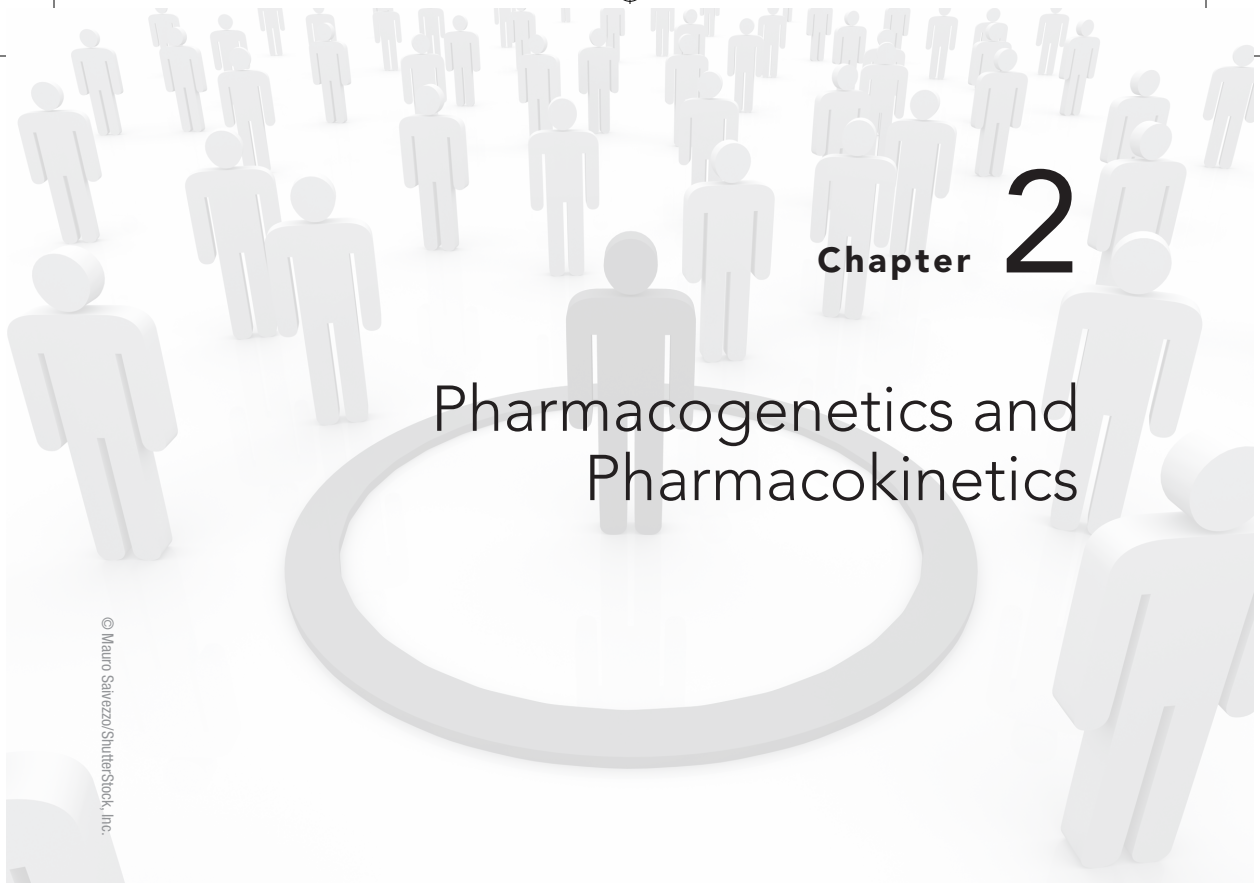

Chapter 2

Pharmacogenetics and Pharmacokinetics

Learning Objectives

Upon completion of this chapter, the student will be able to:

1. Recognize the influence of genetic polymorphisms on the absorption, distribution, metabolism, and excretion of drugs.
2. Differentiate, based on genetic polymorphisms, cytochrome P450 poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers relative to the absorption, distribution, metabolism, and excretion of drugs.
3. Explain how a specific genetic polymorphism would affect the design of a patient's drug dosing regimen.
4. Differentiate between influx and efflux transporters relative to tissue location and influence on the absorption, distribution, metabolism, and excretion of drugs.
5. Propose alterations to a patient's dosing regimen based on the pharmacogenetic influence on absorption, distribution, metabolism, and excretion.

The student should demonstrate an understanding of how drug metabolizing enzymes and drug transporters are influenced by genetic variation. The student should also understand that variation in these proteins results in variation in pharmacokinetics, which can influence how a person absorbs, distributes, metabolizes, and excretes a given drug, all in the context of the patient's response to the drug.

Key Terms	
absorption rate constant (k_a; time^{-1})	The rate constant representing the first-order absorption of a drug from an extravascular site (e.g., the gastrointestinal tract).
area under the curve (AUC; amt/vol · time)	A measure of drug exposure as the integrated area under the plasma drug concentration versus time curve from time zero to infinity.
bioavailability (F)	The rate and extent of drug absorption; the fraction of the dose reaching systemic circulation unchanged.
clearance (CL; vol/time)	The volume of biologic fluid from which drug is removed per unit time.
cytochrome P450 (CYP)	A superfamily of oxidative metabolic enzymes.
efflux transporter	A protein that moves drug out of cells/tissues.
elimination rate constant (k_e; time^{-1})	The rate constant representing the first-order elimination of drug.
extensive metabolizer (EM)	An individual with two "normal-function" alleles relative to a drug metabolizing enzyme.
genotype	The specific set of alleles inherited at a locus on a given gene.
intermediate metabolizer (IM)	In general, an individual with one "loss-of-function" allele and one "normal–function" allele relative to a drug metabolizing enzyme.
loading dose (D_L; amt)	The initial dose of a drug administered with the intent of producing a near steady-state average concentration.
maximum concentration (C_{max}; amt/vol)	The highest concentration of drug in biologic fluid following drug administration during a dosing interval.
pharmacodynamics (PD)	The relationship between drug exposure and pharmacologic response.
pharmacogenetics (PGt)	The study of a gene involved in response to a drug.
pharmacokinetics (PK)	The relationship of time and drug absorption, distribution, metabolism, and excretion.
phase 1 metabolism	Drug metabolizing processes involving oxidation, reduction, or hydrolysis.
phase 2 metabolism	Conjugative drug metabolic processes.
phenotype	An individual's expression of a physical trait or physiologic function due to genetic makeup and environmental and other factors.
poor metabolizer (PM)	In general, an individual with two "reduced–function" or "loss-of-function" alleles relative to a drug-metabolizing enzyme.
prodrug	A drug that requires conversion to an active form.
tau (τ; time)	The dosing interval.

T_{max} (time)	The time of occurrence of the maximum concentration of drug.
ultrarapid metabolizer (UM)	An individual with a "gain-of-function" allele (e.g., overexpression of a metabolic enzyme).
uptake (influx) transporter	A protein that moves drug into cells/tissues.
volume of distribution (V, Vd, V_1, V_{ss}; vol)	A proportionality constant relating the amount of drug in the body to the drug concentration.

Key Equations

$AUC = \frac{Dose}{CL}$	Area under the concentration versus time curve, being directly proportional to the dose and inversely proportional to the clearance (CL).
$C_{ave}^{ss} = \frac{F \cdot Dose}{CL \cdot \tau}$	The average steady-state drug concentration being directly related to the bioavailability and the dose and inversely related to the clearance and the dosing interval.
$D_L = C \cdot Vd$	The loading dose related to a desired concentration and the volume of distribution.
$D_M = C_{ss} \cdot CL$	The maintenance dose related to the desired steady-state concentration and the clearance.
$F = \frac{AUC_{po}}{AUC_{iv}} \cdot \frac{Dose_{iv}}{Dose_{po}} = \frac{\left(\frac{AUC}{Dose}\right)_{po}}{\left(\frac{AUC}{Dose}\right)_{iv}}$	Absolute bioavailability relating the extent of absorption of an extravascular dose to the intravenous dose.
$F = fa \cdot ffp$	Bioavailability related to the fraction of the dose absorbed and the fraction of the dose that escapes first-pass metabolism.
$F = (ff \cdot fg) \cdot ffp$	Bioavailability as above with the fraction of the dose absorbed expanded to include the fraction of the dose that avoids gastrointestinal lumen metabolism/degradation and the fraction that avoids gastrointestinal wall metabolism and/or efflux.
$\tau = \frac{\ln\left(\frac{C_{max}}{C_{min}}\right)}{k_e}$	Tau, the dosing interval, as a function of the ln quotient of C_{max} and C_{min} and inversely proportional to the elimination rate constant, k_e.
$t_{½} = \frac{0.693 \cdot Vd}{CL}; = \frac{0.693}{k_e}$	The half-life, being directly related to the volume of distribution and inversely related to the clearance; inversely related to the elimination rate constant, k_e.
↑, ↓	The number of arrows indicates the relative difference in the magnitude of the change.

