs. The pharmacist must develop competency and experience in clinical pharmacology and therapeutics in addition to the necessary pharmacokinetic skills. Several mathematical approaches to dosage regimen design are given in later sections of this chapter and in .

## Pharmacokinetics of the Drug

Various popular drug references list pharmacokinetic parameters such as clearance, bioavailability, and elimination half-life. The values for these pharmacokinetic parameters are often obtained from small clinical studies. Therefore, it is difficult to determine whether these reported pharmacokinetic parameters are reflected in the general population or in specific patient groups. Differences in study design, patient population, and data analysis may lead to conflicting values for the same pharmacokinetic parameters. For example, values for the apparent volume of distribution and clearance can be estimated by different methods, as discussed in previous chapters.

Ideally, the target drug concentration and the therapeutic window for the drug should be obtained, if available. In using the target drug concentration in the development of a dosage regimen, the clinical pharmacist should know whether the reported target (effective) drug concentration represents an average steady-state drug concentration, a peak drug concentration, or a trough concentration.

## Drug Dosage Form (Drug Product)

The dosage form of the drug will affect drug bioavailability and the rate of absorption and thus the subsequent pharmacodynamics of the drug in the patient. The route of drug administration and the desired onset and duration of the clinical response will affect the choice of drug dosage form. In addition, the selection of an extended-release drug product instead of an immediate-release drug product may affect both the cost of the drug and patient compliance. These biopharmaceutic factors have been discussed in .

## Patient Compliance

Factors that may affect patient compliance include the cost of the medication, complicated instructions, multiple daily doses, difficulty in swallowing, adverse drug reactions, and ambulatory versus institutionalized status. Institutionalized patients may have very little choice as to the prescribed drug and drug dosage form. Moreover, patient compliance in institutions is dictated by the fact that medication is provided by the medical personnel. Ambulatory patients must remember to take the medication as prescribed to obtain the optimum clinical effect of the drug. Therefore, it is very important that the clinician or clinical pharmacist consider the patient's lifestyle and needs when developing a drug dosage regimen.

## Evaluation of Patient's Response

After the drug and drug product are chosen and the patient receives the initial dosage regimen, the practitioner should evaluate the patient's response clinically. If the patient is not responding to drug therapy as expected, then the drug and dosage regimen should be reviewed. The dosage regimen should be reviewed for adequacy, accuracy, and patient compliance to the drug

therapy. In many situations, sound clinical judgment may preclude the need for measuring serum drug concentrations.

### Measurement of Serum Drug Concentrations

Before blood samples are taken from the patient, the practitioner needs to determine whether serum drug concentrations in the patient need to be measured. In some cases, the patient's response may not be related to the serum drug concentration. For example, allergy or mild nausea may not be dose related. In other cases, the response of a drug may be related to its chronopharmacology (see examples in ).

A major assumption made by the practitioner is that serum drug concentrations relate to the therapeutic and/or toxic effects of the drug. For many drugs, clinical studies have demonstrated a therapeutically effective range of serum concentrations. Knowledge of the serum drug concentration may clarify why a patient is not responding to the drug therapy or why the drug is having an adverse effect. In addition, the practitioner may want to verify the accuracy of the dosage regimen.

When ordering serum drug concentrations to be measured, a single serum drug concentration may not yield useful information unless other factors are considered. For example, the dosage regimen of the drug should be known, including the size of the dose and the dosage interval, the route of drug administration, the time of sampling (peak, trough, or steady state), and the type of drug product (eg, immediate release or extended release).

In many cases, a single blood sample gives insufficient information. Several blood samples are often needed to clarify the adequacy of the dosage regimen. In practice, trough serum concentrations are easier to obtain than peak or  $C_{av}^{\infty}$  samples under a multiple-dose regimen. In addition, limitations in terms of the number of blood samples that may be taken, total volume of blood needed for the assay, and time to perform the drug analysis may exist. has suggested that blood sampling times for therapeutic drug monitoring should be taken during the postdistributive phase for loading and maintenance doses, but at steady state for maintenance doses. After distribution equilibrium has been achieved, the plasma drug concentration during the postdistributive phase is better correlated with the tissue concentration and, presumably, the drug concentration at the site of action. In some cases, the clinical pharmacist may want an early-time sample that approximates the peak drug level, whereas a blood sample taken at three or four elimination half-lives will approximate the steady-state drug concentration. The practitioner who orders the measurement of serum concentrations should also consider the cost of the assays, the risks and discomfort for the patient, and the utility of the information gained.

### Assay for Drug

Drug analyses are usually performed by either a clinical chemistry laboratory or a clinical pharmacokinetics laboratory. A variety of analytic techniques are available for drug measurement, including high-pressure liquid chromatography, gas chromatography, spectrophotometry, fluorometry, immunoassay, and radioisotopic methods. The methods used by the analytic laboratory may depend on such factors as the physicochemical characteristics of the drug, target concentration for measurement, amount and nature of the biologic specimen (serum, urine), available instrumentation, cost for each assay, and analytical skills of the laboratory personnel. The laboratory should have a standard operating procedure (SOP) for each drug analysis technique and follow good laboratory practices. Moreover, analytic methods used for the assay of drugs in serum should be validated with respect to specificity, linearity, sensitivity, precision, accuracy, stability, and ruggedness.

Because of cost and equipment constraints, most clinical pharmacokinetic services routinely analyze drugs by immunoassay. Various immunoassay methods are currently available that may differ in assay specificity for the drug, the cost of analyses, and the time to perform the assay and obtain the results. The Abbott TDx system is a fluorescence polarization immunoassay (FPI), which measures most of the antiarrhythmics and aminoglycosides and other drugs of abuse (). TDxFLx is a newer system that allows flexible handling of samples. Other dedicated systems routinely used in hospitals include the Autocarousel (Syva Corp., which markets many EMIT test kits for many drugs). Other makers of instruments or kits for drug testing include Syntex, Eastman Kodak, Hoffman-LaRoche, and Miles Laboratories.

<b>Antiarrhythmics</b>	<b>Antibiotics</b>	<b>Anticonvulsants</b>
Disopyramide	Amikacin	Carbamazepine, free carbamazepine
Flecainide	Gentamicin	Valproic acid, free valproic acid
Lidocaine	Netilmicin	Ethosuximide
<i>N</i> -acetylprocainamide	Tobramycin	Phenobarbital
Procainamide	Vancomycin	Phenytoin, free phenytoin
Quinidine		Primidone
<b>Others</b>	<b>Toxicology Assays</b>	<b>Drug Screening Assays</b>
Digoxin	Acetaminophen	Amphetamine
Digitoxin	Ethanol	Barbiturates
Methotrexate	Salicylate	Salicylate
Benzodiazepines	Tricyclic antidepressants	Cannabinoids
Theophylline		Cocaine
		Methadone
		Opiates

		Phencyclidine
		Propoxyphene

## SPECIFICITY

Chromatographic evidence should be used to demonstrate that the analytic method is specific for detection of the drug. The method should demonstrate that there is no interference between the drug and its metabolites and endogenous or exogenous substances. In addition, the internal standard should be resolved completely and also demonstrate no interference with other compounds. Immunoassays depend on an antibody and antigen (usually the drug to be measured) reaction. The antibody may not be specific for the drug analyte, but may also cross-react with drugs that have similar structures, including related compounds (endogenous or exogenous chemicals) and metabolites of the drug. Colorimetric and spectrophotometric assays are usually less specific. Interference from other materials may inflate the results.

## SENSITIVITY

Sensitivity is the minimum detectable level or concentration of drug in serum that may be approximated as that lowest drug concentration that is two to three times the background noise. A *minimum quantifiable level* (MQL) is a statistical method for the determination of the precision of the lower level.

## LINEARITY AND DYNAMIC RANGE

Dynamic range refers to the relationship between the drug concentration and the instrument response (or signal) used to measure the drug. Many assays show a linear drug concentration-versus-instrument response relationship. Immunoassays generally have a nonlinear dynamic range. High serum drug concentrations, above the dynamic range of the instrument response, must be diluted before assay. The dynamic range is determined by using serum samples that have known (standard) drug concentrations (including a blank serum sample or zero drug concentration). Extrapolation of the assay results above or below the measured standard drug concentrations may be inaccurate if the relationship between instrument response and extrapolated drug concentration is unknown.

## PRECISION

Precision is a measurement of the variability or reproducibility of the data. Precision measurements are obtained by replication of various drug concentrations and by replication of standard concentration curves prepared separately on different days. A suitable statistical measurement of the dispersion of the data, such as standard deviation or coefficient of variation, is then performed.

## ACCURACY

Accuracy refers to the difference between the average assay values and the true or known drug concentrations. Control (known) drug serum concentrations should be prepared by an independent technician using such techniques to minimize any error in their preparation. These samples, including a "zero" drug concentration, are assayed by the technician assigned to the study along with a suitable standard drug concentration curve.

## STABILITY

Standard drug concentrations should be maintained under the same storage conditions as the unknown serum samples and assayed periodically. The stability study should continue for at least the same length of time as the patient samples are to be stored. Freeze-thaw stability studies are performed to determine the effect of thawing and refreezing on the stability of the drug in the sample. On occasion, a previously frozen biologic sample must be thawed and reassayed if the first assay result is uncertain.

Serum samples obtained from subjects on a drug study are usually assayed along with a minimum of three standard processed serum samples containing known standard drug concentrations and a minimum of three control serum samples whose concentrations are unknown to the analyst. These control serum samples are randomly distributed in each day's run. Control samples are replicated in duplicate to evaluate both within-day and between-day precision. The concentration of drug in each serum sample is based on each day's processed standard curve.

## RUGGEDNESS

Ruggedness is the degree of reproducibility of the test results obtained by the analysis of the same samples by different analytical laboratories. The determination of ruggedness measures the reproducibility of the results under normal operational conditions from laboratory to laboratory and from analyst to analyst.

Because each method for drug assay may have differences in sensitivity, precision, and specificity, the pharmacokineticist should be aware of which drug assay method the laboratory used.

## PHARMACOKINETIC EVALUATION

After the serum or plasma drug concentrations are measured, the pharmacokineticist must evaluate the data. Most laboratories report total drug (free plus bound drug) concentrations in the serum. The pharmacokineticist should be aware of the usual therapeutic range of serum concentrations from the literature. However, the literature may not indicate whether the reported values were trough or peak serum levels. Moreover, the assay used in reporting the methodology may be different in terms of specificity and precision.

The assay results from the laboratory may show that the patient's serum drug levels are higher, lower, or similar to the expected serum levels. The pharmacokineticist should evaluate these results while considering the patient and the patient's pathophysiologic condition.

lists a number of factors the pharmacokineticist should consider when interpreting drug serum

concentration. Often, other data, such as a high serum creatinine and high blood urea nitrogen (BUN), may help verify that an observed high serum drug concentration in a patient is due to lower renal drug clearance because of compromised kidney function. In another case, a complaint by the patient of overstimulation and insomnia might collaborate the laboratory's finding of higher-than-anticipated serum concentrations of theophylline. Therefore, the clinician or pharmacokineticist should evaluate the data using sound medical judgment and observation. The therapeutic decision should not be based solely on serum drug concentrations.

**Table 20.4 Pharmacokinetic Evaluation of Serum Drug Concentrations**

<b>Serum Concentrations Lower than Anticipated</b>
Patient compliance
Error in dosage regimen
Wrong drug product (controlled-release instead of immediate-release)
Poor bioavailability
Rapid elimination (efficient metabolizer)
Reduced plasma protein binding
Enlarged apparent volume of distribution
Steady state not reached
Timing of blood sample
Improving renal/hepatic function
Drug interaction due to stimulation of elimination enzyme autoinduction
Changing hepatic blood flow
<b>Serum Concentrations Higher than Anticipated</b>
Patient compliance
Error in dosage regimen
Wrong drug product (immediate release instead of controlled release)
Rapid bioavailability
Smaller than anticipated apparent volume of distribution
Slow elimination (poor metabolizer)
Increased plasma protein binding
Deteriorating renal/hepatic function
Drug interaction due to inhibition of elimination
<b>Serum Concentration Correct but Patient Does Not Respond to Therapy</b>
Altered receptor sensitivity (eg, tolerance)
Drug interaction at receptor site
Changing hepatic blood flow

## Dosage Adjustment

From the serum drug concentration data and patient observations, the clinician or pharmacokineticist may recommend an adjustment in the dosage regimen. Ideally, the new dosage regimen should be calculated using the pharmacokinetic parameters derived from the *patient's* serum drug concentrations. Although there may not be enough data for a complete pharmacokinetic profile, the pharmacokineticist should still be able to derive a new dosage regimen based on the available data and the pharmacokinetic parameters in the literature that are based on average population data.

## Monitoring Serum Drug Concentrations

In many cases, the patient's pathophysiology may be unstable, either improving or deteriorating further. For example, proper therapy for congestive heart failure will improve cardiac output and renal perfusion, thereby increasing renal drug clearance. Therefore, continuous monitoring of serum drug concentrations is necessary to ensure proper drug therapy for the patient. For some drugs, an acute pharmacologic response can be monitored in lieu of actual serum drug concentration. For example, prothrombin clotting time might be useful for monitoring anticoagulant therapy and blood pressure monitoring for hypotensive agents.

## Special Recommendations

At times, the patient may not be responding to drug therapy because of other factors. For example, the patient may not be following instructions for taking the medication (patient noncompliance). The patient may be taking the drug after a meal instead of before, or may not be adhering to a special diet (eg, low salt). Therefore, the patient may need special instructions that are simple and easy to follow.

## DESIGN OF DOSAGE REGIMENS

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Several methods may be used to design a dosage regimen. Generally, the initial dosage of the drug is estimated using average population pharmacokinetic parameters obtained from the literature. The patient is then monitored for the therapeutic response by physical examination and, if necessary, by measurement of serum drug levels. After evaluation of the patient, adjustment of the dosage regimen using the patient's individual pharmacokinetic parameters may be indicated, with further therapeutic drug monitoring.

Many versions of clinical pharmacokinetic software are available for dose calculations of drugs with narrow therapeutic index (eg, DataKinetics [ASHSP], and the Abbottbase pharmacokinetic system). The dosing strategies are based generally on basic pharmacokinetic principles that have been estimated manually. Computer automation and pharmacokinetic software packages improve the accuracy of the calculation, make the calculations "easier," and have an added advantage of maintaining proper documentation (see ).

## Individualized Dosage Regimens

The most accurate approach to dosage regimen design is to calculate the dose based on the pharmacokinetics of the drug in the individual patient. This approach is not feasible for calculation of the initial dose. However, once the patient has been medicated, the readjustment of the dose may be calculated using pharmacokinetic parameters derived from measurement of the serum drug levels from the patient after the initial dose. Most dosing programs record the patient's age and weight and calculate the individual dose based on creatinine clearance and lean body weight.

## Dosage Regimens Based on Population Averages

The method most often used to calculate a dosage regimen is based on average pharmacokinetic parameters obtained from clinical studies published in the drug literature. This method may be based on a fixed or an adaptive model (; ).

The *fixed model* assumes that population average pharmacokinetic parameters may be used directly to calculate a dosage regimen for the patient, without any alteration. Usually, pharmacokinetic parameters such as absorption rate constant  $k_a$ , bioavailability factor  $F$ , apparent volume of distribution  $V_D$ , and elimination rate constant  $k$ , are assumed to remain constant. Most often the drug is assumed to follow the pharmacokinetics of a one-compartment model. When a multiple-dose regimen is designed, multiple-dosage equations based on the principle of superposition ( ) are used to evaluate the dose. The practitioner may use the usual dosage suggested by the literature and then make a small adjustment of the dosage based on the patient's weight and/or age.

The *adaptive model* for dosage regimen calculation uses patient variables such as weight, age, sex, body surface area, and known patient pathophysiology, such as renal disease, as well as the known population average pharmacokinetic parameters of the drug. In this case, calculation of the dosage regimen takes into consideration any changing pathophysiology of the patient and attempts to adapt or modify the dosage regimen according to the needs of the patient. The adaptive model generally assumes that pharmacokinetic parameters such as drug clearance do not change from one dose to the next. However, some adaptive models allow for continuously adaptive change with time in order to simulate more closely the changing process of drug disposition in the patient, especially during a disease state ( ).

## Dosage Regimens Based on Partial Pharmacokinetic Parameters

For many drugs, the entire pharmacokinetic profile for the drug is unknown or unavailable. Therefore, the pharmacokineticist needs to make some assumptions in order to calculate the dosage regimen. For example, a common assumption is to let the bioavailability factor  $F$  equal 1 or 100%. Thus, if the drug is less than fully absorbed systemically, the patient will be undermedicated rather than overmedicated. Some of these assumptions will depend on the safety, efficacy, and therapeutic range of the drug. The use of population pharmacokinetics (discussed later in this chapter) uses average patient population characteristics and only a few serum drug concentrations from the patient. Population pharmacokinetic approaches to therapeutic drug monitoring have increased with the increased availability of computerized databases and the development of statistical tools for the analysis of observational data ( ).

## Empirical Dosage Regimens

In many cases, the physician selects a dosage regimen for the patient without using any pharmacokinetic variables. In such a situation, the physician makes the decision based on empirical clinical data, personal experience, and clinical observations. The physician characterizes the patient as representative of a similar well-studied clinical population that has used the drug successfully.

## CONVERSION FROM INTRAVENOUS INFUSION TO ORAL DOSING

After the patient's dosing is controlled by intravenous infusion, it is often desirable to continue to medicate the patient with the same drug using the oral route of administration. When intravenous infusion is stopped, the serum drug concentration decreases according to first-order elimination kinetics ( ). For most oral drug products, the time to reach steady state depends on the first-order elimination rate constant for the drug. Therefore, if the patient starts the dosage regimen with the oral drug product at the same time as the intravenous infusion is stopped, then the exponential decline of serum levels from the intravenous infusion should be matched by the exponential increase in serum drug levels from the oral drug product.

The conversion from intravenous infusion to a controlled-release oral medication given once or twice daily has become more common with the availability of more controlled-release drug products, such as theophylline ( ) and quinidine. Computer simulation for the conversion of intravenous theophylline (aminophylline) therapy to oral controlled-release theophylline demonstrated that oral therapy should be started at the same time as intravenous infusion is stopped ( ). With this method, minimal fluctuations are observed between the peak and trough serum theophylline levels. Moreover, giving the first oral dose when IV infusion is stopped may make it easier for the nursing staff or patient to comply with the dosage regimen.

Either of these methods may be used to calculate an appropriate oral dosage regimen for a patient whose condition has been stabilized by an intravenous drug infusion. Both methods assume that the patient's plasma drug concentration is at steady state.

### Method 1

Method 1 assumes that the steady-state plasma drug concentration,  $C_{SS}$ , after IV infusion is identical to the desired  $C_{av}^{\infty}$  after multiple oral doses of the drug. Therefore, the following equation may be used:

$$C_{av}^{\infty} = \frac{SFD_0}{kV_D\tau} \quad (20.1)$$

$$\frac{D_0}{\tau} = \frac{C_{av}^{\infty}kV_D}{SF} \quad (20.2)$$

where  $S$  is the salt form of the drug and  $D_0/\tau$  is the dosing rate.

### EXAMPLE

An adult male asthmatic patient (age 55, 78 kg) has been maintained on an intravenous infusion of aminophylline at a rate of 34 mg/hr. The steady-state theophylline drug concentration was 12  $\mu\text{g}/\text{mL}$  and total body clearance was calculated as 3.0 L/hr. Calculate an appropriate oral dosage regimen of theophylline for this patient.

#### Solution

Aminophylline is a soluble salt of theophylline and contains 85% theophylline ( $S = 0.85$ ). Theophylline is 100% bioavailable ( $F = 1$ ) after an oral dose. Because total body clearance,  $Cl_T = kV_D$ , Equation 20.2 may be expressed as

$$\frac{D_0}{\tau} = \frac{C_{av}^{\infty}Cl_T}{SF} \quad (20.3)$$

The dose rate,  $D_0/\tau$  (34 mg/hr), was calculated on the basis of aminophylline. The patient, however, will be given theophylline orally. To convert to oral theophylline,  $S$  and  $F$  should be considered.

$$\text{Theophylline dose rate} = \frac{SFD_0}{\tau} = \frac{(0.85)(1)(34)}{1} = 28.9 \text{ mg/hr}$$

The theophylline dose rate of 28.9 mg/hr must be converted to a reasonable schedule for the patient with a consideration of the various commercially available theophylline drug products. Therefore, the total daily dose is 28.9 mg/hr  $\times$  24 hr or 693.6 mg/day. Possible theophylline dosage schedules might be 700 mg/day, 350 mg every 12 hours, or 175 mg every 6 hours. Each of these dosage regimens would achieve the same  $C_{av}^{\infty}$  but different  $C_{max}^{\infty}$  and  $C_{min}^{\infty}$ , which should be calculated. The dose of 350 mg every 12 hours could be given in sustained-release form to avoid any excessive high drug concentration in the body.

### Method 2

Method 2 assumes that the rate of intravenous infusion (mg/hr) is the same desired rate of oral dosage.

### EXAMPLE

Using the example in method 1, the following calculations may be used.

#### Solution

The aminophylline is given by IV infusion at a rate of 34 mg/hr. The total daily dose of aminophylline is 34 mg/hr  $\times$  24 hr = 816 mg. The equivalent daily dose in terms of theophylline is 816  $\times$  0.85 = 693.6 mg. Thus, the patient should receive approximately 700 mg of theophylline per day or 350 mg controlled-release theophylline every 12 hours.

## DETERMINATION OF DOSE

The drug dose is estimated to deliver a desirable (target) therapeutic level of the drug to the body. The dose of a drug is estimated with the objective of delivering a desirable therapeutic level of the drug in the body. For many drugs, the desirable therapeutic drug levels and pharmacokinetic parameters are available in the clinical literature. However, the literature in some cases may not yield complete drug information, or the information available may be partly equivocal. Therefore, the pharmacokineticist must make certain necessary assumptions in accordance with the best pharmacokinetic information available.

For a drug that is given in multiple doses for an extended period of time, the dosage regimen is usually calculated so that the average steady-state blood level is within the therapeutic range. The dose can be calculated with Equation 20.4, which expresses the  $C_{av}^{\infty}$  in terms of dose ( $D_0$ ), dosing interval ( $\tau$ ), volume of distribution ( $V_D$ ), and the elimination half-life of the drug.  $F$  is the fraction of drug absorbed and is equal to 1 for drugs administered intravenously.

$$C_{av}^{\infty} = \frac{1.44D_0t_{1/2}F}{V_D\tau} \quad (20.4)$$

### Practice Problems

1. Pharmacokinetic data for clindamycin were reported by as follows:

$$k = 0.247 \text{ hr}^{-1}$$

$$t_{1/2} = 2.81 \text{ hr}$$

$$V_D = 43.9 \text{ L}/1.73 \text{ m}^2$$

What is the steady-state concentration of the drug after 150 mg of the drug is given orally every 6 hours for a week? (Assume the drug is 100% absorbed.)

**Solution**

$$C_{av}^{\infty} = \frac{1.44 D_0 t_{1/2} F}{V_D \tau}$$

$$= \frac{1.44 \times 150,000 \times 2.81 \times 1}{43,900 \times 6} \mu\text{g/mL}$$

$$= 2.3 \mu\text{g/mL}$$

2. According to , the elimination half-life of tobramycin was reported to be 2.15 hours and the volume of distribution was reported to be 33.5% of body weight.

a. What is the dose for an 80-kg individual if a steady-state level of 2.5  $\mu\text{g/mL}$  is desired?

Assume that the drug is given by intravenous bolus injection every 8 hours.

**Solution**

Assuming the drug is 100% bioavailable as a result of IV injection,

$$C_{av}^{\infty} = \frac{1.44 D_0 t_{1/2} F}{V_D \tau}$$

$$2.5 = \frac{1.44 \times 2.15 \times 1 \times D_0}{80 \times 0.335 \times 1000 \times 8}$$

$$D_0 = \frac{2.5 \times 80 \times 0.335 \times 1000 \times 8}{1.44 \times 2.15} \mu\text{g}$$

$$D_0 = 173 \text{ mg}$$

The dose should be 173 mg every 8 hours.

b. The manufacturer has suggested that in normal cases, tobramycin should be given at a rate of 1 mg/kg every 8 hours. With this dosage regimen, what would be the average steady-state level?

**Solution**

$$C_{av}^{\infty} = \frac{1.44 \times 1 \times 1000 \times 2.15}{0.335 \times 1000 \times 8}$$

$$C_{av}^{\infty} = 1.16 \mu\text{g/mL}$$

Because the bacteriocidal concentration of an antibiotic varies with the organism involved in the infection, the dose prescribed may change. The average plasma drug concentration is used to indicate whether optimum drug levels have been reached. With certain antibiotics, the steady-state peak and trough levels are sometimes used as therapeutic indicators. (See for discussion of time above minimum effective concentration (mic). For example, the effective concentration of tobramycin was reported to be around 4–5  $\mu\text{g/mL}$  for peak level and around 2  $\mu\text{g/mL}$  for trough level when given intramuscularly every 12 hours (). Although peak and trough levels are frequently reported in clinical journals, these drug levels are only transitory in the body. Peak and trough drug levels are less useful pharmacokinetically, because peak and trough levels fluctuate more and are usually reported less accurately than average plasma drug concentrations. When the average plasma drug concentration is used as a therapeutic indicator, an optimum dosing interval must be chosen. The dosing interval is usually set at approximately one to two elimination half-lives of the drug, unless the drug has a very narrow therapeutic index. In this case the drug must be given in small doses more frequently or by IV infusion.

## EFFECT OF CHANGING DOSE AND DOSING INTERVAL ON $C^{\infty}_{MAX}$ , $C^{\infty}_{MIN}$ , AND $C^{\infty}_{AV}$

During intravenous infusion,  $C_{SS}$  may be used to monitor the steady-state serum concentrations. In contrast, when considering therapeutic drug monitoring of serum concentrations after the initiation of a multiple-dosage regimen, the trough serum drug concentrations or  $C^{\infty}_{min}$  may be used to validate the dosage regimen. The blood sample withdrawn just prior to the administration of the next dose represents  $C^{\infty}_{min}$ . To obtain  $C^{\infty}_{max}$ , the blood sample must be withdrawn exactly at the time for peak absorption, or closely spaced blood samples must be taken and the plasma drug concentrations graphed. In practice, an approximate time for maximum drug absorption is estimated and a blood sample is withdrawn. Because of differences in rates of drug absorption,  $C^{\infty}_{max}$  measured in this manner is only an approximation of the true  $C^{\infty}_{max}$ .

The  $C^{\infty}_{av}$  is used most often in dosage calculation. The advantage of using  $C^{\infty}_{av}$  as an indicator for deciding therapeutic blood level is that  $C^{\infty}_{av}$  is determined on a set of points and generally fluctuates less than either  $C^{\infty}_{max}$  or  $C^{\infty}_{min}$ . Moreover, when

the dosing interval is changed, the dose may be increased proportionally, to keep  $C^{\infty}_{av}$  constant. This approach works well for some drugs. For example, if the drug diazepam is given either 10 mg TID (three times a day) or 15 mg BID (twice daily), the same  $C^{\infty}_{av}$  is obtained, as shown by Equation 20.1. In fact, if the daily dose is the same, the  $C^{\infty}_{av}$  should be the same. However, when monitoring serum drug concentrations,  $C^{\infty}_{av}$  cannot be measured directly but may be obtained from  $AUC/\tau$  during multiple-dosage regimens. As discussed in , the  $C^{\infty}_{av}$  is not the arithmetic average of  $C^{\infty}_{min}$  and  $C^{\infty}_{max}$  because serum concentrations decline exponentially.

The dosing interval must be selected while considering the elimination half-life of the drug; otherwise, the patient may suffer the toxic effect of a high  $C^{\infty}_{max}$  or subtherapeutic effects of a low  $C^{\infty}_{min}$  even if the  $C^{\infty}_{av}$  is kept constant. For example, using the same example of diazepam, the same  $C^{\infty}_{av}$  is achieved at 10 mg TID or 60 mg every other day. Obviously, the  $C^{\infty}_{max}$  of the latter dose regimen would produce a  $C^{\infty}_{max}$  several times larger than that achieved with 10-mg-TID dose regimen. In general, if a drug has a relatively wide therapeutic index and a relatively long elimination half-life, then flexibility exists in changing the dose or dosing interval,  $\tau$ , using  $C^{\infty}_{av}$  as an indicator. When the drug has a narrow therapeutic index,  $C^{\infty}_{max}$  and  $C^{\infty}_{min}$  must be monitored to ensure safety and efficacy.

As the size of the dose or dosage intervals change proportionately, the  $C^{\infty}_{av}$  may be the same but the steady-state peak,  $C^{\infty}_{max}$ , and trough,  $C^{\infty}_{min}$ , drug levels will change.  $C^{\infty}_{max}$  is influenced by the size of the dose and the dosage interval. An increase in the size of the dose given at a longer dosage interval will cause an increase in  $C^{\infty}_{max}$  and a decrease in  $C^{\infty}_{min}$ . In this case  $C^{\infty}_{max}$  may be very close or above the minimum toxic drug concentration (MTC). However, the  $C^{\infty}_{min}$  may be lower than the minimum effective drug concentration (MEC). In this latter case the low  $C^{\infty}_{min}$  may be subtherapeutic and dangerous for the patient, depending on the nature of the drug.

## DETERMINATION OF FREQUENCY OF DRUG ADMINISTRATION

The size of a drug dose is often related to the frequency of drug administration. The more frequently a drug is administered, the smaller the dose must be to obtain the same  $C^{\infty}_{av}$ . Thus, a dose of 250 mg every 3 hours could be changed to 500 mg every 6 hours without affecting the average steady-state plasma concentration of the drug. However, as the dosing intervals get longer, the size of the dose required to maintain the average plasma drug concentration gets correspondingly larger. When an excessively long dosing interval is chosen, the large dose may result in peak plasma levels that are above toxic drug concentration, even though  $C^{\infty}_{av}$  will remain the same (see ).

In general, the dosing interval for most drugs is determined by the elimination half-life. Drugs such as the penicillins, which have relatively low toxicity, may be given at intervals much longer than their elimination half-lives without any toxicity problems. Drugs having a narrow therapeutic range, such as digoxin and phenytoin, must be given relatively frequently to minimize excessive "peak-and-trough" fluctuations in blood levels. For example, the common maintenance schedule for digoxin is 0.25 mg/day and the elimination half-life of digoxin is 1.7 days. In contrast, penicillin G is given at 250 mg every 6 hours, while the elimination half-life of penicillin G is 0.75 hour. Penicillin is given at a dosage interval equal to 8 times its elimination half-life, whereas digoxin is given at a dosing interval only 0.59 times its elimination half-life. The toxic plasma concentration of penicillin G is over 100 times greater than its effective concentration, whereas digoxin has an effective concentration of 1–2 ng/mL and a toxicity level of 3 ng/mL. The toxic concentration of digoxin is only 1.5 times effective concentration. Therefore, a drug with a large therapeutic index (ie, a large margin of safety) can be given in large doses and at relatively long dosing intervals.

## DETERMINATION OF BOTH DOSE AND DOSAGE INTERVAL

Both the dose and the dosage interval should be considered in the dosage regimen calculations. Ideally, the calculated dosage regimen should maintain the serum drug concentrations between  $C^{\infty}_{max}$  and  $C^{\infty}_{min}$ . For intravenous multiple-dosage regimens the ratio of  $C^{\infty}_{max}/C^{\infty}_{min}$  may be expressed by

$$\frac{C^{\infty}_{max}}{C^{\infty}_{min}} = \frac{C_p^0 / (1 - e^{-k\tau})}{C_p^0 e^{-k\tau} / (1 - e^{-k\tau})} \quad (20.5)$$

which can be simplified to

$$\frac{C^{\infty}_{max}}{C^{\infty}_{min}} = \frac{1}{e^{-k\tau}} \quad (20.6)$$

From Equation 20.6, a maximum dosage interval,  $\tau$ , may be calculated that will maintain the serum concentration between  $C^{\infty}_{min}$  and  $C^{\infty}_{max}$ . After the dosage interval is calculated, then a dose may be calculated.