Introduction

Pharmacokinetics (PK) is the study of the time course of drug absorption, distribution, metabolism, and excretion (ADME), describing how the body handles a given drug. Thus, these processes determine the plasma concentration versus time profile of a given drug. The pharmacologic effect(s) of a given drug are related to that drug interacting with biologic receptors. As it is not possible to easily measure the drug concentration at the site of the receptors, plasma concentrations are related to the effect(s) based on the assumption that there is equilibration between the drug concentration in plasma and that at the

site of the receptors. The study of the relationship between the plasma concentrations of a drug and the observed pharmacologic effects is referred to as **pharmacodynamics (PD)**, and it describes how the drug affects the body. The common variable relating pharmacokinetics and pharmacodynamics is the drug concentration; this relationship is depicted in **Figure 2–1**.

The pharmacokinetics of a given drug "drives" the pharmacodynamics of that drug in such a way that the drug concentration in the plasma will be in equilibrium with the drug concentration at the receptor site, and responses to the drug, whether therapeutic or toxic, will be a consequence of the drug concentration. The variability in the response to a given drug is due, in part, to the variability in the pharmacokinetics of the drug, although pharmacodynamic variability is typically greater than pharmacokinetic variability. The variability in the pharmacokinetics and pharmacodynamics can be explained, in part, by **pharmacogenetics (PGt)**.

The clinical application of pharmacokinetics is aimed at optimizing drug therapy by designing a **loading dose** (where appropriate) and an initial maintenance regimen, including the maintenance dose and dosing interval, to keep the drug concentration within the desired therapeutic range. This is followed by dosage adjustment based on drug concentration determination for drugs that have a narrow therapeutic range. (i.e., the drug concentrations eliciting a therapeutic effect are close to or overlap those that elicit an adverse effect).

The design of a loading dose is based on the individual's **volume of distribution (Vd)**, which can be influenced, in part, by drug movement into tissues via transporters that are under genetic regulation. Here, a greater Vd will require a higher loading dose to

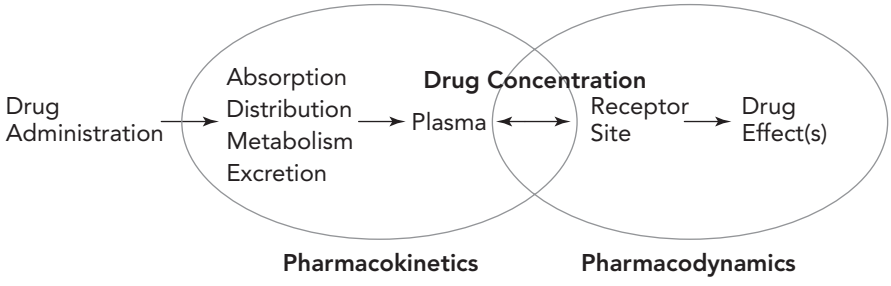

Figure 2-1 The relationship between pharmacokinetics and pharmacodynamics, with the "linking variable" being the drug concentration. As pharmacokinetics determines the plasma concentration versus time profile of the drug, the concentration at the receptor site (i.e., site of action), in equilibrium with the drug in the plasma, elicits the pharmacologic effect(s), which is pharmacodynamics.

achieve a desired drug concentration in the patient. A lesser Vd in a patient would require a lower loading dose. The maintenance dose of a given drug is determined using the drug's **clearance (CL)**. For some drugs, the CL is determined by drug metabolism via specific drug enzymes that also are under genetic regulation. With a greater CL, a higher maintenance dose is required; conversely, a patient with a lower CL would require a lower maintenance dose. The half-life ($t_{1/2}$) of a drug determines its dosing interval. Here, the Vd and CL influence the $t_{1/2}$. With a larger volume of distribution, the drug has to "travel" farther to the eliminating organ for removal from the body. If the CL is held constant, the increased Vd results in a longer $t_{1/2}$ and the drug will remain in the body longer, meaning that the dosing interval, the time to the next dose, will be longer. For a drug that is eliminated from the body by metabolic routes, an increase in CL is related to increased metabolism. This results in a shorter $t_{1/2}$. With a decrease in metabolism, the CL decreases and the $t_{1/2}$ increases. The relationships among Vd, CL, and $t_{1/2}$ are presented in the Key Equations list. Numerous factors influence these relationships, including the patient's genetic constitution. Many of these relationships are discussed further in this chapter.

A number of pharmacokinetic/pharmacodynamic resources describe the mathematical detail of drug-concentration, concentration-effect relationships. The equations in this chapter are presented only to provide a conceptual "framework" of altered pharmacokinetics, here related to PGt.

Absorption and Bioavailability

Oral drug absorption is the process by which a drug moves from the gastrointestinal lumen, crosses biologic membranes, and reaches systemic circulation. With oral administration, the drug travels down the esophagus to the stomach and then to the small intestine. Although some drug can be absorbed from the stomach, it is the small intestine that is the main site of drug absorption. The small intestine's large surface area, permeable membranes, and capillary blood flow create a favorable environment for drug absorption.[1,2]

In order for a drug to be absorbed, it must first be in solution. With oral administration, dissolution of the dosage form, such as a tablet or capsule, results in the drug being in solution in the gastrointestinal lumen, thus creating a concentration gradient of drug across the membranes of the small intestine. This creates a favorable situation for drug absorption, especially via passive diffusion. While passive diffusion is a major mechanism of drug absorption, other absorption mechanisms include active transport,

facilitated diffusion (facilitated transport), pinocytosis, and ionic diffusion.[3] When considering mechanisms of absorption, variability in drug absorption has been related to drug transporters, both **uptake** (**influx**) **transporters** and **efflux transporters**, which are controlled by the patient's genetic constitution.[4,5]

Oral drug absorption is characterized by the drug's bioavailability, which has clinical relevance. **Bioavailability (F)** can be defined as the rate and extent to which a drug (the active ingredient) is absorbed from a drug product and reaches the general systemic circulation unchanged, being made available to the site of action; that is, once a drug reaches systemic circulation it can be "delivered" to the site of action.[6] As per-oral (po; oral) dosing is the most common route of drug administration, it is the absorption of the drug from the gastrointestinal tract that is of interest and defines oral bioavailability, which will be discussed here. **Figure 2-2** depicts the path a drug takes to reach systemic circulation following oral administration.

The rate of drug absorption is one component of its defined bioavailability. For most clinical purposes, the rate of drug absorption is adequately expressed by the parameter $\mathbf{T_{max}}$. This parameter represents the time of occurrence of the maximum drug concentration following extravascular (e.g., oral) dosing of a drug and is determined by the **absorption rate constant (k_a)** and the **elimination rate constant (k_e)**. The k_a is a rate constant representing the first-order absorption rate of a given drug. The k_e is the rate constant representing the first-order elimination rate of the drug. **Figure 2-3a** presents the concentration versus time profiles of a given drug following oral administration where only the absorption rate constant is altered. **Figure 2-3b** presents the concentration versus time profiles of a given drug following oral administration where only the elimination rate constant is altered for three metabolizer "types" (i.e., poor metabolizer, intermediate metabolizer, extensive metabolizer).

Genetic–Kinetic Interface: T_{max}

An individual may have the genetic constitution that results in the production of an enzyme that is efficient in metabolizing a given drug. In this case, the patient is considered to be an **extensive metabolizer (EM)** of that drug, and the k_e for the drug in this patient is increased relative to that of an **intermediate metabolizer (IM)** or a **poor metabolizer (PM)**. Because the k_e is increased in this individual, indicating that the drug is eliminated faster, the T_{max} will occur sooner. Here, the highest concentration of the drug in this individual will occur sooner rather than later (see Figure 2-3b).