### Practice Problem

The elimination half-life of an antibiotic is 3 hours with an apparent volume of distribution equivalent to 20% of body weight. The usual therapeutic range for this antibiotic is between 5 and 15  $\mu\text{g/mL}$ . Adverse toxicity for this drug is often observed at serum concentrations greater than 20  $\mu\text{g/mL}$ . Calculate a dosage regimen (multiple IV doses) that will just maintain the serum drug

concentration between 5 and 15 µg/mL.

**Solution**

From Equation 20.6, determine the maximum possible dosage interval  $\tau$ .

$$\frac{15}{5} = \frac{1}{e^{-(0.693/3)\tau}}$$

$$e^{-0.231\tau} = 0.333$$

Take the natural logarithm (ln) on both sides of the equation.

$$-0.231\tau = -1.10$$

$$\tau = 4.76 \text{ hr}$$

Then determine the dose required to produce  $C^\infty_{\max}$  from Equation 20.7 after substitution of  $C^0_p = D_0/V_D$ :

$$C^\infty_{\max} = \frac{D_0/V_D}{1 - e^{-k\tau}} \quad (20.7)$$

Solve for dose  $D_0$ , letting  $V_D = 200 \text{ mL/kg}$  (20% body weight).

$$15 = \frac{D_0/200}{1 - e^{-(0.231)(4.76)}}$$

$$D_0 = 2 \text{ mg/kg}$$

To check this dose for therapeutic effectiveness, calculate  $C^\infty_{\min}$  and  $C^\infty_{\text{av}}$ .

$$C^\infty_{\min} = \frac{(D_0/V_D)e^{-k\tau}}{1 - e^{-k\tau}} = \frac{(2000/200)e^{-(0.231)(4.76)}}{1 - e^{-(0.231)(4.76)}}$$

$$C^\infty_{\min} = 4.99 \text{ µg/mL}$$

As a further check on the dosage regimen, calculate  $C^\infty_{\text{av}}$ .

$$C^\infty_{\text{av}} = \frac{D_0}{V_D k \tau} = \frac{2000}{(200)(0.231)(4.76)}$$

$$C^\infty_{\text{av}} = 9.09 \text{ µg/mL}$$

By calculation, the dose of this antibiotic should be 2 mg/kg every 4.76 hours to maintain the serum drug concentration between 5 and 15 µg/mL.

In practice, rather than a dosage interval of 4.76 hours, the dosage regimen and the dosage interval should be made as convenient as possible for the patient, and the size of the dose should take into account the commercially available drug formulation. Therefore, the dosage regimen should be recalculated to have a convenient value (below the maximum possible dosage interval) and the size of the dose adjusted accordingly.

**NOMOGRAMS AND TABULATIONS IN DESIGNING DOSAGE REGIMENS**

For ease of calculation of dosage regimens, many clinicians rely on nomograms to calculate the proper dosage regimen for their patients. The use of a nomogram may give a quick dosage regimen adjustment for patients with characteristics requiring adjustments, such as age, body weight, and physiologic state. In general, the nomogram of a drug is based on population pharmacokinetic data collected and analyzed using a specific pharmacokinetic model. In order to keep the dosage regimen calculation simple, complicated equations are often solved and the results displayed diagrammatically on special scaled axes to produce a simple dose recommendation based on patient information. Some nomograms make use of certain physiologic parameters, such as serum creatinine concentration, to help modify the dosage regimen according to renal function ().

For many marketed drugs, the manufacturer provides tabulated general guidelines for use in establishing a dosage regimen for patients, including loading and maintenance doses. For example, the initial doses and subsequent serum monitoring of theophylline anhydrous sustained-action capsules (Theo-Dur Sprinkle) and theophylline extended-release tablets (Theo-Dur tablets) are shown in and , respectively.

<b>Table 20.5 Maintenance Dose of Theophylline When the Serum Concentration Is Not Measured<sup>a</sup></b>		
<b>Age</b>	<b>Dose</b>	<b>Dose per 12 Hours</b>
6–9 yrs	24 mg/kg/day	12.0 mg/kg
9–12 yrs	20 mg/kg/day	10.0 mg/kg
12–16 yrs	18 mg/kg/day	9.0 mg/kg
Over 16 yrs	13 mg/kg/day or 900 mg, whichever is less	6.5 mg/kg

<sup>a</sup>Warning: Do not attempt to maintain a dose that is not tolerated.

Adapted from product information for Theo-Dur Sprinkle ( ) and *Facts and Comparisons* (1991).

<b>Table 20.6 Dosage Guidelines for Rapid Theophyllinization<sup>a</sup></b>	
<b>Patient Group</b>	<b>Maintenance Dose</b>
Children 1–9 yrs	4 mg/kg every 6 hr
Children 9–16 and young adult smokers	3 mg/kg every 6 hr
Otherwise healthy nonsmoking adults	3 mg/kg every 8 hr
Older patients and patients with cor pulmonale	2 mg/kg every 8 hr
Patients with congestive heart failure	1–2 mg/kg every 8 hr

<sup>a</sup>In patients not receiving theophylline. The recommended loading dose for each patient group is 5 mg/kg.

Adapted from *Facts and Comparisons* (1991), with permission.

For drugs with a narrow therapeutic range, such as theophylline, a guide for monitoring serum drug concentrations is given. Another example is the aminoglycoside antibiotic, tobramycin sulfate USP (Nebcin, Eli Lilly), which is eliminated primarily by renal clearance. Thus, the dosage of tobramycin sulfate should be reduced in direct proportion to a reduction in creatinine clearance (see ). The manufacturer provides a nomogram for estimating the percent of the normal dose of tobramycin sulfate assuming the serum creatinine level (mg/100 mL) has been obtained.

## DETERMINATION OF ROUTE OF ADMINISTRATION

Selection of the proper route of administration is an important consideration in drug therapy. The rate of drug absorption and the duration of action are influenced by the route of drug administration. Moreover, the use of certain routes of administration is precluded by physiologic and safety considerations. For example, intra-arterial and intrathecal drug injections are less safe than other routes of drug administration and are used only when absolutely necessary. Drugs that are unstable in the gastrointestinal tract or drugs that undergo extensive first-pass effect are not suitable for oral administration. For example, insulin is a protein that is degraded in the gastrointestinal tract by proteolytic enzymes. Drugs such as xylocaine and nitroglycerin are not suitable for oral administration because of first-pass effect. These drugs, therefore, must be given by an alternative route of administration.

Intravenous administration is the fastest and most reliable way of delivering a drug into the circulatory system. Drugs administered intravenously are removed more rapidly because the entire dose is subject to elimination immediately. Consequently, more frequent drug administration is required. Drugs administered extravascularly must be absorbed into the bloodstream, and the total absorbed dose is eliminated more slowly. The frequency of administration can be lessened by using routes of administration that give a sustained rate of drug absorption. Intramuscular injection generally provides more rapid systemic absorption than oral administration of drugs that are not very soluble.

Certain drugs are not suitable for administration intramuscularly because of erratic drug release, pain, or local irritation. Even though the drug is injected into the muscle mass, the drug must reach the circulatory system or other body fluid to become bioavailable. The anatomic site of drug deposition following intramuscular injection will affect the rate of drug absorption. A drug injected into the deltoid muscle is more rapidly absorbed than a drug injected similarly into the gluteus maximus, because there is better blood flow in the former. In general, the method of drug administration that provides the most consistent and greatest bioavailability should be used to ensure maximum therapeutic effect. The various routes of drug administration can be classified as either *extravascular* or *intravascular* and are listed in (see also ).

<b>Table 20.7 Common Routes of Drug Administration</b>	
<b>Parenteral</b>	<b>Extravascular</b>
Intravascular	Enteral
Intravenous injection (IV bolus)	Buccal
Intravenous infusion (IV drip)	Sublingual
Intra-arterial injection	Oral
Intramuscular injection	Rectal
Intradermal injection	Inhalation
Subcutaneous injection	Transdermal
Intradermal injection	
Intrathecal injection	

Precipitation of an insoluble drug at the injection site may result in slower absorption and a delayed response. For example, a dose of 50 mg of chlordiazepoxide (Librium) is more quickly absorbed after oral administration than after intramuscular injection. Some drugs, such as haloperidol decanoate, are very oil-soluble products that release very slowly after intramuscular injection ( ).

## DOSING OF DRUGS IN INFANTS AND CHILDREN

Infants and children have different dosing requirements than adults. Dosing of drugs in this population requires a thorough

consideration of the differences in the pharmacokinetics and pharmacology of a specific drug in the preterm newborn infant, newborn infant (birth to 28 days), infant (28 days to 23 months), young child (2 to 5 years), older child (6 to 11 years), adolescent (12 to 18 years), and the adult (*FDA Guidance for Industry*, 2000). Unfortunately, the pharmacokinetics and pharmacodynamics of most drugs are not well known in children under 12 years of age. The variation in body composition and the maturity of liver and kidney function are potential sources of differences in pharmacokinetics with respect to age. For convenience, "infants" are here arbitrarily defined as children 0 to 2 years of age. However, within this group, special consideration is necessary for infants less than 4 weeks (1 month) old, because their ability to handle drugs often differs from that of more mature infants.

In addition to different dosing requirements for the pediatric population, there is a need to consider the use of pediatric dosage forms that permit more accurate dosing and patient compliance. For example, liquid pediatric drug products may come with a calibrated dropper or a premeasured teaspoon (5 mL) for accurate dosing and have a cherry flavor for pediatric patient compliance. Pediatric drug formulations may also contain different drug concentrations compared to the adult drug formulation. Furthermore, alternative drug delivery such as an intramuscular antibiotic drug injection into the gluteus medius may be considered for a pediatric patient, as opposed to the deltoid muscle for an adult patient.

In general, complete hepatic function is not attained until the third week of life. Oxidative processes are fairly well developed in infants, but there is a deficiency of conjugative enzymes. In addition, many drugs exhibit reduced binding to plasma albumin in infants.

Newborns show only 30–50% of the renal activity of adults on the basis of activity per unit of body weight ( $\text{mL}/\text{min}/\text{kg}$ ). Drugs that are heavily dependent on renal excretion will have a sharply decreased elimination half-life. For example, the penicillins are excreted for the most part through the kidney. The elimination half-lives of such drugs are much reduced in infants, as shown in .

	<b>Average Infant</b>	<b>Average Adult</b>
Body weight (kg)	3.5	70
Body water (%)	77	58
(L)	2.7	41
Inulin clearance (mL/min)	Approx 3	130
$k$ ( $\text{min}^{-1}$ )	$3/2700 = 0.0011$	$130/41,000 = 0.0032$
$t_{1/2}$ (min)	630	220
PAH clearance (mL/min)	Approx 12	650
$k$ ( $\text{min}^{-1}$ )	$12/2800 = 0.0043$	$650/41,000 = 0.016$
$t_{1/2}$ (min)	160	43

<sup>a</sup>Computations are for a drug distributed in the whole body water, but any other  $V_D$  would give the same relative values.

Data for average infant from , with permission from Charles C Thomas and Cambridge University Press.

<b>Drug</b>	<b>Half-Life in Neonates<sup>a</sup> (hr)</b>	<b>Half-Life in Adults (hr)</b>
Penicillin G	3.2	0.5
Ampicillin	4	1–1.5
Methicillin	3.3/1.3	0.5
Carbenicillin	5–6	1–1.5
Kanamycin	5–5.7	3–5
Gentamicin	5	2–3

<sup>a</sup>0–7 days old.

## Practice Problem

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The elimination half-life of penicillin G is 0.5 hour in adults and 3.2 hours in neonates (0 to 7 days old). Assuming that the normal adult dose of penicillin G is 4 mg/kg every 4 hours, calculate the dose of penicillin G for an 11-pound infant.

**Solution**

$$\frac{\tau_1}{\tau_2} = \frac{(t_{1/2})_1}{(t_{1/2})_2}$$
$$t_{1/2} = 0.5 \text{ hr}$$
$$\tau_2 = \frac{4 \times 3.2}{0.5} = 25.6 \text{ hr}$$

Therefore, this infant may be given the following dose:

$$\text{Dose} = 4 \text{ mg/kg} = \frac{11 \text{ lb}}{2.2 \text{ lb/kg}} = 20 \text{ mg every 24 hr}$$

Alternatively, 10 mg every 12 hours would achieve the same  $C_{av}^{\infty}$ .

Various methods have been used in the past to estimate doses for a child. Methods such as Young's rule or Clark's rule for dose adjustment are at best crude approximations in that they take into account only body age and size change attributable to growth and do not consider the rate of drug elimination. Another dose adjustment method is based on body surface area. This approach has the advantage of avoiding bias due to obesity or unusual body weight, because the height and weight of the patient are both considered. The body surface area method gives only a rough estimation of the proper dose, because the pharmacokinetic differences of specific drugs are not considered.

## DOSING OF DRUGS IN THE ELDERLY

Defining "elderly" is difficult. The geriatric population is often arbitrarily defined as patients who are older than 65 years, and many of these people live active and healthy lives. In addition, there is an increasing number of people who are living more than 85 years, who are often considered as the "older elderly" population. The aging process is more often associated with physiologic changes during aging rather than purely chronological age. Chronologically, the elderly have been classified as the *young old* (ages 65–75 years), the *old* (ages 75–85 years), and the *old old* (age > 85 years) ().

Performance capacity and the loss of homeostatic reserve decreases with advanced age but occurs to a different degree in each organ and in each patient. Physiologic and cognitive functions tend to change with the aging process and can affect compliance and the therapeutic safety and efficacy of a prescribed drug. The elderly also tend to be on multiple drug therapy due to concomitant illness. Decreased cognitive function in some geriatric patients, complicated drug dosage schedules, and/or the high cost of drug therapy may result in poor drug compliance, resulting in lack of drug efficacy, possible drug interactions, and/or drug intoxication.

Several vital physiologic functions related to age as measured by markers show that renal plasma flow, glomerular filtration, cardiac output, and breathing capacity can drop from 10% to 30% in elderly subjects compared to those at age 30. The physiologic changes due to aging may necessitate special considerations in administering drugs in the elderly. For some drugs, an age-dependent increase in adverse drug reactions or toxicity may be observed. This apparent increased drug sensitivity in the elderly may be due to pharmacodynamic and/or pharmacokinetic changes (; ).

The pharmacodynamic hypothesis assumes that age causes alterations in the quantity and quality of target drug receptors, leading to enhanced drug response. Quantitatively, the number of drug receptors may decline with age, whereas qualitatively, a change in the affinity for the drug may occur. Alternatively, the pharmacokinetic hypothesis assumes that age-dependent increases in adverse drug reactions are due to physiologic changes in drug absorption, distribution, and elimination, including renal excretion and hepatic clearance.

In the elderly, age-dependent alterations in drug absorption may include a decline in the splanchnic blood flow, altered gastrointestinal motility, increase in gastric pH, and alteration in the gastrointestinal absorptive surface. The incidence of achlorhydria in the elderly may have an effect on the dissolution of certain drugs such as weak bases and certain dosage forms that require an acid environment for disintegration and release (). From a distribution consideration, drug protein binding in the plasma may decrease as a result of decrease in the albumin concentration, and the apparent volume of distribution may change due to a decrease in muscle mass and an increase in body fat. Renal drug excretion generally declines with age as a result of decrease in the glomerular filtration rate and/or active tubular secretion. Moreover, the activity of the enzymes responsible for drug biotransformation may decrease with age, leading to a decline in hepatic drug clearance.

Elderly patients may have several different pathophysiologic conditions that require multiple drug therapy that increases the likelihood for a drug interaction. Moreover, increased adverse drug reactions and toxicity may result from poor patient compliance. Both penicillin and kanamycin show prolonged  $t_{1/2}$  in the aged patient, as a consequence of an age-related gradual reduction in the kidney size and function. The Gault–Cockcroft rule for calculating creatinine clearance clearly quantitates a reduction in clearance with increased age (). Age-related changes in plasma albumin and  $\alpha_1$ -acid glycoprotein may also be a factor in the binding of drugs in the body.

## Practice Problems

1. An aminoglycoside has a normal elimination half-life of 107 minutes in young adults. In patients 70 to 90 years old, the elimination half-life of the aminoglycoside is 282 minutes. The normal dose of the aminoglycoside is 15 mg/kg per day divided into

two doses. What is the dose for a 75-year-old patient, assuming that the volume of distribution per body weight is not changed by the patient's age?

**Solution**

The longer elimination half-life of the aminoglycoside in elderly patients is due to a decrease in renal function. A good inverse correlation has been obtained of elimination half-life to the aminoglycoside and creatinine clearance. To maintain the same average concentration of the aminoglycoside in the elderly as in young adults, the dose may be reduced.

$$C_{av}^{\infty} = \frac{1.44D_N(t_{1/2})_N}{\tau_N V_N} = \frac{1.44D_0(t_{1/2})_0}{\tau_0 V_0}$$

$$\frac{D_N(t_{1/2})_N}{\tau_N} = \frac{D_0(t_{1/2})_0}{\tau_0}$$

Keeping the dose constant,

$$D_N = D_0$$

where  $D_N$  is the new dose and  $D_0$  is the old dose.

$$\frac{\tau_0}{\tau_N} = \frac{(t_{1/2})_0}{(t_{1/2})_N}$$

$$\tau_0 = 12 \times \frac{282}{107} = 31.6 \text{ hr}$$

Therefore, the same dose of the aminoglycoside may be administered every 32 hours without affecting the average steady-state level of the aminoglycoside.

2. The clearance of lithium was determined to be 41.5 mL/min in a group of patients with an average age of 25 years. In a group of elderly patients with an average age of 63 years, the clearance of lithium was 7.7 mL/min. What percentage of the normal dose of lithium should be given to a 65-year-old patient?

**Solution**

The dose should be proportional to clearance; therefore,

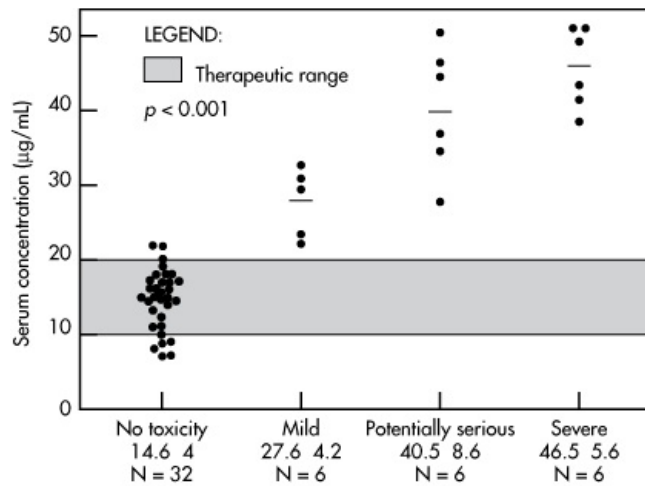
$$\text{Dose reductions (\%)} = \frac{7.7 \times 100}{41.5} = 18.5\%$$

The dose of lithium may be reduced to about 20% of the regular dose in the 65-year-old patient without affecting the steady-state blood level.

**Clinical Example**

Hypertension is common in elderly patients. The pharmacokinetics of felodipine (Plendil), a calcium channel antagonist for hypertension, was studied in young and elderly subjects. After a dose of 5 mg oral felodipine, the AUC and  $C_{max}$  in the elderly patients (67–79 years of age, mean weight 71 kg) were three times that of the young subjects (20–34 years of age, mean weight 75 kg), as shown in . Side effects of felodipine in the elderly patients, such as flushing, were reported in 9 of 11 subjects, and palpitation was reported in 3 of 11 subjects, whereas, only 1 of 12 of the young subjects reported side effects. Systemic clearance in the elderly was  $248 \pm 108$  L/hr compared to  $619 \pm 214$  L/hr in the young subjects. The bioavailability of felodipine was reported to be about 15.5% in the elderly and 15.3% in the young subjects. (Concomitant medications included a diuretic and a  $\beta$ -blocker.)

**Figure 20-2.**



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>

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Plasma concentrations (mean ± SD) of felodipine after an oral dose during steady-state treatment with 5 mg twice daily in healthy subjects ( $n = 12$ ) [■] and elderly hypertensive patients ( $n = 1$ ) [●].

()

- What is the main cause for the difference in the observed AUC between the elderly and young subjects?
- What would be the steady-state level of felodipine in the elderly if dose and dosing interval are unchanged?
- Can felodipine be given safely to elderly patients?

#### Solution

- The higher AUC in the elderly compared to young adults is due to the decreased drug clearance in the older subjects.
- The elderly have more side effects with felodipine compared to young adults. Factors that may have increased side effects in the elderly could be (1) reduced hepatic blood flow, (2) potassium depletion in the body, (3) increased bioavailability, or (4) reduced clearance.

$$c. \quad C_{av}^{\infty} = \frac{FD_0}{Cl_T} \quad (20.8)$$

If  $D_0$ ,  $F$ , and  $\tau$  are the same, the steady-state drug concentration  $C_{av}^{\infty}$  will be inversely proportional to clearance:

$$\frac{C_{av \text{ elderly}}^{\infty}}{C_{av \text{ young}}^{\infty}} = \frac{Cl_{\text{young}}}{Cl_{\text{elderly}}}$$

$$\frac{C_{av \text{ elderly}}^{\infty}}{C_{av \text{ young}}^{\infty}} = \frac{619}{248} = 2.5$$

(Note:  $Cl$  is in the denominator in Equation 20.8 and is inversely related to concentration.) The steady concentration of felodipine will be 250% or 2.5 times that in the young subjects.

### Changes in Renal Function with Age

Many studies have shown a general decline in glomerular filtration rate (GFR) with age. reported that the GFR as measured by creatinine clearance (see ) decreases at a mean rate of 1% per year after 40 years of age. However, there is considerable variation in this rate of decline in normal healthy aging adults. In a previous study by , approximately two-thirds of the subjects (162 of 254) had declining creatinine clearances, whereas about one-third of the subjects (92 of 254) had no decrease in creatinine clearance. Since muscle mass and urinary creatinine excretion decrease at nearly the same rate in the elderly, mean serum concentrations may stay relatively constant. Creatinine clearance measured by serum creatinine concentrations only (see ) may yield inaccurate GFR function if urinary creatinine excretion is not measured.

### Examples

1. An elderly 85-year-old adult patient with congestive heart failure has a serum creatinine of 1.0 mg/dL. The 24-hour urinary creatinine excretion was 0.7 g. Based on the serum creatinine only, this patient has normal renal function, whereas based on both serum creatinine concentration and total 24-hour urinary creatinine excretion, the patient has a GFR of less than 50 mL/min. In practice, serum creatinine clearance is often estimated from serum creatinine concentration alone for dose adjustment. In elderly subjects, the clinician should carefully assess the patient, since substantial deviation from the true clearance may occur in some elderly subjects.

2. Diflunisal pharmacokinetics were studied in healthy young and old subjects. After a single dose of diflunisal, the terminal

plasma half-life, mean residence time, and apparent volume of distribution were higher in elderly subjects than in young adults ( ). This study shows that renal function in elderly subjects is generally reduced somewhat compared to younger patients because of a diminished rate of glomerular filtration.

## DOSING OF DRUGS IN THE OBESE PATIENT

Obesity is a major problem in the United States and is also becoming a problem in other countries. Obesity has been associated with increased mortality resulting from increases in the incidence of hypertension, atherosclerosis, coronary artery disease, diabetes, and other conditions compared to nonobese patients ( ; ). A patient is considered obese if actual body weight exceeds ideal or desirable body weight by 20%, according to Metropolitan Life Insurance Company data (latest published tables). Ideal or desirable body weights are based on average body weights and heights for males and for females considering age. Athletes who have a greater body weight due to greater muscle mass are not considered obese. Obesity often is defined by *body mass index* (BMI), a value that normalizes body weight based on height. BMI is expressed as body weight (kg) divided by the square of the person's height (meters) or kg/m<sup>2</sup>. BMI is calculated according to the following two equations:

$$\text{BMI} = \left[ \frac{\text{weight (lb)}}{\text{height (in)}^2} \right] \times 703$$

$$\text{BMI} = \left[ \frac{\text{weight (kg)}}{\text{height (cm)}^2} \right] \times 10,000$$

An extensive study on obesity has been published by the , giving five weight classifications based on BMI:

	<b>BMI</b>
Underweight:	<18.5
Normal body weight:	18.5–24.9
Overweight:	25–29.9
Obese:	30–39.9
Extreme obesity	>40

The obese patient (BMI > 30) has a greater accumulation of fat tissue than is necessary for normal body functions. Adipose (fat) tissue has a smaller proportion of water compared to muscle tissue. Thus, the obese patient has a smaller proportion of total body water to total body weight compared to the patient of ideal body weight, which could affect the apparent volume of distribution of the drug. For example, showed a significant difference in the apparent volume of distribution of antipyrine in obese patients (0.46 L/kg) compared to ideal-body-weight patients (0.62 L/kg) based on actual total body weight. *Ideal body weight* (IBW) refers to the appropriate or normal weight for a male or female based on age, height, weight, and frame size; ideal body weights are generally obtained from the latest table of desirable weights for men and women compiled by the Metropolitan Life Insurance Company.

In addition to differences in total body water per kilogram body weight in the obese patient, the greatest proportion of body fat in these patients could lead to distributional changes in the drug's pharmacokinetics due to partitioning of the drug between lipid and aqueous environments ( ). Drugs such as digoxin and gentamicin are very polar and tend to distribute into water rather than into fat tissue. Although lipophilic drugs are associated with larger volumes of distribution in obese patients compared to hydrophilic drugs, there are exceptions and the effect of obesity on specific drugs must be considered for accurate dosing strategy.

Other pharmacokinetic parameters may be altered in the obese patient as a result of physiologic alterations, such as fatty infiltration of the liver affecting biotransformation and cardiovascular changes that may affect renal blood flow and renal excretion ( ).

Dosing by actual body weight may result in overdosing of drugs such as aminoglycosides (eg, gentamicin), which are very polar and are distributed in extracellular fluids. Dosing of these drugs is based on ideal body weight. *Lean body weight* has been estimated by several empirical equations based on the patient's height and actual (total) body weight. The following equations have been used for estimating lean body weight, particularly for adjustment of dosage in renally impaired patients:

$$\text{LBW (males)} = 50 \text{ kg} + 2.3 \text{ kg for each inch over 5 ft} \quad (20.9)$$

$$\text{LBW (females)} = 45.5 \text{ kg} + 2.3 \text{ kg for each inch over 5 ft} \quad (20.10)$$

where LBW is lean body weight.

### Example

Calculate the lean body weight for an adult male patient who is 5 ft 9 in (175.3 cm) tall and weighs 264 lb (120 kg).

#### Solution

Using Equation 20.9,

$$\text{LBW} = 50 + (2.3 \times 9) = 70.7 \text{ kg}$$

## PHARMACOKINETICS OF DRUG INTERACTIONS

*Drug interaction* generally refers to a modification of the expected drug response in the patient as a result of exposure of the patient to another drug or substance. Some unintentional drug interactions produce adverse reactions in the patient, whereas some drug interactions may be intentional, to provide an improved therapeutic response or to decrease adverse drug effects. Drug interactions may include drug–drug interactions, food–drug interactions, or chemical–drug interactions, such as the interaction of a drug with alcohol or tobacco. A listing of food interactions is given in . A drug–laboratory test interaction pertains to an alteration in a diagnostic laboratory test result because of the drug.

The risk of a drug interaction increases with multiple drug therapy, multiple prescribers, poor patient compliance, and patient risk factors, such as predisposing illness (diabetes, hypertension, etc) or advancing age. Multiple drug therapy has become routine in most acute and chronic care settings. Elderly patients and patients with various predisposing illnesses tend to be a population using multiple drug therapy. A recent student survey found an average of 8 to 12 drugs per patient used in a group of hospital patients.

Screening for drug interactions should be performed whenever multiple drug uses are involved. Many computer programs will "flag" a potential drug interaction. However, the pharmacist needs to determine the clinical significance of the interaction. The determination of the clinical significance of a potential drug interaction should be documented in the literature. The likelihood of a drug interaction may be classified as an established drug interaction, probable drug interaction, possible drug interaction, or unlikely drug interaction. The size of the dose and the duration of therapy, the onset (rapid, delayed), the severity (major, minor) of the potential interaction, and extrapolation to related drugs should also be considered.

Preferably, drugs that interact should be avoided or given sufficiently far apart so that the interaction is minimized. In situations involving two drugs of choice that may interact, dose adjustment based on pharmacokinetic and therapeutic considerations of one or both of the drugs may be necessary. Dose adjustment may be based on clearance or elimination half-life of the drug. Assessment of the patient's renal function, such as serum creatinine concentration, and liver function indicators, such as alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or other markers of hepatic metabolism (), should be undertaken. In general, if the therapeutic response is predictable from serum drug concentration, dosing at regular intervals may be based on a steady-state concentration equation such as Equation 20.1. When the elimination half-life is changed by drug interaction, the dosing interval may be extended or the dose reduced according to Equation 20.4. Some examples of pharmacokinetic drug interactions are listed in . A more complete discussion of pharmacologic and therapeutic drug interactions of drugs is available in standard textbooks on clinical pharmacology.