The extent of drug absorption is defined by two parameters: the **maximum concentration (C_{max})** and the area under the drug

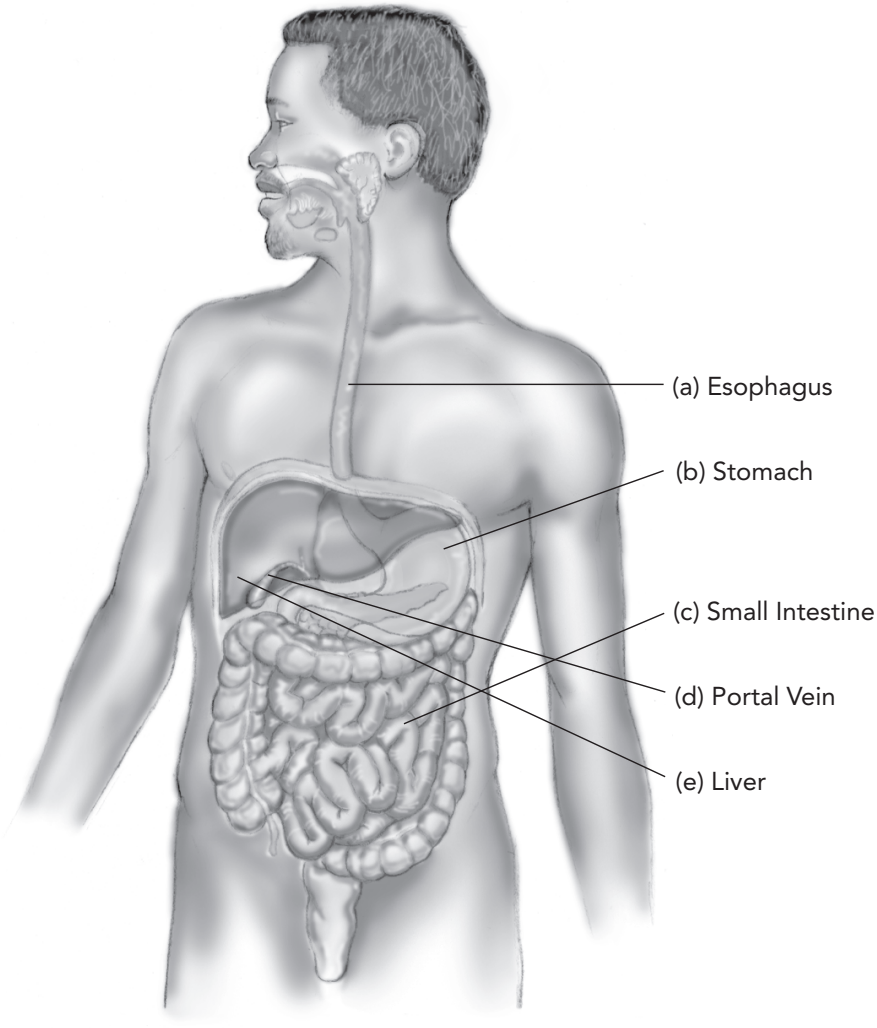

Figure 2-2 Upon oral drug administration, the dosage form (e.g., tablet, capsule) moves down the esophagus (a) to the stomach (b). Although some of the drug may be released from its dosage form and absorbed from the stomach, it is the large surface area of the small intestine (c), with villi and microvilli (not shown), that is the main site of drug absorption. Once drug molecules move across the gastrointestinal wall via various mechanisms, they are carried to the liver (e), via hepatic portal vein blood flow (d), where they may be metabolized. Drug that passes through the liver and reaches systemic circulation is considered to be bioavailable.

concentration versus time curve (AUC_{po}). As a component of bioavailability, the values of these parameters for an orally administered drug are compared to those of the same dose of the drug administered intravenously. Equation 1 describes the calculation of a drug's absolute bioavailability, comparing the **area under the**

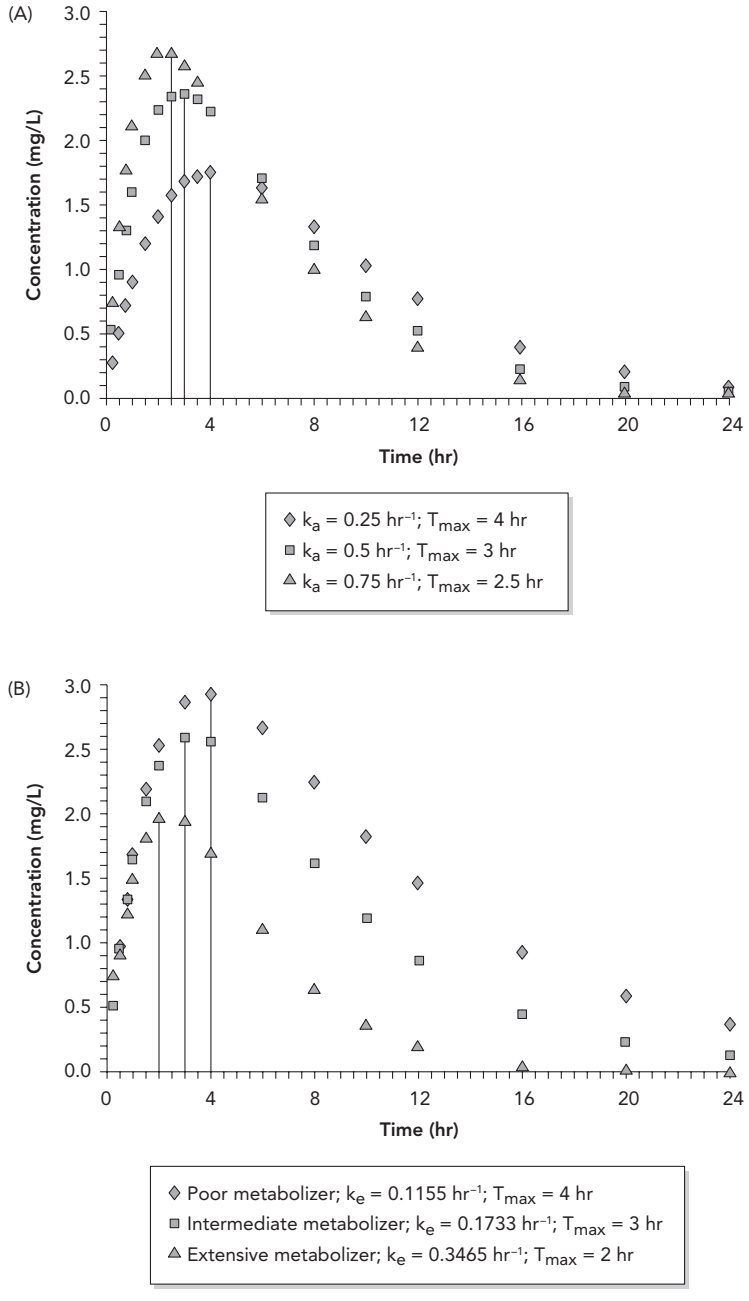

Figure 2-3 (a) The time of the occurrence of the maximum concentration of a drug (T_{max}) is dependent, in part, on the absorption rate constant (k_a). With the elimination rate constant (k_e) fixed, as the k_a increases, the sooner the drug reaches its maximum concentration. The T_{max} is one of the parameters used to describe a drug's bioavailability. (b) The time of the occurrence of the maximum concentration of a drug (T_{max}) is dependent, in part, on the elimination rate constant (k_e). With the absorption rate constant (k_a) fixed, an increased k_e represents increased drug elimination with the maximum concentration being observed earlier (T_{max} occurring sooner). Here, with the examples of a poor metabolizer, intermediate metabolizer, and an extensive (normal) metabolizer. T_{max} is one of the parameters used to describe a drug's bioavailability.

curve (AUC) obtained following oral dosing to that obtained after intravenous dosing:

$$F = \frac{AUC_{po}}{AUC_{iv}} \cdot \frac{Dose_{iv}}{Dose_{po}} = \frac{\left(\frac{AUC}{Dose}\right)_{po}}{\left(\frac{AUC}{Dose}\right)_{iv}} \qquad \text{(eq. 1)}$$

Drug administered via the intravenous route is placed directly into systemic circulation, with 100% of the dose reaching systemic circulation, something considered to be "absolute." The ratio of the dose normalized AUC_{po} to the dose normalized AUC_{iv} provides the fraction of the oral dose of the drug that reaches systemic circulation and is termed the absolute bioavailability of the drug and is considered the oral bioavailability.

Genetic–Kinetic Interface: C_{max} and AUC

An individual may have the genetic constitution that results in the production of an enzyme that is inefficient with respect to drug metabolism. In this case, the patient is considered to be a poor metabolizer of that drug, and the C_{max} and AUC for the drug in this patient is increased relative to an intermediate metabolizer or an extensive metabolizer. Such an individual may be at risk of experiencing toxicity, because the drug concentrations will be relatively high (see **Figure 2-4**).

A number of drugs must be "bioactivated" before being able to exert their effects and are administered in the form of a **prodrug**.[7] The bioavailability related to a prodrug points to the active drug reaching systemic circulation. The active drug is formed by metabolic conversion of the "parent" compound. With oral dosing, as the drug moves along the gastrointestinal tract and reaches the small intestine it is presented to and absorbed through the gut wall and then travels to the liver via portal blood flow. Metabolic conversion can take place in the gut wall and/or the liver, with the active drug then reaching systemic circulation. With efficient conversion of the prodrug to the active compound in the gut wall and/or the liver, the active compound will be bioavailable. In the case of inefficient metabolic conversion of a prodrug, more of the parent compound will reach systemic circulation because it will not have been converted to the active compound. **Figure 2–5** shows the concentration versus time profiles for the parent compound and the active compound in an extensive metabolizer and a poor metabolizer.

The bioavailability of a drug is the fraction of the dose that reaches systemic circulation unchanged and is "made available" to the site of action. Conceptually, this fraction is a product of the fraction of the

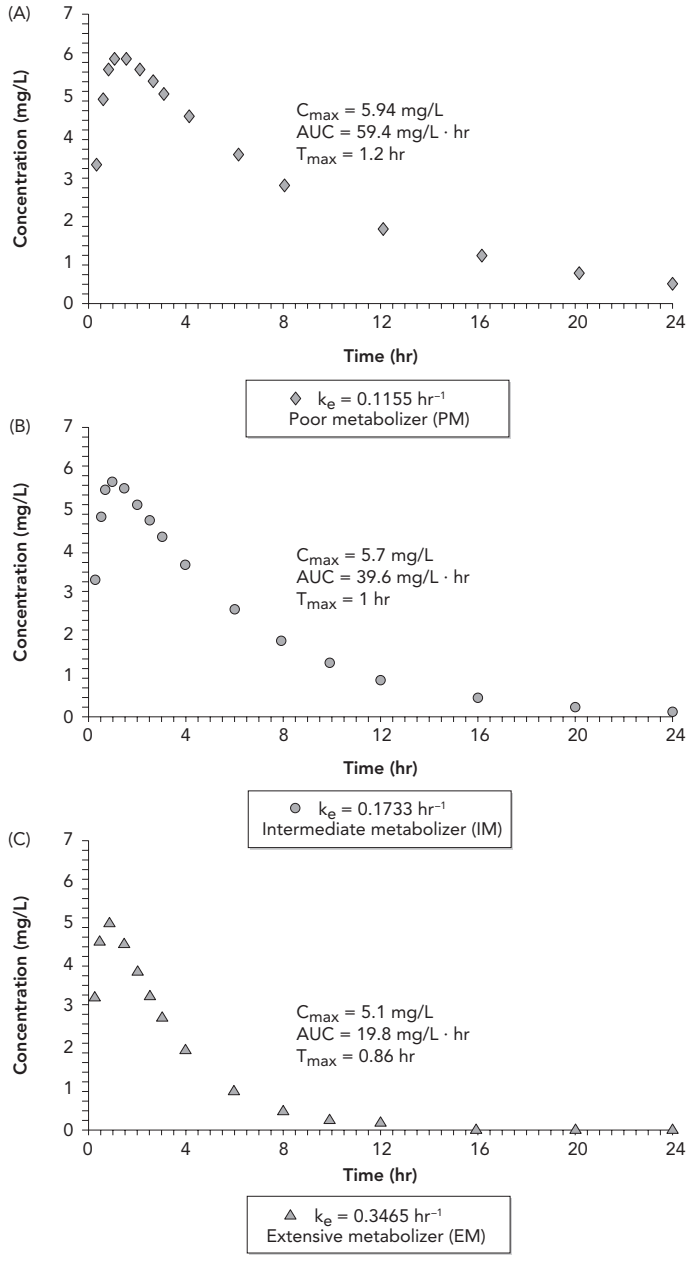

Figure 2-4 As the elimination rate constant (k_e) increases the C_{max} and AUC are lower and the T_{max} occurs earlier. Panel (a) shows the concentration versus time data for a drug that reaches systemic circulation when the k_e is 0.1155 hr^{-1}. The relatively low elimination rate constant may be seen in a poor metabolizer and result in higher drug concentrations. Panels (b) and (c) show the concentration versus time data when the k_e is increased to 0.1733 hr^{-1} and 0.3465 hr^{-1}, respectively, as may be seen in an intermediate metabolizer and an extensive (normal) metabolizer.

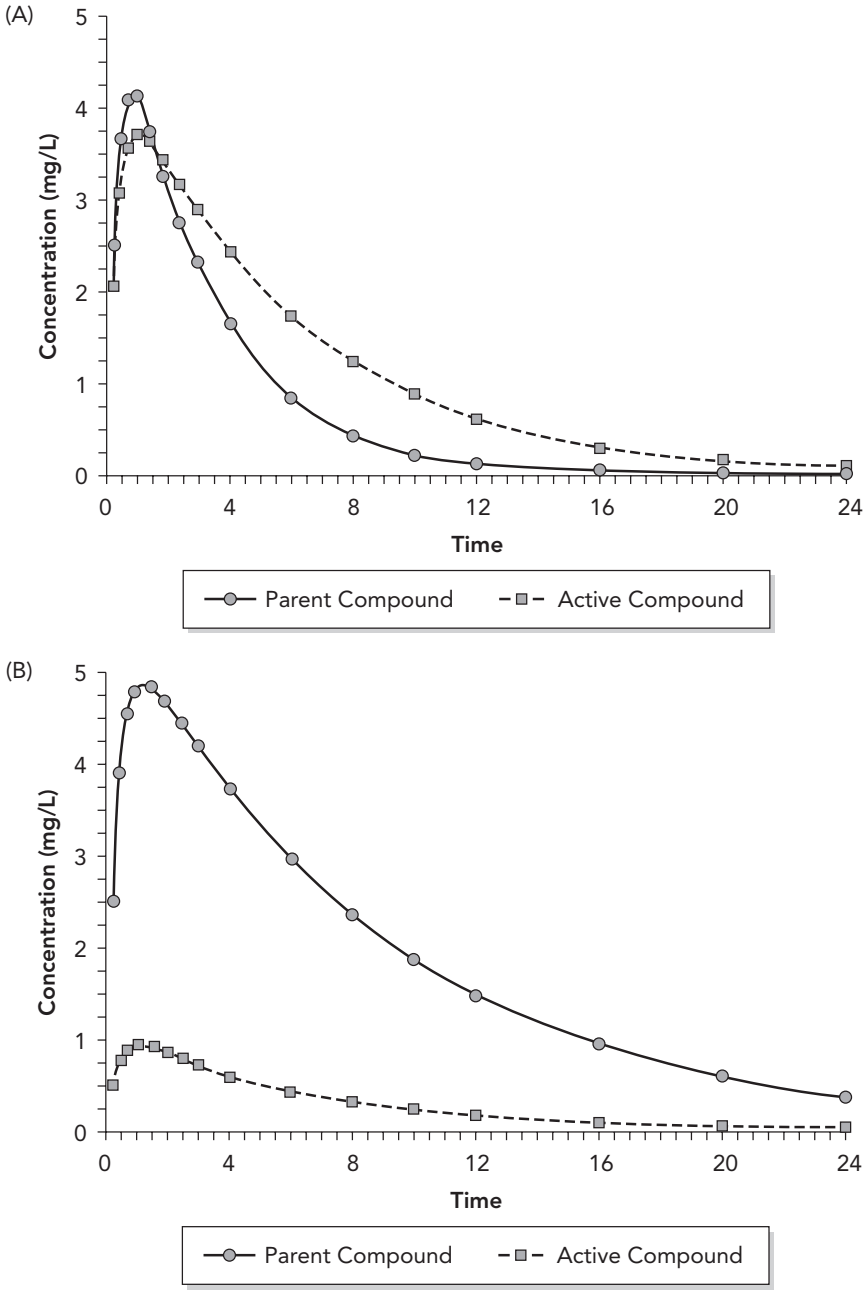

Figure 2-5 Concentration vs. time profile of parent compound (prodrug) and active compound in an extensive metabolizer (EM; panel a) and a poor metabolizer (PM; panel b).