**Table 20.10 Pharmacokinetic Drug Interactions**

Drug Interaction	Examples (Precipitant Drugs)	Effect (Object Drugs)
<b>Bioavailability</b>		
Complexation/chelation	Calcium, magnesium, or aluminum and iron salts	Tetracycline complexes with divalent cations, causing a decreased bioavailability
Adsorption binding/ionic interaction	Cholestyramine resin (anion-exchange resin binding)	Decreased bioavailability of thyroxine, and digoxin; binds anionic drugs and reduces absorption
Adsorption	Antacids (adsorption)	Decreased bioavailability of antibiotics
	Charcoal, antidiarrheals	Decreased bioavailability of many drugs
Increased GI motility	Laxatives, cathartics	Increases GI motility, decreases bioavailability for drugs which are absorbed slowly; may also affect the bioavailability of drugs from controlled-release products
Decreased GI motility	Anticholinergic agents	Propantheline decreases the gastric emptying of acetaminophen (APAP), delaying APAP absorption from the small intestine
Alteration of gastric pH	H-2 blockers, antacids	Both H-2 blockers and antacids increase gastric pH; the dissolution of ketoconazole is reduced, causing decreased drug absorption
Alteration of intestinal flora	Antibiotics (eg, tetracyclines, penicillin)	Digoxin has better bioavailability after erythromycin; erythromycin administration reduces bacterial inactivation of digoxin
Inhibition of drug metabolism in intestinal cells	Monoamine oxidase inhibitors (MAO-I) (eg, tranlycypromine, phenelzine)	Hypertensive crisis may occur in patients treated with MAO-I and foods containing tyramine
<b>Distribution</b>		
Protein binding	Warfarin–phenylbutazone	Displacement of warfarin from binding
	Phenytoin–valproic acid	Displacement of phenytoin from binding
<b>Hepatic elimination</b>		
Enzyme induction	Smoking (polycyclic aromatic hydrocarbons)	Smoking increases theophylline clearance
	Barbiturates	Phenobarbital increases the metabolism of warfarin
Enzyme inhibition	Cimetidine	Decreased theophylline, diazepam metabolism
Mixed-function oxidase		

	Fluvoxamine	Diazepam $t_{1/2}$ longer
	Quinidine	Decreased nifedipine metabolism
	Fluconazole	Increased levels of phenytoin, warfarin
Other enzymes	Monoamine oxidase inhibitors, MAO-I (eg, pargyline, tranylcypromine)	Serious hypertensive crisis may occur following ingestion of foods with a high content of tyramine or other pressor substances (eg, cheddar cheese, red wines)
Inhibition of biliary secretion	Verapamil	Decreased biliary secretion of digoxin causing increased digoxin levels
<b>Renal clearance</b>		
Glomerular filtration rate (GFR) and renal blood flow	Methylxanthines (eg, caffeine, theobromine)	Increased renal blood flow and GFR will decrease time for reabsorption of various drugs, leading to more rapid urinary drug excretion
Active tubular secretion	Probenecid	Probenecid blocks the active tubular secretion of penicillin and some cephalosporin antibiotics
Tubular reabsorption and urine pH	Antacids, sodium bicarbonate	Alkalinization of the urine increases the reabsorption of amphetamine and decreases its clearance
<b>Diet</b>		Alkalinization of urine pH increases the ionization of salicylates, decreases reabsorption and increases its clearance
	Charcoal hamburgers	Theophylline
	Grapefruit	Terfenadine, cyclosporin
<b>Virus drug interactions</b>		
Reye's syndrome	Aspirin	Aspirin in children exposed to certain viral infections such as influenza B virus leads to Reye's syndrome

Many drugs affect the cytochrome P-450 (CYP) family of hemoprotein enzymes that catalyze drug biotransformation (see also and ). Dr. David A. Flockhart, Indiana University School of Medicine, has compiled an excellent website that lists various drugs that may be substrates or inhibitors of cytochrome P-450 isozymes (<http://medicine.iupui.edu/flockhart>). Some examples of substrates of CYPs are

CYP1A2	Amitriptyline, fluvoxamine
CYP2B6	Cyclophosphamide
CYP2C9	Ibuprofen, fluoxetine, tolbutamide, amitriptyline
CYP2C19	Omeprazole, S-methenytoin, amitriptyline
CYP2D6	Propranolol, amitriptyline, fluoxetine, paroxetine
CYP2E1	Halothane
CYP3A4	Erythromycin, clarithromycin, midazolam, diazepam
CYP3A5	Clarithromycin, simvastatin, indinavir
CYP3A6	Erythromycin, clarithromycin, diltiazam

Many calcium channel blockers, macrolides, and protease inhibitors are substrates of CYP3A4, CYP3A5, or CYP3A6. An enzyme substrate may competitively interfere with other substrates metabolism if co-administered. Drug inducers of CYPs may also result in drug interactions by accelerating the rate of drug metabolism. When an unusually high plasma level is observed as a result of co-administration of a second drug, pharmacists should check whether the two drugs share a common CYP substrate. New substrates are still being discovered. For example, many proton inhibitors share the common CYP2C19 substrate, and many calcium channel blockers are CYP3A4 substrates. It is important to assess the clinical significance with the clinician before alarming the patient. It is also important to suggest an alternative drug therapy to the clinician if a clinically significant drug interaction is likely to be occurring.

Some examples of pharmacokinetic drug interactions are discussed in more detail below and in . Many side effects occur as a result of impaired or induced (stimulated) drug metabolism. Changes in pharmacokinetics due to impaired drug metabolism should be evaluated quantitatively. For example, acetaminophen is an OTC drug that has been used safely for decades, but incidences of severe hepatic toxicity leading to coma have occurred in some subjects with impaired liver function because of chronic alcohol use. Drugs that have reactive intermediates, active metabolites, and or metabolites with a longer half-life than the parent drug need to be considered carefully if there is a potential for a drug interaction. A polar metabolite may also distribute to a smaller fluid volume, leading to high concentration in some tissues. Drug interactions involving metabolism may be temporal, observed as a delayed effect. Temporal drug interactions are more difficult to detect in a clinical situation.

## INHIBITION OF DRUG METABOLISM

Numerous clinical instances of severe adverse reactions as a result of drug interaction involving a change in the rate of drug metabolism have been reported. Knowledge of pharmacokinetics allows the clinical pharmacist to evaluate the clinical significance of the drug interaction. Pharmacokinetic models help to determine the need for dose reduction or discontinuing a drug. In assessing the situation, the pathophysiology of the patient and the effect of chronic therapy on drug disposition in the patient must be considered. A severe drug reaction in a patient with liver impairment has resulted in near-fatal reaction in subjects taking otherwise safe doses of acetaminophen. In some patients with injury or severe cardiovascular disease, blood flow may be impaired, resulting in delayed drug absorption and distribution. Many incidents of serious toxicity or accidents are caused by premature administration of a "booster dose" when the expected response is not immediately observed. Potent drugs such as morphine, midazolam, lidocaine, pentothal, and fentanyl can result in serious adverse reactions if the kinetics of multiple dosing are not carefully assessed.

## Examples

**1. Fluvoxamine doubles the half-life of diazepam.** The effect of fluvoxamine on the pharmacokinetics of diazepam was investigated in healthy volunteers (). Concurrent fluvoxamine intake increased mean peak plasma diazepam concentrations from 108 to 143 ng/mL, and oral diazepam clearance was reduced from 0.40 to 0.14 mL/min/kg. The half-life of diazepam increased from 51 to 118 hours. The area under the plasma concentration–time curve for the diazepam metabolite N-desmethyldiazepam was also significantly increased during fluvoxamine treatment. These data suggest that fluvoxamine inhibits the biotransformation of diazepam and its active N-demethylated metabolite.

In this example, the dosing interval,  $\tau$ , may be increased twofold to account for the doubling of elimination half-life to keep average steady-state concentration unchanged based on Equation 20.4. The rationale for this recommendation may be demonstrated by sketching a diagram showing how the steady-state plasma drug level of diazepam differs after taking 10 mg orally twice a day with or without taking fluvoxamine for a week.

$$C_{av}^{\infty} = \frac{1.44D_0t_{1/2}F}{V_D\tau}$$

**2. Quinidine inhibits the metabolism of nifedipine and other calcium channel-blocking agents.** Quinidine co-administration significantly inhibited the aromatization of nifedipine to its major first-pass pyridine metabolite and prolonged the elimination half-life by about 40% (). The interaction between quinidine and nifedipine supports the involvement of a common cytochrome P-450 (P450 3A4) in the metabolism of the two drugs. Other calcium channel antagonists may also be affected by a similar interaction. What could be a potential problem if two drugs metabolized by the same isozyme are co-administered?

**3. Theophylline clearance is decreased by cimetidine.** Controlled studies have shown that cimetidine can decrease theophylline plasma clearance by 20–40% (apparently by inhibiting demethylation) (). Prolongation of half-life by as much as 70% was found in some patients. Elevated theophylline plasma concentrations with toxicity may lead to nausea, vomiting, cardiovascular instability, and even seizure. What could happen to an asthmatic patient whose meals are high in protein and low in carbohydrate, and who takes Tagamet 400 mg BID? (*Hint: Check the effect of food on theophylline, below.*)

**4. Interferon- $\beta$  reduces metabolism of theophylline.** Theophylline pharmacokinetics were also examined before and after interferon treatment (). Interferon- $\beta$  treatment reduced the activities of both O-dealkylases by 47%. The total body clearance of theophylline was also decreased (from 0.76 to 0.56 mL/kg/min) and its elimination half-life was increased (from 8.4 to 11.7 hr;  $P < 0.05$ ). This study provided the first direct evidence that interferon- $\beta$  can depress the activity of drug-metabolizing enzymes in the human liver. What percent of steady-state theophylline plasma concentration would be changed by the interaction? (Use Equation 20.8.)

**5. Torsades de pointes interaction.** A life-threatening ventricular arrhythmia associated with prolongation of the QT interval, known as torsades de pointes, caused the removal of the antihistamine terfenadine (Seldane) from the market because of drug interactions with cisapride, astemizole, and ketoconazole. Clinical symptoms of torsades de pointes include dizziness, syncope, irregular heartbeat, and sudden death. The active metabolite of terfenadine is not cardiac toxic and is now marketed as fexofenadine (Allegra), a non-sedative antihistamine.

**6. Cimetidine and diazepam interaction.** The administration of 800 mg of cimetidine daily for 1 week increased the steady-state plasma diazepam and nordiazepam concentrations due to a cimetidine-induced impairment in microsomal oxidation of diazepam and nordiazepam. The concurrent administration of cimetidine caused a decrease in total metabolic clearance of diazepam and its metabolite, nordiazepam (). How would the following pharmacokinetic parameters of diazepam be affected by the co-administration of cimetidine?

- Area under the curve in the dose interval ( $AUC_{0-24 \text{ hr}}$ )
- Maximum plasma concentration ( $C_{\text{max}}$ )
- Time to peak concentration ( $t_p$ )
- Elimination rate constant ( $k$ )
- Total body clearance ( $Cl_T$ )

## INHIBITION OF BILIARY EXCRETION

The interaction between digoxin and verapamil () was studied in six patients (mean age  $61 \pm 5$  years) with chronic atrial fibrillation. The effects of adding verapamil (240 mg/day) on steady-state plasma concentrations of digoxin were studied. Verapamil induced a 44% increase in steady-state plasma concentrations of digoxin. The biliary clearance of digoxin was

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determined by a duodenal perfusion technique. The biliary clearance of digoxin decreased by 43%, from  $187 \pm 89$  to  $101 \pm 55$  mL/min, whereas the renal clearance was not significantly different ( $153 \pm 31$  versus  $173 \pm 51$  mL/min).

## INDUCTION OF DRUG METABOLISM

Cytochrome P-450 isozymes are often involved in the metabolic oxidation of many drugs (). Many drugs can stimulate the production of hepatic enzymes. Therapeutic doses of phenobarbital and other barbiturates accelerate the metabolism of coumarin anticoagulants such as warfarin and substantially reduce the hypoprothrombinemic effect. Fatal hemorrhagic episodes can result when phenobarbital is withdrawn and warfarin dosage maintained at its previous level. Other drugs known to stimulate drug metabolism include carbamazepine, rifampin, valproic acid, and phenytoin. Enzymatic stimulation can shorten the elimination half-life of the affected drug. For example, phenobarbital can result in lower levels of dexamethasone in asthmatic patients taking both drugs.

## ALTERED RENAL REABSORPTION DUE TO CHANGING URINARY PH

The normal adult urinary pH ranges from 4.8 to 7.5 but can increase due to chronic antacid use. This change in urinary pH affects the ionization and reabsorption of weak electrolyte drugs (). An increased ionization of salicylate due to an increase in urine pH reduces salicylate reabsorption in the renal tubule, resulting in increased renal excretion. Magnesium aluminum hydroxide gel (Maalox), 120 mL/day for 6 days, decreased serum salicylate levels from 19.8 to 15.8 mg/dL in six subjects who had achieved a control serum salicylate level of 0.10 mg/dL with the equivalent of 3.76 g/day aspirin (). Single doses of magnesium aluminum hydroxide gel did not alter urine pH significantly. Five milliliters of Titalac (calcium carbonate with glycine) 4 times a day or magnesium hydroxide for 7 days also increased urinary pH. In general, drugs with  $pK_a$  values within the urinary pH range are affected the most. Basic drugs tend to have longer half-lives when urinary pH is increased, especially near its  $pK_a$ .

### Practical Focus

Which of the following treatments would be most likely to decrease the  $t_{1/2}$  of aspirin?

1. Calcium carbonate PO
2. Sodium carbonate PO
3. IV sodium bicarbonate

(Hint: Which drug can be absorbed and change urinary pH and the reabsorption of aspirin?)

## INHIBITION OF DRUG ABSORPTION

Various drugs and dietary supplements can decrease the absorption of drugs from the gastrointestinal tract. Antacids containing magnesium and aluminum hydroxide often interfere with absorption of many drugs. Co-administration of magnesium and aluminum hydroxide caused a decrease of plasma levels of perfloracin. The drug interaction is caused by the formation of chelate complexes and is possibly also due to adsorption of the quinolone to aluminum hydroxide gel. Perfloracin should be given at least 2 hours before the antacid to ensure sufficient therapeutic efficacy of the quinolone.

Sucralfate is an aluminum glycopyranoside complex that is not absorbed but retards the oral absorption of ciprofloxacin. Sucralfate is used in the local treatment of ulcers. Cholestyramine is an anion-exchange resin that binds bile acid and many drugs in the gastrointestinal tract. Cholestyramine can bind digitoxin in the GI tract and shorten the elimination half-life of digitoxin by approximately 30–40%. Absorption of thyroxine may be reduced by 50% when it is administered closely with cholestyramine.

## EFFECT OF FOOD ON DRUG DISPOSITION

### Diet–Theophylline Interaction

Theophylline disposition is influenced by diet. A protein-rich diet will increase theophylline clearance. Average theophylline half-lives in subjects on a low-carbohydrate, high-protein diet increased from 5.2 to 7.6 hours when subjects were changed to a high-carbohydrate, low-protein diet. A diet of charcoal-broiled beef, which contains polycyclic aromatic hydrocarbons from the charcoal, resulted in a decrease in theophylline half-life of up to 42% when compared to a control non-charcoal-broiled-beef diet. Irregular intake of vitamin K may modify the anticoagulant effect of warfarin. Many foods, especially green, leafy vegetables such as broccoli and spinach, contain high concentrations of vitamin K. In one study, warfarin therapy was interfered with in patients receiving vitamin K, broccoli, or spinach daily for 1 week ().

### Grapefruit–Drug Interactions

Recent investigations have shown that the ingredients in a common food product, grapefruit juice, taken in usual dietary quantities, can significantly inhibit the metabolism by gut-wall cytochrome P-450 3A4 (CYP3A4) (). For example, grapefruit juice increases average felodipine levels about threefold, increases cyclosporine levels, and increases the levels of terfenadine, a common antihistamine. In the case of terfenadine, reported the death of a 29-year-old male who had been taking terfenadine and drinking grapefruit juice 2 to 3 times per week. Death was attributed to terfenadine toxicity. Grapefruit juice can also affect P-gp mediated efflux of some drugs.

## ADVERSE VIRAL DRUG INTERACTIONS

Recent findings have suggested that some interactions of viruses and drugs may predispose individuals to specific disease outcomes (). For example, Reye's syndrome has been observed in children who had been taking aspirin and were concurrently exposed to certain viruses, including influenza B virus and varicella zoster virus. The mechanism by which salicylates and certain viruses interact is not clear. However, the publication of this interaction has led to the prevention of morbidity and mortality due

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to this complex interaction ( ).

## POPULATION PHARMACOKINETICS

### Introduction to Bayesian Theory

Bayesian theory was originally developed to improve forecast accuracy by combining subjective prediction with improvement from newly collected data. In the diagnosis of disease, the physician may make a preliminary diagnosis based on symptoms and physical examination. Later, the results of laboratory tests are received. The clinician then makes a new diagnostic forecast based on both sets of information. Bayesian theory provides a method to weigh the prior information (eg, physical diagnosis) and new information (eg, results from laboratory tests) to estimate a new probability for predicting the disease.

In developing a drug dosage regimen, we assess the patient's medical history and then use average or population pharmacokinetic parameters appropriate for the patient's condition to calculate the initial dose. After the initial dose, plasma or serum drug concentrations are obtained from the patient that provide new information to assess the adequacy of the dosage. The dosing approach of combining old information with new involves a "feedback" process and is, to some degree, inherent in many dosing methods involving some parameter readjustment when new serum drug concentrations become known. The advantage of the Bayesian approach is the improvement in estimating the patient's pharmacokinetic parameters based on Bayesian probability versus an ordinary least-squares-based program. An example comparing the Bayesian method with an alternative method for parameter estimation from some simulated theophylline data will be shown in the next section. The method is particularly useful when only a few blood samples are available.