dose of the drug absorbed (fa) and the fraction of the dose of the drug that escapes hepatic first-pass metabolism (ffp; first pass through the liver; Equation 2):

$$F = fa \cdot ffp \qquad \text{(eq. 2)}$$

The fraction of the dose absorbed can further be defined as the fraction of the dose of the drug that is available for absorption (i.e., that which is neither metabolized/degraded in the gastrointestinal lumen nor eliminated in the feces; ff) and the fraction of the dose of the drug that avoids gastrointestinal wall metabolism and/or efflux (fg). Equation 3 defines the bioavailability of a drug as:

$$F = (ff \cdot fg) \cdot ffp \qquad \text{(eq. 3)}$$

Gastrointestinal Wall Influx and Efflux Transporters

Drug molecules that are available for absorption may be "taken up" into intestinal epithelial cells and made available to portal blood flow by influx transporters that serve as a mechanism of drug absorption.[8] Along with other mechanisms of absorption, facilitated transport is recognized as a contributing factor to the bioavailability of some compounds. For instance, a number of organic anion transporting polypeptides (OATP) act as influx transporters.[9] **Table 2–1** lists examples of influx (and efflux) transporters found in the intestinal epithelia that impact drug absorption, thus influencing the bioavailability of drugs that are substrates for such transporters.

Table 2-1

Examples of Gastrointestinal Genes, Transporters, and Drug Substrates

Gene	Transporter/Type	Example Substrates
SLC01A2	OATP/influx	OATP1: enalapril OATP2: digoxin, thyroxine, pravastatin OATP1/P2: fexofenadine
SLC15A1	PEPT1/influx	β-lactam antibiotics, ACE inhibitors
SLC10A2	ASBT/influx	Benzothiazepine, dimeric bile acid derivatives
SLC16A1	MCT1/influx	Salicylic acid, nicotinic acid
ABCC2	MRP2/efflux	Tamoxifen
ABCG2	BCRP/efflux	Methotrexate, mitoxantrone
ABCB1	P-gp/efflux	Lansoprazole

Genetic–Kinetic Interface: Influx Transporters, F, and $C_{ss,ave}$

An individual may have the genetic constitution that results in the overproduction of a protein that acts to move drug from within the gastrointestinal lumen into the epithelial cells (i.e., an influx transporter). If the drug avoids efflux and/or gastrointestinal epithelial metabolism and escapes first-pass metabolism, the bioavailability will increase for that given drug:

$$\uparrow F = (ff \cdot \uparrow fg) \cdot ffp$$

The increased bioavailability will result in a higher drug concentration (Equation 4):

$$\uparrow C_{ave}^{ss} = \frac{\uparrow F \cdot Dose}{CL \cdot \tau} \qquad \text{(eq. 4)}$$

Here, the individual may be at risk of toxicity as the resultant drug concentration may be too high.

Drug molecules available for absorption may not traverse the gastrointestinal wall because efflux transporters move drug back into the gastrointestinal lumen.[4,5,9,10] These efflux transporters are proteins embedded in the cell membrane that remove drug from the cells. Although these transporters are found on many different cell membranes, the discussion here will focus on the gastrointestinal epithelium.

A number of efflux transporters can impact the bioavailability of a given drug. Two superfamilies of efflux transporters have been studied extensively. These include the adenosine triphosphate (ATP) binding cassette transporters (ABC transporters), which include P-glycoprotein (P-gp), among others, and the solute carrier transporters (SLC transporters).[5,11,12]

As drug in solution crosses the intestinal epithelium, efflux transporters move the drug back to the gastrointestinal lumen. Here, the fraction of the drug that avoids gastrointestinal wall efflux (fg) decreases, and thus bioavailability (F) is decreased. The resultant concentration of the drug in the blood also would be decreased:

$$\downarrow C_{ave}^{ss} = \frac{\downarrow F \cdot Dose}{CL \cdot \tau}$$

Genetic–Kinetic Interface: Efflux Transporters, F, and $C_{ss,ave}$

An individual may have the genetic constitution that results in the overexpression (overproduction) of a protein that acts to move drug from within gastrointestinal epithelium cells back into the gastrointestinal lumen (i.e., an efflux transporter; e.g., P-glycoprotein). In this case, less of the given drug in this patient avoids efflux (fg), and F is decreased:

$$\downarrow F = (ff \cdot \downarrow fg) \cdot ffp$$

The decreased bioavailability will result in a lower drug concentration:

$$\downarrow C_{ave}^{ss} = \frac{\downarrow F \cdot Dose}{CL \cdot \tau}$$

Here, the individual may be at risk of treatment failure because the drug concentrations will be relatively low (i.e., subtherapeutic) (see **Figure 2-6**). The dose of the drug may need to be increased or an alternative drug may need to be used.

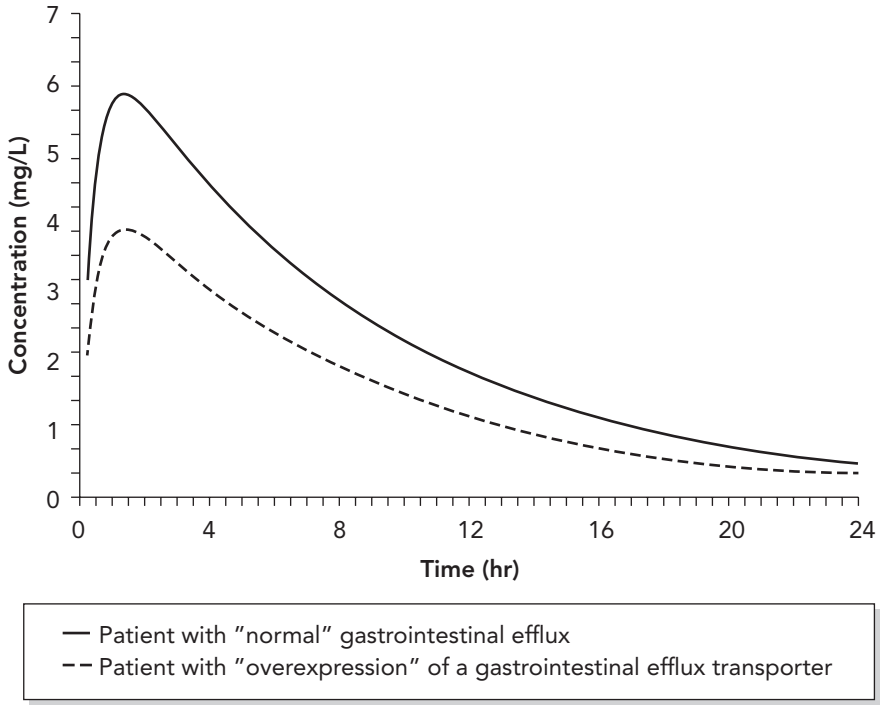

Figure 2-6 Overexpression of an efflux transporter in the gastrointestinal tract results in a decrease in the fraction of the dose that avoids efflux, thus decreasing bioavailability and drug concentration.

Efflux transporters in the gastrointestinal tract can play a major role in the bioavailability of drugs that require transport across the gut wall. Succinctly, with all other processes remaining constant relative to the pharmacokinetics of a drug, "overexpression," or increased activity of gastrointestinal efflux transporters, results in decreased bioavailability and lower systemic drug concentrations, whereas "underexpression," or decreased activity of gastrointestinal efflux transporters, results in increased bioavailability and higher systemic drug concentrations.

Gastrointestinal Wall Metabolism

As drug in solution in the gastrointestinal lumen makes its way into the gastrointestinal epithelium, it may be subject to metabolism by enzymes in the epithelium. Drug metabolized by gastrointestinal wall enzymes does not reach systemic circulation, and thus results in decreased bioavailability; that is, the fraction of the dose avoiding gastrointestinal wall metabolism (f_g) decreases, as does the fraction of the dose that reaches circulation (Equation 3). This, too, will affect the drug concentration. Although there is large interindividual variability in the

content of gastrointestinal wall cytochrome P450 isozymes, the average percent content of CYP3A, CYP2C9, CYP2C19, CYP2J2, and CYP2D6 in the gastrointestinal tract is 82%, 14%, 2%, 1.4%, and 0.7%, respectively.[13]

Poor metabolizers would be expected to have more drug avoid gut wall metabolism. Conversely, extensive and ultrarapid metabolizers would be expected to have less drug avoid gut wall metabolism. Not only will less drug reach the portal vein to be carried to the liver, but hepatic metabolism will further affect the amount of drug that reaches systemic circulation. In the case of individuals who are extensive or ultrarapid metabolizers, too little of the drug may be available systemically to be effective, and other therapeutic modalities may be required. **Figure 2-7** shows the relative differences in the concentration versus time data for a poor metabolizer, an intermediate metabolizer, an extensive metabolizer (normal; wild-type), and an ultrarapid metabolizer. With ultrarapid metabolizers, an alternative therapy may be required, because the drug concentration may not achieve therapeutic levels.

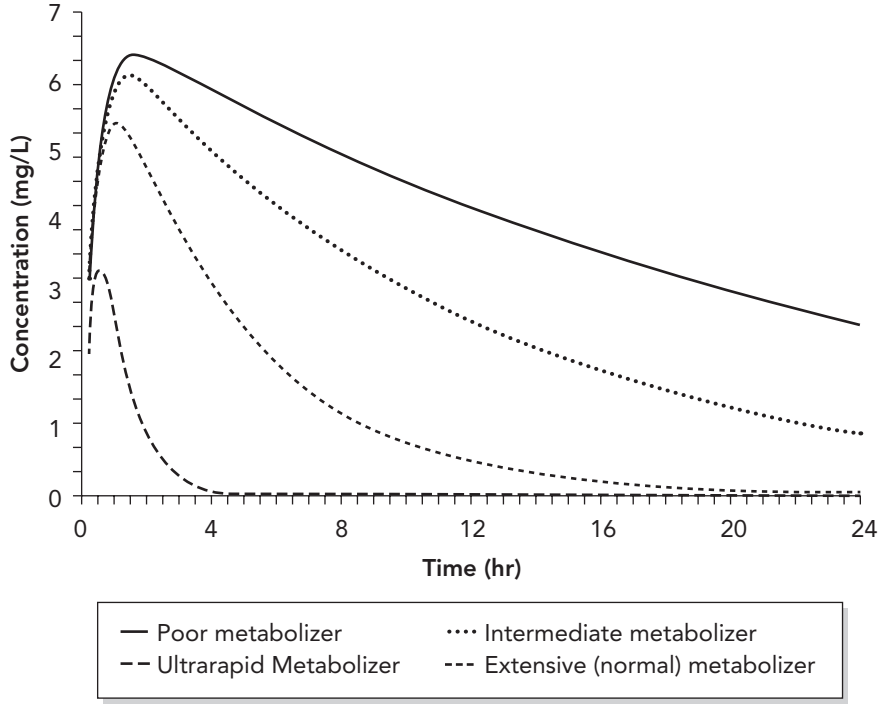

Figure 2-7 Gastrointestinal wall metabolism influences the bioavailability of a given drug. Compared to the extensive (wild type; "normal") metabolizer (EM), the poor metabolizer (PM) exhibits a concentration versus time profile with a T_{max} that occurs later and a C_{max} and AUC that are higher. The intermediate metabolizer (IM) falls between the PM and the EM. The EM and UM have a T_{max} that occurs earlier, and a C_{max} and AUC that are lower, relative to the IM and PM. The bioavailability for a given drug in each individual may be different, due, in part, to genetic (single nucleotide polymorphism) differences between the individuals.

Genetic–Kinetic Interface: Gut Wall Metabolism

An individual may have the genetic constitution that results in CYP2C19 ultrarapid metabolism, (e.g., the *17/*17 genotype). In this case, following per-oral administration of a CYP2C19 substrate drug, less of the drug avoids gastrointestinal wall metabolism (*fg*), and F is decreased:

$$\downarrow F = (ff \cdot \downarrow fg) \cdot ffp$$

The decreased bioavailability will result in a lower drug concentration:

$$\downarrow C_{ave}^{ss} = \frac{\downarrow F \cdot Dose}{CL \cdot \tau}$$

Here, the individual may be at risk of treatment failure because the drug concentrations will be relatively low. The dose of the drug may need to be increased, or an alternative drug may need to be used.

Hepatic First-Pass Metabolism

Following oral dosing, drug that is available for absorption and that avoids gastrointestinal efflux and gut wall metabolism is carried via hepatic portal blood flow to the liver, where it may be subject to hepatic metabolism, thus undergoing first-pass metabolism. Drug that escapes hepatic metabolism and reaches systemic circulation is said to be bioavailable.

The same potential differences exist for drug metabolism in the liver as were described for gut wall metabolism. Drug that does make it to the liver may be efficiently metabolized in a patient who is an extensive metabolizer or an ultrarapid metabolizer, leaving little drug reaching systemic circulation. Conversely, the patient may be a poor metabolizer with inefficient hepatic metabolism, thus allowing a higher fraction of the drug to reach systemic circulation, resulting in relatively higher bioavailability. The percentage content of cytochrome P450s in the liver has been reported to be 40%, 25%, 18%, 9%, 6%, 2%, and <1%, for CYP3A, CYP2C, CYP1A2, CYP2E1, CYP2A6, CYP2D6, and CYP2B6, respectively.[14]

Genetic–Kinetic Interface: Hepatic First-Pass Metabolism

An individual may have the genetic constitution that results in the under expression of a drug-metabolizing enzyme (e.g., CYP2C19). In this case, more of the given drug in this patient avoids hepatic first-pass metabolism (*ffp*), and F is increased:

$$\uparrow F = (ff \cdot fg) \cdot \uparrow ffp$$

The increased bioavailability will result in a higher drug concentration:

$$\uparrow C_{ave}^{ss} = \frac{\uparrow F \cdot Dose}{CL \cdot \tau}$$

Here, the individual may be at risk of toxicity because the drug concentration will be relatively high. The dose of the drug may need to be decreased, or an alternative drug may need to be used.

Gastrointestinal Wall Efflux, Metabolism, and Hepatic First-Pass Metabolism

The genetic constitution of an individual will influence each of the variables that determine bioavailability. For instance, a patient may overexpress the efflux transporter protein P-gp while also being an ultrarapid metabolizer who overexpresses CYP2C19. If a drug is subject to efflux by P-gp and is a metabolic substrate for CYP2C19, the bioavailability of that drug would be expected to be quite low because the fraction avoiding efflux, escaping gut wall metabolism, and escaping hepatic first-pass metabolism would be low:

$$\downarrow\downarrow\downarrow F = ff \cdot \downarrow\downarrow fg) \cdot \downarrow ffp$$

A drug "handled" in this way by the body may not be suitable for oral administration and may need to be administered by a route that avoids gastrointestinal efflux, gastrointestinal wall metabolism, and first-pass metabolism, such as the intravenous or sublingual route, or an alternative drug may need to be used. **Figure 2–8** shows the potential consequences for a drug molecule relative to oral absorption and bioavailability. Recognize that all the potential processes of a given drug's absorption are influenced by the patient's genetic constitution.

Distribution and Volume of Distribution

Influx and efflux transporters are found in many tissues and play a role in the distribution of drugs throughout the body. As discussed previously, transporters in the gastrointestinal epithelium can influence drug absorption and bioavailability. However, these transporters do not influence the distribution of a drug because distribution occurs after the drug reaches systemic circulation. The volume of distribution (Vd) is the proportionality constant relating the amount of drug in the body to the drug concentration.