Because of inter- and intraindividual variability, the pharmacokinetic parameters of an individual patient must be estimated from limited data in the presence of unknown random error (assays, etc), known covariates and variables such as clearance, weight, and disease factor, etc, and possible structural (kinetic model) error. From knowledge of mean population pharmacokinetic parameters and their variability, Bayesian methods often employ a special *weighted least-squares* (WLS) approach and allow improved estimation of patient pharmacokinetic parameters when there is a lot of variation in data. The methodology is discussed in more detail under the Bayes estimator in the next section and also under pharmacokinetic analysis.

### EXAMPLE

After diagnosing a patient, the physician gave the patient a probability of 0.4 of having a disease. The physician then ordered a clinical laboratory test. A positive laboratory test value had a probability of 0.8 of positively identifying the disease in patients with the disease (true positive) and a probability of 0.1 of positive identification of the disease in subjects without the disease (false positive). From the prior information (physician's diagnosis) and current patient-specific data (laboratory test), what is the posterior probability of the patient having the disease using the Bayesian method?

#### Solution

Prior probability of having the disease (positive) = 0.4

Prior probability of not having the disease (negative) = 1 - 0.4 = 0.6

Ratio of disease positive/disease negative = 0.4/0.6 = 2/3, or, the physician's evaluation shows a 2/3 chance for the presence of the disease

The probability of the patient actually having the disease can be better evaluated by including the laboratory findings. For this same patient, the probability of a positive laboratory test of 0.8 for the detection of disease in positive patients (with disease) and the probability of 0.1 in negative patients (without disease) are equal to a ratio of 0.8/0.1 or 8/1. This ratio is known as the *likelihood ratio*. Combining with the prior probability of 2/3, the posterior probability ratio is

$$\text{Posterior probability ratio} = (2/3)(8/1) = 16/3$$

$$\text{Posterior probability} = 16/(16 + 3) = 84.2\%$$

Thus, the laboratory test that estimates the likelihood ratio and the preliminary diagnostic evaluation are both used in determining the posterior probability. The results of this calculation show that with a positive diagnosis by the physician and a positive value for the laboratory test, the probability that the patient actually has the disease is 84.2%.

Bayesian probability theory when applied to dosing of a drug involves a given pharmacokinetic parameter ( $P$ ) and plasma or serum drug concentration ( $C$ ), as shown in Equation 20-11. The probability of a patient with a given pharmacokinetic parameter  $P$ , taking into account the measured concentration, is  $\text{Prob}(P/C)$ :

$$\text{Prob}(P/C) = \frac{\text{Prob}(P) \cdot \text{Prob}(C/P)}{\text{Prob}(C)} \quad (20.11)$$

where  $\text{Prob}(P)$  = the probability of the patient's parameter within the assumed population distribution,  $\text{Prob}(C/P)$  = the probability of measured concentration within the population, and  $\text{Prob}(C)$  = the unconditional probability of the observed concentration.

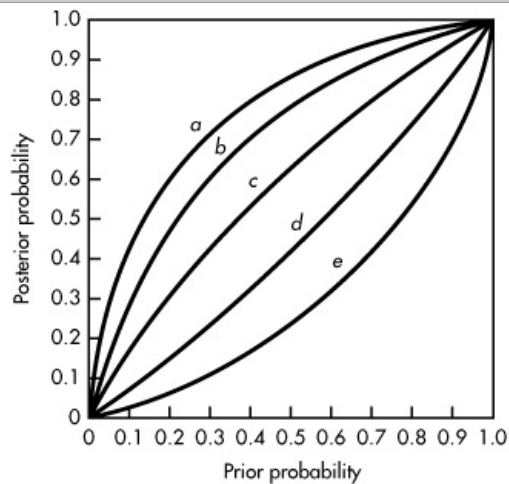
### EXAMPLE

Theophylline has a therapeutic window of 10–20  $\mu\text{g/mL}$ . Serum theophylline concentrations above 20  $\mu\text{g/mL}$  produce mild side effects, such as nausea and insomnia; more serious side effects, such as sinus tachycardia, may occur at drug concentrations above 40  $\mu\text{g/mL}$ ; at serum concentrations above 45  $\mu\text{g/mL}$ , cardiac arrhythmia and seizure may occur ( ). However, the probability of some side effect occurring is by no means certain. Side effects are not determined solely by plasma concentration, as other known or unknown variables (called covariates) may affect the side-effect outcome. Some patients have initial side effects of

nausea and restlessness (even at very low drug concentrations) that later disappear when therapy is continued. The clinician should therefore assess the probability of side effects in the patient, order a blood sample for serum theophylline determination, and then estimate a combined (or posterior) probability for side effects in the patient.

The decision process is illustrated graphically in . The probability of initial (prior) estimation of side effects is plotted on the x axis, and the final (posterior) probability of side effects is plotted on the y axis for various serum theophylline concentrations. For example, a patient was placed on theophylline and the physician estimated the chance of side effects to be 40%, but therapeutic drug monitoring showed a theophylline level of 27  $\mu\text{g/mL}$ . A vertical line of prior probability at 0.4 intersects curve *a* at about 0.78 or 78%. Hence, the Bayesian probability of having side effects is 78% taking both the laboratory and physician assessments into consideration. The curves (a–e in ) for various theophylline concentrations are called *conditional probability curves*. Bayesian theory does not replace clinical judgment, but it provides a quantitative tool for incorporating subjective judgment (human) with objective (laboratory assay) in making risk decisions. When complex decisions involving several variables are involved, this objective tool can be very useful.

**Figure 20-3.**



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>

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Conditional probability curves relating prior probability of toxicity to posterior probability of toxicity of STC, theophylline serum concentrations: (a) 27–28.9; (b) 23–24.9; (c) 19–20.9; (d) 15–16.9; and (e) 11–12.9 (all STC in  $\mu\text{g/mL}$ ).

( )

Bayesian probability is used to improve forecasting in medicine. One example is its use in the diagnosis of healed myocardial infarction (HMI) from a 12-lead electrocardiogram (ECG) by artificial neural networks using the Bayesian concept. Bayesian results were comparable to those of an experienced electrocardiographer ( ). In pharmacokinetics, Bayesian theory is applied to "feed-forward neural networks" for gentamicin concentration predictions ( ). A brief literature search of Bayesian applications revealed over 400 therapeutic applications between 1992 to 1996. Bayesian parameter estimations were most frequently used for drugs with narrow therapeutic ranges, such as the aminoglycosides, cyclosporin, digoxin, anticonvulsants (especially phenytoin), lithium, and theophylline. The technique has now been extended to cytotoxic drugs, factor VIII, and warfarin. Bayesian methods have also been used to limit the number of samples required in more conventional pharmacokinetic studies with new drugs ( ). The main disadvantage of Bayesian methods is the subjective selection of prior probability. Therefore, it is not considered to be unbiased by many statisticians for drug approval purposes.

### Adaptive Method or Dosing with Feedback

In dosing drugs with narrow therapeutic ratios, an initial dose is calculated based on mean population pharmacokinetic parameters. After dosing, plasma drug concentrations are obtained from the patient. As more blood samples are drawn from the patient, the calculated individualized patient pharmacokinetic parameters become increasingly more reliable. This type of approach has been referred to as *adaptive*, or *Bayesian adaptive method with feedback* when a special extended least-squares algorithm is used. Many ordinary least-squares computer software packages are available to clinical practice for parameter and dosage calculation ( ). Some software packages record medical history and provide adjustments for weight, age, and in some cases, disease factors. A common approach is to estimate the clearance and volume of distribution from intermittent infusion (see ). Abbottbase Pharmacokinetic Systems (1986 and 1992) is an example of patient-oriented software that records patient information and dosing history based on 24-hour clock time. An adaptive-type algorithm is used to estimate pharmacokinetic parameters. The average population clearance and volume of distribution of drugs are used for initial estimates and the program computes patient-specific  $Cl$  and  $V_D$  as serum drug concentrations are entered. The program accounts for renal dysfunction based on creatinine clearance, which is estimated from serum creatinine concentration using the Cockcroft–Gault equation (see ). The software package allows specific parameter estimation for digoxin, theophylline, and aminoglycosides, although other drugs can also be analyzed manually.

Many *least-squares* (LS) and *weighted-least-squares* (WLS) algorithms are available for estimating patient pharmacokinetic parameters. Their common objective involves estimating the parameters with minimum bias and good prediction, often as evaluated by mean predictive error. The advantage of the Bayesian method is the ability to input known information into the program, so that the search for the real pharmacokinetic parameter is more efficient and, perhaps, more precise. For example, a drug is administered by intravenous infusion at a rate,  $R$ , to a patient. The drug is infused over  $t$  hours ( $t$  may be 0.5 to 2 hours for a typical infusion). The patient's clearance,  $Cl_T$ , may be estimated from plasma drug concentration taken at a known time according to a one-compartment-model equation. simulated a set of theophylline data and estimated parameters from the data using one- and two-serum concentrations, assuming different variabilities. These investigators tested the method with a Bayesian approach and with an *ordinary least-squares method*,  $OBJ_{OLS}$ .

$$C_i = f(P, t_i) + \varepsilon_i \quad (20.12)$$

$$OBJ_{OLS} = \sum_{i=1}^n \frac{(C_i - \hat{C}_i)^2}{\sigma_i^2} \quad (20.13)$$

## The Bayes Estimator

When the pharmacokinetic parameter,  $P$ , is estimated from a set of plasma drug concentration data ( $C_i$ ) having several potential sources of error with different variance, the ordinary least-squares (OLS) method for parameter estimation is no longer adequate (it yields trivial estimates). The intersubject variation, intrasubject variance, and random error must be minimized properly to allow efficient parameter estimation. The weighted least-squares function in Equation 20.14 was suggested by . The equation represents the least-squares estimation of the concentration by minimizing deviation squares (first summation term of Eq. 20.14), and deviation of population parameter squares (second summation term). Equation 20.14 is called the *Bayes estimator*. This approach is frequently referred to as *extended least-squares* (ELS).

$$\text{Intrasubject } C_i = f(P, X_i) + \varepsilon_i$$

$$\text{Intersubject } P_k = \hat{P}_k + \eta_k \quad (20.14)$$

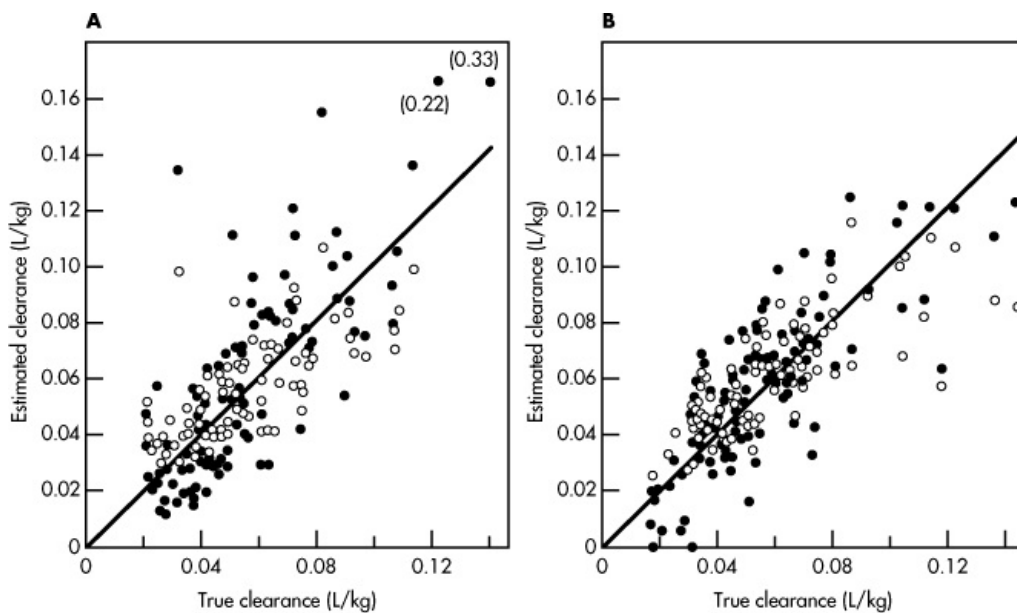
$$OBJ_{BAYES} = \sum_{i=1}^n \frac{(C_i - \hat{C}_i)^2}{\sigma_i^2} + \sum_{k=1}^s \frac{(P_k - \hat{P}_k)^2}{\omega_k^2}$$

For  $n$  number of drug plasma concentration data,  $i$  is an index to refer to each data item,  $C_i$  is the  $i$ th concentration,  $\hat{C}_i$  is the  $i$ th model-estimated concentration, and  $\sigma^2$  is the variance of random error,  $\varepsilon_i$  (assay errors, random intrasubject variation, etc). There is a series of population parameters in the model for the  $k$ th population parameter,  $P_k$ .  $\hat{P}_k$  is the estimated population parameter and  $\eta_k$  is the  $k$ th parameter random error with variance of  $\omega_k^2$ .

To compare the performance of the Bayesian method to other methods in drug dosing, generated some theophylline plasma drug concentrations based on known clearance. They added various error levels to the data and divided the patients into groups with one and two plasma drug samples. The two pharmacokinetic parameters used were based on population pharmacokinetics for theophylline derived from the literature: (1) for  $P_1$ , a  $V_D$  of 0.5 L/kg and coefficient of variation of 32%; and (2) for  $P_2$ , clearance of 0.052 L/kg/hr and coefficient of variation of 44%.

The data were then analyzed using the Bayesian method and a second (alternative) approach in determining the pharmacokinetic parameter ( $Cl_T$ ). In the presence of various levels of error, the Bayesian approach was robust and resulted in better estimation of clearance in both the one- and two-sample groups ( and ). The success of the Bayesian approach is due to the ability of the algorithm to minimize the total mean square terms of errors. A more precise clearance estimation will lead to more accurate dose estimation in the patient.

**Figure 20-4.**



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>

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Plots of predicted clearance versus true (simulated) clearance for predictions by the Bayesian (○) and alternative (●) methods. The diagonal line on each graph is the line of identity. **A** shows results for one-sample group; **B** shows results for two-sample group.

( )

**Table 20.11 Performance of Clearance Estimation Methods**

		Mean Clearance Error ( $\pm$ SEM) as Percent of Mean Clearance				
		Error		Absolute Error		
Method	$\frac{\omega_{Cl}^a}{\sigma}$	$\frac{\omega_{V_D}^a}{\sigma}$	Example 1	Example 2	Example 1	Example 2
Alternative	—	—	-5.77(5.8)	-2.82(3.3)	37.1(4.5)	26.4(2.1)
Bayesian	1	1	-1.02(3.0)	-1.08(3.1)	22.2(2.0) <sup>b</sup>	21.7(2.2) <sup>b</sup>
	3/2	1	-4.94(3.4)	-3.77(3.0)	25.6(2.3) <sup>b</sup>	23.1(2.1) <sup>b</sup>
	2/3	1	5.02(3.2)	2.52(3.4)	23.7(2.2) <sup>b</sup>	23.5(2.4)
	1	3/2	0.44(3.0)	-0.26(3.1)	22.5(2.1) <sup>b</sup>	21.4(2.2) <sup>b</sup>
	1	2/3	-0.76(3.0)	-1.56(3.1)	22.5(1.9) <sup>b</sup>	21.7(2.2)

<sup>a</sup>Ratio of standard deviation of clearance (or  $V_D$ ) to  $\sigma$  used in the Bayesian method. All ratios are divided by the correct ratio so that a value of unity signifies that the correct ratio itself was used.

<sup>b</sup>Mean absolute error of Bayesian method less than that of alternative ( $P < 0.05$ ).

From , with permission.

The implementation of the Bayesian (ELS) approach uses the NONMEM computer software, facilitated by response criteria defined through a first-order (FO) Taylor series expansion. Among other computer software packages available, the NPME2 (USC\*PACK) is a nonparametric maximum expectation maximization method that makes no parametric assumptions about the mean and standard deviation of the distribution. The program can also discover unrecognized subpopulations. NONMEM also features FOEM, a first-order expectation maximization method. Generally, finding a set of best parameter estimates to describe the data involves minimizing the error terms; alternatively, another paradigm that maximizes the probability of the parameter estimates in the distribution serves the same purpose equally well or better. Thus, the first-order expectation maximization (FOEM) paradigm is also available in NONMEM and in other programs, such as P-PHARM ( ).