As traditionally described, the volume of distribution is a primary independent pharmacokinetic parameter that influences the half-life (Equation 5) and is used in the calculation of a drug's loading dose (Equation 6):[15]

$$t_{1/2} = \frac{0.693 \cdot Vd}{CL} \qquad \text{(eq. 5)}$$

$$D_L = C \cdot Vd \qquad \text{(eq. 6)}$$

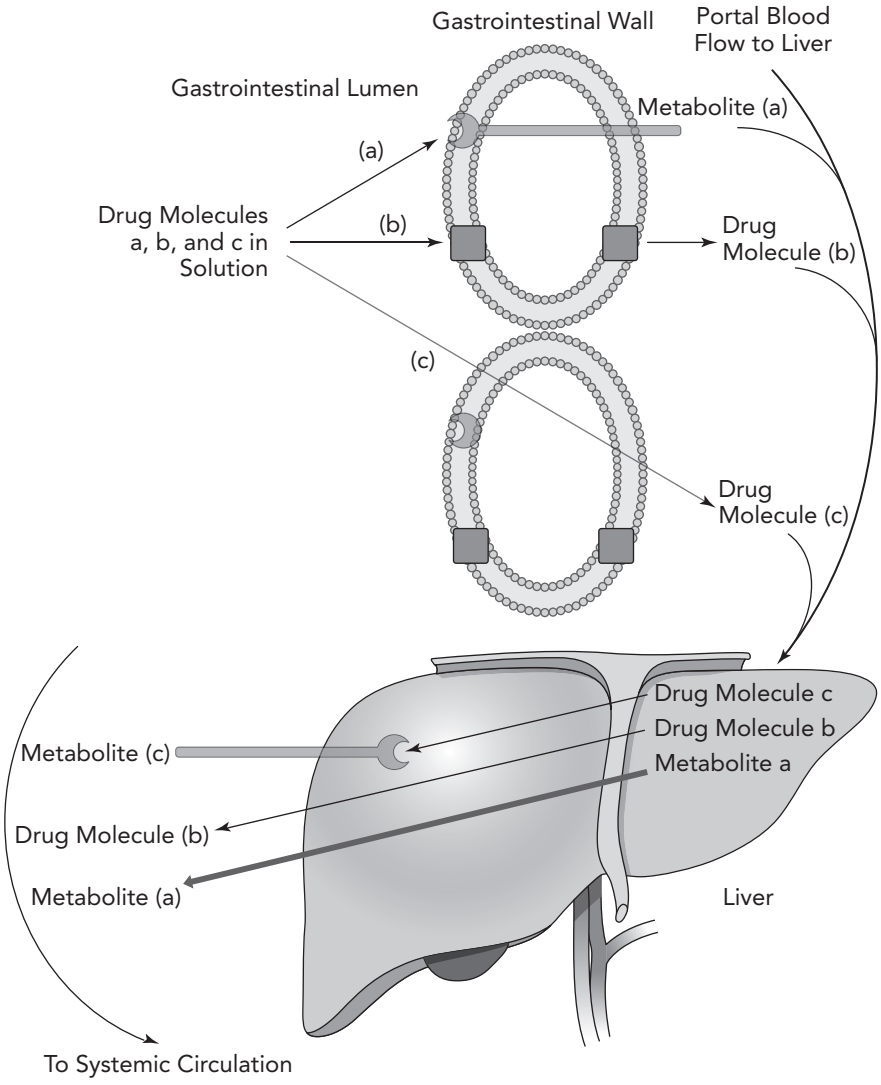

Figure 2-8 Drug being absorbed from the gastrointestinal tract. Upon oral dosing of a given drug, drug molecules a, b, and c, in solution in the gastrointestinal tract, are presented for absorption. Drug molecule (a) is metabolized by an enzyme in the gastrointestinal wall and does not reach systemic circulation and is therefore not bioavailable. The resulting metabolite travels to the liver, via portal blood flow, and then to systemic circulation. Drug molecule (b) is transported, via a protein, from the gastrointestinal lumen to portal blood flow, where it travels to the liver. The molecule moves through the liver and reaches systemic circulation, thus being bioavailable. Drug molecule (c) passively diffuses through the gastrointestinal wall and travels to the liver via portal blood flow. The drug molecule does not reach systemic circulation and is not bioavailable as it is metabolized in the liver (i.e., first-pass metabolism).

Alterations in a drug's volume of distribution can effect the drug's plasma concentration and its efficacy and/or the likelihood of producing toxicity. Rearrangement of Equation 6 shows the implications of an altered volume of distribution relative to the drug concentration:

$$C = \frac{D_L}{Vd} \qquad \text{(eq. 6a)}$$

Equations 5, 6, and 6a represent relationships for a one-compartment pharmacokinetic model where a drug distributes efficiently throughout the body and administration and elimination are into and from a single compartment. This model describes drugs that exhibit a single declining slope on a semi-log plot, following the maximum concentration, when concentrations are observed over time following drug administration.

Following drug administration, many drugs however exhibit more than one declining log-concentration slope over time, suggesting that the drug distributes at different rates into different tissues and that the rate of elimination is slower than the rate of distribution. In this case, the drug concentration versus time data are best described by multi-compartment models. Here, these models describe drug typically administered into the initial volume (V_1), which represents a component of the total volume of distribution (V_{ss}). Ideally, the initial volume of distribution is calculated by dividing the intravenous push (bolus) dose by the initial drug concentration observed immediately after administration of the intravenous push dose. By definition, volumes of a multi-compartment model are additive, thus V_1 (the volume of the first compartment) is smaller than the V_{ss}. Typically, for a multi-compartment model, V_1 is relatively small because immediately after a push dose drug has not yet moved into slowly perfused tissues (i.e., the drug has not equilibrated with other tissue volumes). Also in these models, drug is typically shown to be eliminated from V_1 because the major, "high blood flow" eliminating organs (i.e., kidneys and liver) are considered to be in V_1. Relationships of pharmacokinetic parameters and calculation of the loading dose for a multi-compartment drug as shown in Equations 7 and 7a are related to a multi-compartment model and are similar to the equations for a one-compartment model (Equations 6 and 6a).

$$D_L = C \cdot V_1 \text{ or } D_L = C \cdot V_{ss} \qquad \text{(eq. 7)}$$

$$C = \frac{D_L}{V_1} \text{ or } C = \frac{D_L}{V_{ss}} \qquad \text{(eq. 7a)}$$

For calculation of the loading dose for a drug that has its concentration versus time profile best described by a multi-compartment model, V_1 is used when distribution from the first compartment to the other

compartments is relatively slow, whereas V_{ss} is used when distribution from the first compartment to other compartments is relatively rapid.

The distribution of a given drug may depend on the function of a drug transporter such that its overexpression or underexpression alters the volume of distribution, which then may alter the half-life. Additionally, as we have learned more regarding the location and function of certain transporters, it has become clear that in some cases there is a relationship between the volume of distribution and clearance, a measure of drug removal from the body, that may or may not influence the half-life.[16]

As noted earlier, P-gp, an efflux transporter, is expressed in many tissues in the human body, including the liver, kidney, lung tissue, and, to a lesser extent, muscle, mammary glands, and other tissues. As P-gp works to keep drugs out of tissues, underexpression of P-gp would allow for greater distribution of a P-gp substrate drug; the drug would not be removed from the tissue as it would if P-gp were normally expressed. This would increase the volume of distribution of the drug. If the Vd or V_1 (and hence V_{ss}) of the drug were to be the only altered parameter, it would be expected, that the $t_{1/2}$would be increased also (Equation 5). It also is noted that the calculated loading dose would be higher (Equations 6 and 7). The above scenario implies that the tissue "protected" by P-gp would not serve to metabolize and/or eliminate the given drug, because the volume of distribution was the sole parameter that was altered, with clearance remaining unchanged.[12,16]

Genetic–Kinetic Interface: Drug Distribution, Vd, CL, $t_{1/2}$, and Drug Concentration

An individual with a reduced-function allele for OATP1B1 (resulting in underexpression in liver tissue) is receiving atorvastatin for the treatment of hypercholesterolemia. Atorvastatin is a substrate for OATP1B1 and is metabolized in the liver. The genetic constitution of this individual results in a decreased volume of distribution and a decreased clearance of atorvastatin:

$$\leftrightarrow t_{1/2} = \frac{0.693 \cdot Vd \downarrow}{CL \downarrow}$$

Here, conceptually, it would be expected that the drug concentration would increase because the initial dose is administered into what is effectively a smaller volume of distribution in this individual:

$$\uparrow C = \frac{D_L}{\downarrow Vd}$$

Additionally, as a maintenance dose (D_M) is continued in this individual, the average steady-state concentration will be increased further as the clearance is decreased (Equation 8):

$$D_M = CL \cdot C_{ave}^{ss} \qquad \text{(eq. 8)}$$

$$\uparrow C_{ave}^{ss} = \frac{F \cdot Dose}{\downarrow CL \cdot \tau}$$

Although the half-life may not be altered, increases in the drug concentration put the patient at potential risk of toxicity.