### Comparison of Bayes, Least-Squares, Steady-State, and Chiou Methods

For theophylline dosing, the Bayes method and others, including the conventional steady-state method, were compared by . The

Bayes method compared favorably with other methods ( and ). The steady-state method was also useful, but none of the methods was sufficiently accurate, probably due to other variables, such as saturation kinetics or use of an inappropriate compartment model.

<b>Table 20.12 Pharmacokinetic Parameter Estimates (Mean ± SD)</b>			
<b>Method</b>	<b>Cl<sup>a</sup> (L/h/kg IBW)</b>	<b>k<sup>b</sup> (hr<sup>-1</sup>)</b>	<b>V<sub>D</sub> (L/kg IBW)</b>
Least-squares			
Day 1	0.0383 ± 0.0129	0.105 ± 0.014	0.519 ± 0.291
Final	0.0391 ± 0.0117	0.095 ± 0.064	0.511 ± 0.239
Chiou			
1	0.0399 ± 0.0306		
2	0.0437 ± 0.0193		
3	0.0438 ± 0.0212		
Steady-state clearance			
	0.0408 ± 0.0174		
Bayesian			
1	0.0421 ± 0.0143	0.081 ± 0.030	0.534 ± 0.0745
2	0.0424 ± 0.0158	0.082 ± 0.035	0.532 ± 0.0802
3	0.0408 ± 0.0182	0.078 ± 0.037	0.531 ± 0.0820
4	0.0403 ± 0.0147	0.077 ± 0.027	0.530 ± 0.0787
Final	0.0372 ± 0.0113	0.070 ± 0.026	0.536 ± 0.0741

Cl = total body clearance, k = elimination rate constant, V<sub>D</sub> = volume of distribution, IBW = ideal body weight.

<sup>a</sup>Calculated from least-squares estimates.

<sup>b</sup>Calculated by Bayesian estimates.

From , with permission.

<b>Table 20.13 Predictive Accuracy at the End of Infusion 1<sup>a</sup></b>		
<b>Method</b>	<b>Mean Prediction Error (mg/L)</b>	<b>Mean Percent Absolute Prediction Error (%)</b>
Least-squares		
Day 1	-0.06 (-1.1, 0.95)	17.6 (13.4, 21.7)
Chiou		
1	0.96 (-1.7, 3.60)	36.8 (27.3, 46.3)
2	-1.7 (-3.3, -0.08)	20.8 (14.1, 27.5)
3	-1.5 (-3.7, 0.80)	27.7 (17.8, 37.5)
Bayesian		
1	-0.61 (-1.7, 0.50)	18.8 (14.1, 23.6)
2	-0.65 (-2.0, 0.69)	22.7 (16.3, 29.2)
3	0.16 (-1.1, 1.40)	21.7 (16.1, 27.2)
4	-0.15 (-1.2, 0.96)	19.8 (15.6, 24.1)

<sup>a</sup>Figures in parentheses are 95% confidence intervals.

From , with permission.

Model fitting in pharmacokinetics often involves the search for a set of parameters that fits the data, a situation analogous to finding a point within a large geometric space. The ordinary least-squares (OLS) approach of iteratively minimizing the error terms may not be adequate when data are sparse, but are fine when sufficient data and good initial estimates are available. The Bayesian approach uses prior information, and, in essence, guides the search pointer to a proximity in the geometric space where the estimates are more likely to be found (reducing variability but increasing subjectivity). Many algorithms use some form of gradient- or derivative-based method; other algorithms use a variable sequential simplex method. A discussion of the pharmacokinetic estimation methods was given by . Some common pharmacokinetic algorithms for parameter estimation are: (1) Newton-Raphson with first and second derivative, (2) Gauss-Newton method, (3) Levenberg-Marquardt method, and (4) Nelder-Mead simplex method. The Gauss-Newton method was used in the early versions of NONLIN. As discussed in relation to the mixed-effect models in later sections, assuming a relationship such as Cl<sub>R</sub> proportional to Cl<sub>cr</sub> (technically called linearization)

---

reduces the minimum number of data necessary for parameter estimation.

## Analysis of Population Pharmacokinetic Data

Traditional pharmacokinetic studies involve taking multiple blood samples periodically over time in a few individual patients, and characterizing basic pharmacokinetic parameters such as  $k$ ,  $V_D$ , and  $Cl$ ; because the studies are generally well designed, there are fewer parameters than data points (ie, that provide sufficient degree of freedom to reflect lack of fit of the model), and the parameters are efficiently estimated from the model with most least-squares programs. Traditional pharmacokinetic parameter estimation is very accurate, provided that enough samples can be taken for the individual patient. The disadvantage is that only a few relatively homogeneous healthy subjects are included in pharmacokinetic studies, from which dosing in different patients must be projected.

In the clinical setting, patients are usually not very homogeneous; patients vary in sex, age, body weight; they may have concomitant disease and may be receiving multiple drug treatments. Even the diet, lifestyle, ethnicity, and geographic location can differ from a selected group of "normal" subjects. Further, it is often not possible to take multiple samples from the same subject, and, therefore, no data are available to reflect intrasubject difference, so that iterative procedures for finding the maximum likelihood estimate can be complex and unpredictable due to incomplete or missing data. However, the vital information needed about the pharmacokinetics of drugs in patients at different stages of their disease with various therapies can only be obtained from the same population, or from a collection of pooled blood samples. The advantages of population pharmacokinetic analysis using pooled data were reviewed by and included a summary of population pharmacokinetics for dozens of drugs. Pharmacokinetic analysis of pooled data of plasma drug concentration from a large group of subjects may reveal much information about the disposition of a drug in a population. Unlike data from an individual subject collected over time, inter- and intrasubject variations must be considered. Both pharmacokinetic and nonpharmacokinetic factors, such as age, weight, sex, and creatinine concentration, should be examined in the model to determine the relevance to the estimation of pharmacokinetic parameters.

The *nonlinear mixed effect model* (or NONMEM) is so called because the model uses both fixed and random factors to describe data. Fixed factors such as patient weight, age, gender, and creatinine concentration are assumed to have no error, whereas random factors include inter- and intraindividual differences. NONMEM is a statistical program written in Fortran (see ) that allows Bayesian pharmacokinetic parameters to be estimated using an efficient algorithm called the *first-order* (FO) method. The parameters may now be estimated also with a *first-order conditional estimate* (FOCE) algorithm. In addition, to pharmacokinetic parameters, many examples of population plasma data have been analyzed to determine population factors. Multiplicative coefficients or parameters for patient factors may also be estimated.

NONMEM fits plasma drug concentration data for all subjects in the groups simultaneously and estimates the population parameter and its variance. The parameter may be clearance and/or  $V_D$ . The model may also test for other fixed effects on the drug due to factors such as age, weight, and creatinine concentration.

The model describes the observed plasma drug concentration ( $C_i$ ) in terms of a model with:

1.  $P_k$  = fixed effect parameters, which include pharmacokinetic parameters or patient factor parameters. For example,  $P_1$  is  $Cl$ ,  $P_2$  is the multiplicative coefficient including creatinine factor, and  $P_3$  is the multiplicative coefficient for weight.
2. Random effect parameters, including (a) the variance of the structural (kinetic) parameter  $P_k$  or intersubject variability within the population  $\omega^2_k$ ; and (b) the residual intrasubject variance or variance due to measurement errors, fluctuations in individual parameter values, and all other errors not accounted for by the other parameters.

There are generally two reliable and practical approaches to population pharmacokinetic data analysis. One approach is the *standard two-stage* (STS) *method*, which estimates parameters from the plasma drug concentration data for an individual subject during the first stage. The estimates from all subjects are then combined to obtain an estimate of the parameters for the population. The method is useful because unknown factors that affect the response in one patient will not carry over and bias parameter estimates of the others. The method works well when sufficient drug concentration–time data are available.

A second approach, the *first-order* (FO) *method*, is also used but is perhaps less well understood. The estimation procedure is based on minimization of an extended least-squares criterion, which was defined through a first-order Taylor series expansion of the response vector about the fixed effects and which utilized a Newton–Raphson-like algorithm (). This method attempts to fit the data and partition the unpredictable differences between theoretical and observed values into random error terms. When this model includes concomitant effects, it is called a *mixed-effect statistical model* ().

The advantage of the first-order model is that it is applicable even when the amount of time–concentration data obtained from each individual is small, provided that the total number of individuals is sufficiently large. For example, in the example cited by , 116 plasma concentrations were collected from 39 patients with various weight, age, gender, serum creatinine, and congestive heart failure conditions. The two-stage method was not suitable, but the FO method was useful for analyzing this set of data. With a large number of factors and only limited data, and with hidden factors possibly affecting the pharmacokinetics of the drug, the analysis may sometimes be misleading. suggested that the main concomitant factor should be measured whenever possible. Several examples of population pharmacokinetic data analysis using clinical data are listed below. Typically, a computer method is used in the data analysis based on a statistical model using either the weighted least-squares (WLS) or the extended least-squares (ELS) method in estimating the parameters. In the last few years, NONMEM has been regularly updated and improved. Many drugs have been analyzed with population pharmacokinetics to yield information not obtainable using the traditional two-stage method (). An added feature is the development of a population model involving both pharmacokinetics and pharmacodynamics, the so-called population PK/PD models.

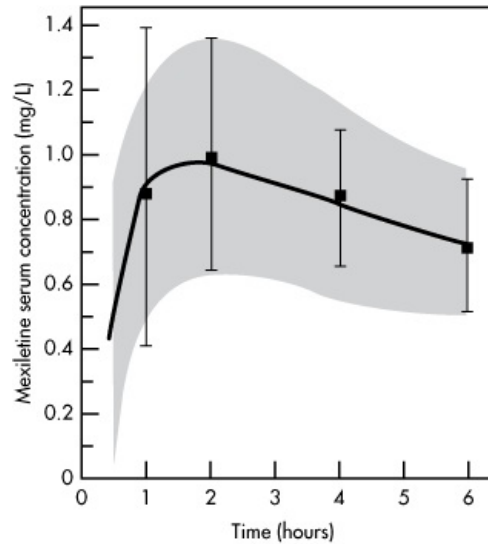
One example involving analysis of population plasma concentration data involved the drug procainamide. The drug clearance of an individual in a group may be assumed to be affected by several factors (). These factors include body weight, creatinine clearance, and a clearance factor  $P_1$  described in the following equation:

$$Cl_{drug\ j} = P_1 + P_2 (C_{creatinine\ j}) + P_3 (\text{weight}_j) + \eta_{Clj} \quad (20.15)$$

where  $\eta_{Clj}$  is the intersubject error of clearance and its variance is  $\omega^2_{Clj}$ .

In another mixed-effect model involving the analysis of lidocaine and mexiletine (), tested age, sex, time on drug therapy, and congestive heart failure (CHF) for effects on drug clearance. The effects of CHF and weight on  $V_D$  were also examined. The test statistic, DELS, or *difference extended least-squares*, was significant for CHF and moderately significant for weight on lidocaine clearance ().

**Figure 20-5.**



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>  
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The solid line and shaded area represent the average serum concentration and the interindividual variability ( $\pm$ SD) calculated from parameter estimates obtained from data for 58 patients. Squares and bars represent measured serum concentration (mean  $\pm$  SD) in 26 of the 58 patients.

()

**Table 20.14 Testing for Factors Affecting Lidocaine Pharmacokinetics**

Hypothesis	$\Delta$ ELS <sup>a</sup>
<i>Cl</i> influenced by:	
Age	0.1
Sex	2.4
Time on therapy	1.0
CHF [ $Cl_{CHF} = Cl_{no}(1-\theta_5)$ ]	52.7
$V_1$ influenced by CHF [ $V_{1CHF} = V_{1no}(1-\theta_6)$ ]	9.0
<i>Cl</i> and $V_1$ normalized for body weight	13.4

<sup>a</sup> $\Delta$ ELS = change in extended least squares.

From .

## CLINICAL EXAMPLE

### Fitting Warfarin Population Data

Population pharmacokinetics may be analyzed from various clinical sites. The population pharmacokinetics of racemic warfarin

was evaluated using 613 measured warfarin plasma concentrations from 32 adult hospitalized patients and 131 adult outpatients (). Warfarin concentrations were measured in duplicate using a high-performance liquid chromatographic procedure. The pharmacokinetic model used was a one-compartment open model with first-order absorption and first-order elimination. The extent of availability was assumed to be 1. A linear regression model was used to evaluate the influence of various disease and demographic factors () on warfarin drug clearance. Age appeared to be an important determinant of warfarin clearance in this adult population. There was about a 1% per year decrease in oral clearance over the age range 20–70 years. Smoking appeared to result in a 10% increase in warfarin clearance, while co-administration of the inducer phenytoin or phenobarbital yielded about a 30% increase in clearance. Other factors such as race, gender, and hospital site did not significantly affect  $Cl_T$  based on this model. This study yielded a predictive model that, when combined with appropriate pharmacologic response data, may be useful in the design and adjustment of warfarin regimens.

**Table 20.15 Population Pharmacokinetics of Warfarin Regression**

Parameter	Regression Value	Explanation
P1	7.85 L/70 kg	Factor relating TBW to $V_D$ exponential factor relating TBW to SIZECL
P2	0.460	
P3	3.31 L/day	Factor relating SIZECL to $Cl$
P4	0	Factors relating CHF to $Cl$
P5	0	Factor relating VAH site to $Cl$
P6	-0.0214 L/day/year of age	Factor relating age to $Cl$
P7	0	Factor relating gender to $Cl$
P8	0.367 L/day	Factor relating smoking to $Cl$
P9	0	Factor relating Caucasian vs Latin difference to $Cl$
P10	0	Factor relating Black vs Latin difference to $Cl$
P11	0	Factor relating drug inhibitor to $Cl$
P12	1.16 L/day	Factor relating drug inducer to $Cl$
P13	0	Factor relating drug displacer to $Cl$

From .

$$SIZEVD = TBW/70$$

$$VD = SIZEVD (P1)$$

$$SIZECL = (TBW/70)^{P2}$$

$$Cl = SIZECL (P3 + P4 CHF + P5 VAH + P6 AGE + P7 GEN + P8 SKG + P9 ANG + P10 BLK + P11 INH + P12 IND + P13 DIS)$$

The patient variables are the following: 1 = present; 0 = absent; CHF = congestive heart failure; VAH = VA hospital site; AGE = age in year; GEN = 1 for male and 0 for female; SKG = smoker; ANG = 1 if Caucasian; BLK = 1 if Black; INH = 1 if taking an inhibitor drug; IND = 1 if taking an inducer drug; DIS = 1 if taking a displacer (protein-binding) drug.

Thus, the information content is better when sampling is strategically designed. Proper sampling can yield valuable information about the distribution of pharmacokinetic parameters in a population. Pooled clinical drug concentrations taken from hospital patients are generally not well controlled and are much harder to analyze. This example shows that a mixed-effect model can yield valuable information about various demographic and pathophysiologic factors that may influence drug disposition in the patient population.

### Model Selection Criteria

Data analysis in pharmacokinetics frequently selects either a monoexponential or polyexponential that will better describe the concentration–time relationship. The selection criteria for the better model is determined by the goodness-of-fit, taking into account the number of parameters involved. Three common model selection criteria are (1) the Akaike Information Criterion (AIC), (2) the Schwarz Criterion (SC), and (3) the  $F$  test ( $\alpha = 0.05$ ). The performance characteristics of these criteria were examined by using Monte Carlo (random or stochastic) simulations. The precision and bias of the estimated parameters were considered. The Akaike Information Criterion and the Schwarz Criterion lead to selection of the correct model more often than does the  $F$  test, which tends to choose the simpler model even when the more complex model is correct. The  $F$  test is also more sensitive to deficient sampling designs. Clearance was quite robust among the different methods and generally well estimated. Other pharmacokinetic parameters are more sensitive to model choice, particularly the apparent elimination rate constant. Prediction of concentrations is generally more precise when the correct model is chosen.

### Decision Analysis Involving Diagnostic Tests

Diagnostic tests may be performed to determine the presence or absence of a disease. A scheme for the predictability of a

disease by a diagnostic test is shown in . A true positive, represented by  $a$  indicates that the laboratory test correctly predicted the disease, whereas a false positive, represented by  $b$ , shows that the laboratory test incorrectly predicted that the patient had the disease when, in fact, the patient did not have the disease. In contrast, a true negative, represented by  $d$ , correctly gave a negative test in patients without the disease, whereas a false negative, represented by  $c$ , incorrectly gave a negative test when, in fact, the patient did have the disease.

<b>Table 20.16 Errors in Decision Predictability</b>			
<b>Decision</b>	<b>Diagnostic Test Result</b>		<b>Totals</b>
	<b>Disease Present</b>	<b>Disease Absent</b>	
Accept disease Present	Test positive (True positive) $a$	Test positive (False positive) $b$	$a + b$
Reject disease Present	Test negative (False negative) $c$	Test negative (True negative) $d$	$c + d$
Totals	$a + c$	$b + d$	$a + b + c + d$

### CLINICAL EXAMPLE

A new diagnostic test for HIV<sup>+</sup>/AIDS was developed and tested in 5772 intravenous drug users. The results of this study are tabulated in . From the results in , a total of 2863 subjects had a positive diagnostic test for HIV<sup>+</sup>/AIDS and 2909 subjects had a negative diagnostic test for HIV<sup>+</sup>/AIDS. Further tests on these subjects showed that 2967 subjects actually had HIV<sup>+</sup>/AIDS, although 211 of these subjects had negative diagnostic test results. Moreover, 107 subjects who had a positive diagnostic test result did not, in fact, have HIV<sup>+</sup>/AIDS after further tests were made.

<b>Table 20.17 Results of HIV<sup>+</sup>/AIDS Test</b>			
<b>Decision</b>	<b>Diagnostic Test Result</b>		<b>Totals</b>
	<b>Disease Present</b>	<b>Disease Absent</b>	
Accept HIV <sup>+</sup> /AIDS Present	2756	107	2863
Reject HIV <sup>+</sup> /AIDS Present	211	2698	2909
Totals	2967	2805	5772

1. The *positive predictability* of the test is the likelihood that the test will correctly predict the disease if the test is positive and is estimated as

$$\text{Positive predictability} = \frac{a}{a + b} = \frac{2756}{2863} = 0.963 \quad (96.3\%)$$

2. The *negative predictability* of the test is the likelihood that the patient will not have the disease if the test is negative and is estimated as

$$\text{Negative predictability} = \frac{d}{c + d} = \frac{2698}{2909} = 0.927 \quad (92.7\%)$$

3. The *total predictability* of the test is the likelihood that the patient will be predicted correctly and is estimated as

$$\text{Total predictability} = \frac{a + d}{a + b + c + d} = \frac{2756 + 2698}{5772} = 0.945 \quad (94.5\%)$$

4. The *sensitivity* of the test is the likelihood that a test result will be positive in a patient with the disease and is estimated as

$$\text{Sensitivity} = \frac{a}{a + c} = \frac{2756}{2967} = 0.929 \quad (92.9\%)$$

5. The *specificity* of the test is the likelihood that a test result will be negative in a patient without the disease and is estimated as

$$\text{Specificity} = \frac{d}{b + d} = \frac{2698}{2805} = 0.962 \quad (96.2\%)$$

---

Analysis of the results in shows that a positive result from the new test for HIV<sup>+</sup>/AIDS will only predict the disease correctly 94.5% of the time. Therefore, the clinician must use other measures to predict whether the patient has the disease. These other measures may include physical diagnosis of the patient, other laboratory tests, normal incidence of the disease in the patient population (in this case, intravenous drug users), and the experience of the clinician. Each test has different predictive values.

## REGIONAL PHARMACOKINETICS

Pharmacokinetics is the study of the time course of drug concentrations in the body. Pharmacokinetics is based generally on the time course of drug concentrations in systemic blood sampled from either a vein or an artery. This general approach is useful as long as the drug concentrations in the tissues of the body are well reflected by drug concentrations in the blood. Clinically, the blood drug concentration may not be proportional to the drug concentration in tissues. For example, after IV bolus administration, the distributive phase is attributed to temporally different changes in mixing and redistribution of drug in organs such as the lung, heart, and kidney ( ). The time course for the pharmacodynamics of the drug may have no relationship to the time course for the drug concentrations in the blood. The pharmacodynamics of the drug may be related to local tissue drug levels and the status of homeostatic physiologic functions. After an IV bolus dose, reported that lignocaine (lidocaine) rapidly accumulates in the spleen and kidney but is slowly sequestered into fat. More than 30 minutes were needed before the target-site (heart and brain) drug levels established equilibrium with drug concentrations in the blood. These *regional equilibrium factors* are often masked in conventional pharmacokinetic models that assume rapid drug equilibrium.

*Regional pharmacokinetics* is the study of pharmacokinetics within a given tissue region. The tissue region is defined as an anatomic area of the body between specified afferent and efferent blood vessels. For example, the myocardium includes the region perfused by the coronary arterial (afferent) and the coronary sinus (efferent) blood vessels. The selection of a region bounded by its network of blood vessel is based on the movement of drug between the blood vessels and the interstitial and intracellular spaces of the region. The conventional pharmacokinetic approach for calculating systemic clearance and volume of distribution tends to average various drug distributions together, such that the local perturbations are neglected. Regional pharmacokinetics (see , chap. 10) supplement systemic pharmacokinetics when inadequate information is provided by conventional pharmacokinetics.

Various homeostatic physiologic functions may be responsible for the nonequilibrium of drug concentrations between local tissue regions and the blood. For example, most cells have an electrochemical difference across the cell membrane consisting of a membrane potential of negative 70 mV inside the membrane relative to the outside. Moreover, regional differences in pH normally exist within a cell. For example, the pH within the lysosome is between 4 and 5, which could allow a basic drug to accumulate within the lysosome with a concentration gradient of 400-fold to 160,000-fold over the blood. Other explanations for regional drug concentration differences have been reviewed by , who also considers that dynamic processes may be more important than equilibrium processes in affecting dynamic response. Thus, regional pharmacokinetics is another approach in applying pharmacokinetics to pharmacodynamics and clinical effect.

## FREQUENTLY ASKED QUESTIONS

1. Can therapeutic drug monitoring be performed without taking blood samples?
2. What is meant by population pharmacokinetics? What advantages does population pharmacokinetics have over classical pharmacokinetics?
3. What are the major considerations in therapeutic drug monitoring?
4. Why is it possible to estimate individual pharmacokinetic parameters with just a few data points using the Bayesian method?
5. Why is pharmacokinetics important in studying drug interactions?

## LEARNING QUESTIONS

1. Why is it harder to titrate patients with a drug whose elimination half-life is 36 hours compared to a drug whose elimination is 6 hours?
2. Penicillin G has a volume of distribution of 42 L/1.73 m<sup>2</sup> and an elimination rate constant of 1.034 hr<sup>-1</sup>. Calculate the maximum peak concentration that would be produced if the drug were given intravenously at a rate of 250 mg every 6 hours for a week.
3. Dicloxacillin has an elimination half-life of 42 minutes and a volume of distribution of 20 L. Dicloxacillin is 97% protein bound. What would be the steady-state free concentration of dicloxacillin if the drug were given intravenously at a rate of 250 mg every 6 hours?
4. The normal elimination half-life of cefamandole is 1.49 hours and the apparent volume of distribution ( $V_D$ ) is 39.2% of body weight. The elimination half-life for a patient with a creatinine clearance of 15 mL/min was reported by to be 6.03 hour, and cefamandole's  $V_D$  is 23.75% of body weight. What doses of cefamandole should be given the normal and the uremic patient (respectively) if the drug is administered intravenously every 6 hours and the desired objective is to maintain an average steady concentration of 2 µg/mL?
5. The maintenance dose of digoxin was reported to be 0.5 mg/day for a 60-kg patient with normal renal function. The half-life of digoxin is 0.95 days and the volume of distribution is 306 L. The bioavailability of the digoxin tablet is 0.56.
  - a. Calculate the steady-state concentration of digoxin.
  - b. Determine whether the patient is adequately dosed (effective serum digoxin concentration is 1–2 ng/mL).
  - c. What is the steady-state concentration if the patient is dosed with the elixir instead of the tablet? (Assume the elixir to be

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100% bioavailable.)

**6.** An antibiotic has an elimination half-life of 2 hours and an apparent volume of distribution of 200 mL/kg. The minimum effective serum concentration is 2  $\mu\text{g/mL}$  and the minimum toxic serum concentration is 16  $\mu\text{g/mL}$ . A physician ordered a dosage regimen of this antibiotic to be given at 250 mg every 8 hours by repetitive intravenous bolus injections.

**a.** Comment on the appropriateness of this dosage regimen for an adult male patient (23 years, 80 kg) whose creatinine clearance is 122 mL/min.

**b.** Would you suggest an alternative dosage regimen for this patient? Give your reasons and suggest an alternative dosage regimen.

**7.** Gentamycin (Garamycin, Schering) is a highly water-soluble drug. The dosage of this drug in obese patients should be based on an estimate of the lean body mass or ideal body weight. Why?

**8.** Why is the calculation for the loading dose ( $D_L$ ) for a drug based on the apparent volume of distribution, whereas the calculation of the maintenance dose is based on the elimination rate constant?

**9.** A potent drug with a narrow therapeutic index is ordered for a patient. After making rounds, the attending physician observes that the patient is not responding to drug therapy and orders a single plasma-level measurement. Comment briefly on the value of measuring the drug concentration in a single blood sample and on the usefulness of the information that may be gained.

**10.** Calculate an oral dosage regimen for a cardiotonic drug for an adult male (63 years old, 68 kg) with normal renal function. The elimination half-life for this drug is 30 hours and its apparent volume of distribution is 4 L/kg. The drug is 80% bioavailable when given orally, and the suggested therapeutic serum concentrations for this drug range from 0.001 to 0.002  $\mu\text{g/mL}$ .

**a.** This cardiotonic drug is commercially supplied as 0.075-mg, 0.15-mg, and 0.30-mg white, scored, compressed tablets. Using these readily available tablets, what dose would you recommend for this patient?

**b.** Are there any advantages for this patient to give smaller doses more frequently compared to a higher dosage less frequently? Any disadvantages?

**c.** Would you suggest a loading dose for this drug? Why? What loading dose would you recommend?

**d.** Is there a rationale for preparing a controlled-release product of this drug?

**11.** The dose of sulfisoxazole (Gantrisin, Roche) recommended for an adult female patient (age 26, 63 kg) with a urinary tract infection was 1.5 g every 4 hours. The drug is 85% bound to serum proteins. The elimination half-life of this drug is 6 hours and the apparent volume of distribution is 1.3 L/kg. Sulfisoxazole is 100% bioavailable.

**a.** Calculate the steady-state plasma concentration of sulfisoxazole in this patient.

**b.** Calculate an appropriate loading dose of sulfisoxazole for this patient.

**c.** Gantrisin (sulfisoxazole) is supplied in tablets containing 0.5 g of drug. How many tablets would you recommend for the loading dose?

**d.** If no loading dose was given, how long would it take to achieve 95–99% of steady state?

**12.** The desired plasma level for an antiarrhythmic agent is 5  $\mu\text{g/mL}$ . The drug has an apparent volume of distribution of 173 mL/kg and an elimination half-life of 2.0 hours. The kinetics of the drug follow the kinetics of a one-compartment open model.

**a.** An adult male patient (75 kg, 56 years of age) is to be given an IV injection of this drug. What loading dose ( $D_L$ ) and infusion rate ( $R$ ) would you suggest?

**b.** The patient did not respond very well to drug therapy. Plasma levels of drug were measured and found to be 2  $\mu\text{g/mL}$ . How would you readjust the infusion rate to increase the plasma drug level to the desired 5  $\mu\text{g/mL}$ ?

**c.** How long would it take to achieve 95% of steady-state plasma drug levels in this patient assuming no loading dose was given and the apparent  $V_D$  was unaltered?

**13.** An antibiotic is to be given to an adult male patient (75 kg, 58 years of age) by intravenous infusion. The elimination half-life for this drug is 8 hours and the apparent volume of distribution is 1.5 L/kg. The drug is supplied in 30-mL ampules at a concentration of 15 mg/mL. The desired steady-state serum concentration for this antibiotic is 20 mg/mL.

**a.** What infusion rate ( $R$ ) would you suggest for this patient?

**b.** What loading dose would you suggest for this patient?

**c.** If the manufacturer suggests a starting infusion rate of 0.2 mL/hr per kilogram of body weight, what is the expected steady-state serum concentration in this patient?

**d.** You would like to verify that this patient received the proper infusion rate. At what time after the start of the IV infusion would you take a blood sample to monitor the serum antibiotic concentration? Why?

**e.** Assume that the serum antibiotic concentration was measured and found to be higher than anticipated. What reasons, based on sound pharmacokinetic principles, would account for this situation?

**14.** Nomograms are frequently used in lieu of pharmacokinetic calculations to determine an appropriate drug dosage regimen for a patient. Discuss the advantages and disadvantages for using nomograms to calculate a drug dosage regimen.

**15.** Based on the following pharmacokinetic data for drugs A, B, and C: **(a)** Which drug takes the longest time to reach steady state? **(b)** Which drug would achieve the highest steady-state drug concentration? **(c)** Which drug has the largest apparent volume of distribution?

	Drug A	Drug B	Drug C
Rate of infusion (mg/hr)	10	20	15
$k$ ( $\text{hr}^{-1}$ )	0.5	0.1	0.05
$Cl$ (L/hr)	5	20	5

**16.** The effect of repetitive administration of phenytoin (PHT) on the single-dose pharmacokinetics of primidone (PRM) was investigated by in three healthy male subjects. The peak concentration of unchanged PRM was achieved at 12 and 8 hours after the administration of PRM in the absence and the presence of PHT, respectively. The elimination half-life of PRM was decreased from  $19.4 \pm 2.2$  (mean  $\pm$  SE) to  $10.2 \pm 5.1$  hours ( $p < 0.05$ ) and the total body clearance was increased from  $24.6 \pm 3.1$  to  $45.1 \pm 5.1$  ml/hr/kg ( $p < 0.01$ ) in the presence of PHT. No significant change was observed for the apparent volume of distribution between the two treatments. Based on pharmacokinetics of the two drugs, what are the possible reasons for phenytoin to reduce primidone elimination half-life and increase its renal clearance?

**17.** Tracozazole (Sporanox, Janssen) is a lipophilic drug with extensive lipid distribution. The drug levels in fatty tissue and organs contains 2 to 20 times the drug levels in the plasma. Little or no drug was found in the saliva and in the cerebrospinal fluid and the half-life is  $64 \pm 32$  hours. The drug is 99.8% bound. How does **(a)** plasma drug protein binding, **(b)** tissue drug distribution, and **(c)** lipid tissue partitioning contribute to the long elimination half-life for traconazole?

**18.** JL (29-year-old male, 180 kg) received oral ofloxacin 400 mg twice a day for presumed bronchitis due to *S. pneumoniae*. His other medications were the following: 400 mg cimetidine, orally, three times a day; 400 mg metronidazole, as directed. JL was still having a fever of  $100.1^\circ\text{C}$  a day after taking the quinolone antibiotic. Comment on any appropriate action.

**19.** CK (70-year-old male, 177 lb). Scr = 0.9 mg/dL. Allergy: PCN. Claudication, rhinitis: URI infection. His medication includes: Ilosone, 250 QID  $\times$  1 wk; Trental, 200 mg TID; Colace, 100 mg BID; Seldane, 1 TID PRN. Which of the following should the pharmacist conclude from this information?

- a. There is an interaction between colace and seldane.
- b. The dose of Trental is too high for this patient based on his renal function.
- c. Seldane should be substituted with a therapeutic alternative because of an interaction.

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