Table 2-2

Examples of Overexpression of Drug Transporters in Tissues in Humans and Effects on the Volume of Distribution and the Drug Concentration

Transporter (Type)	Example Tissue	Gene	Effect on Volume of Distribution	Effect on the Plasma Drug Concentration
P-gp (efflux)	Liver	ABCB1	Decrease	Increase
OATP1B1 (influx)	Brain	SLC01B1	Increase	Decrease
OCT1 (influx)	Kidney	SLC22A1	Increase	Decrease

The influx transporter OATP1B1, an organic anion transporter, is expressed in human liver tissue. If a given drug is an uptake substrate for OATP1B1 and also is metabolized in the liver, alterations in the expression of OATP1B1 will have an effect on the volume of distribution and on the clearance of the drug.[17–19] Here, Vd and CL will change in the same direction. The magnitude of change in each parameter will determine whether the $t_{1/2}$ remains constant or is altered (Equation 5). In this situation, clearance is related to the Vd of the drug.

The relationship between Vd and CL can be thought of as a relationship between the physical volume in which the drug resides and the functional mechanism of drug elimination that occurs in that volume.

The genetically controlled tissue expression of a given drug transporter is critical in understanding how a drug's pharmacokinetics are related to the drug concentration. **Table 2-2** shows the tissue distribution of example drug transporters in humans and how genetic variation influences drug distribution and drug concentration.

Metabolism

Many drugs are not excreted from the body unchanged; therefore, they require metabolic conversion to be inactivated and primed for removal via excretory pathways. Genetic variation in the expression and/or activity of drug metabolizing enzymes can have a profound effect on the concentration versus time profiles of these drugs and, more importantly, on the therapeutic outcomes of drug therapy. With two phases of drug metabolism, the potential exists for genetic variability to disrupt drug metabolism, especially for a drug which undergoes each phase of metabolism.

Phase I metabolism refers to chemical reactions involving oxidation, reduction, or hydrolysis. These reactions work to make the drug more polar by adding functional amino, sulfhydral, hydroxyl, and carboxyl groups that make the given drug more hydrophilic, thus promoting excretion of the drug from the body, such as being

eliminated in urine.[20] **Phase II metabolism** typically refers to conjugation reactions, including glucuronidation, sulfation, acetylation, and methylation, among other reactions. Phase II metabolism, like phase I metabolism, works to make molecules more water soluble, promoting drug excretion. Both phase I and phase II metabolic reactions are under genetic control, and polymorphisms have been identified for specific enzymes that perform these metabolic functions.

A drug undergoing phase I metabolism may be converted to inactive metabolite(s) that may be excreted or act as substrate(s) for phase II metabolic reactions. Alternatively, a drug may undergo phase I metabolism, resulting in the drug being "activated,"which is the premise for the development of prodrugs. Finally, in some cases, the "inactivation" of a drug by phase I and/or phase II metabolism may result in the formation of a toxic metabolite. In this case, the drug is inactivated and no longer produces the desired therapeutic response; however, the metabolite is toxic, eliciting an adverse reaction or unwanted effect.

With respect to phase I oxidative metabolism, the **cytochrome P450 enzyme (CYP)** superfamily has been the focus of extensive research. Although there are numerous CYP enzyme families, three families in particular (CYP1, CYP2, and CYP3) encompass the major drug metabolizing enzymes, with CYP3A being the most prominent.[21] **Table 2-3** presents examples of the CYP enzymes with polymorphisms involved in drug metabolism and the tissues in which these enzymes are expressed. **Figure 2-9** shows the nomenclature for cytochrome P450 enzymes, and **Figure 2-10** presents the contribution of various CYPs in drug metabolism.

Table 2-3

Examples of Cytochrome P450 Drug Metabolizing Enzyme Tissue Expression, Allele Variation, Metabolic Consequence, and Influence on Drug Concentration

CYP Enzyme	Example Tissue Expression	Gene (SNP) rs#[a]	Primary Pharmacokinetic Alteration	Effect on Drug Concentration
CYP2C9	Small intestine/ liver	CYP2C9*2 (C>430>T) rs1799853	Poor metabolizer: increased *ffp*, decreased CL	Increased fraction of drug dose presented to the liver. Increased concentration.
CYP2C19	Liver	CYP2C19*2 (G>681>A) rs4244285	Poor metabolizer: decreased CL	Increased concentration.
CYP2D6	Liver	CYP2D6*4 (G>1846>A) rs3892097	Poor metabolizer: decreased CL	Increased concentration.

[a] Reference SNP (refSNP) number. These numbers are unique and consistent identifiers of the given SNP.

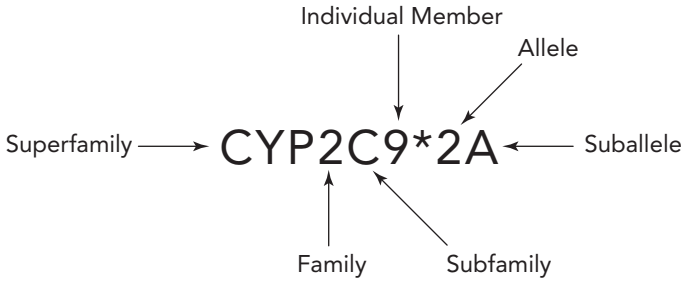

Figure 2-9 Naming nomenclature of cytochrome P450 enzymes. Here CYP2C9*2A is the example CYP enzyme.

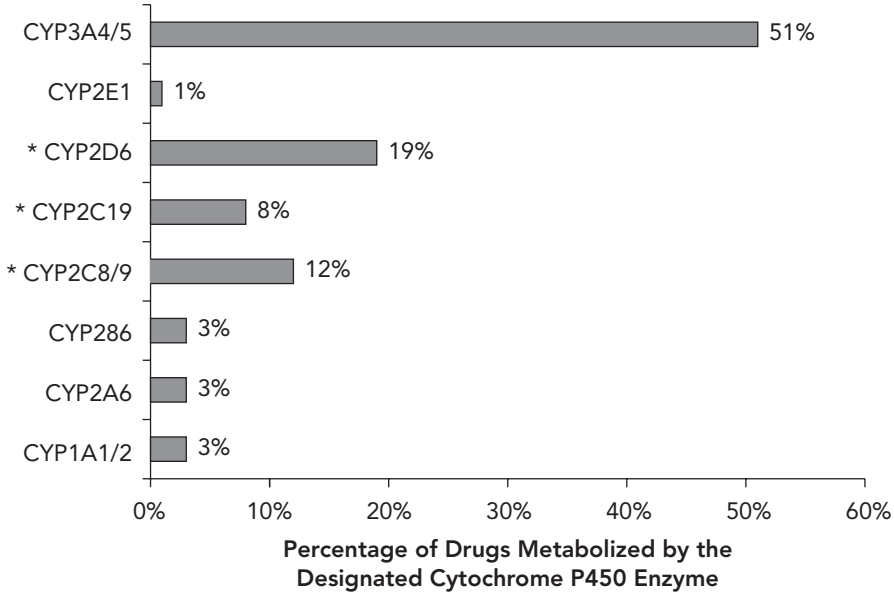

Figure 2-10 Percentage of drugs metabolized by designated cytochrome P450 (CYP) enzymes. Polymorphic (*) expression of certain CYP enzymes confounds the concentration vs. time profile of the drug and may alter the therapeutic response in individuals, thus requiring specific dosing considerations.

Because metabolism of a given drug influences the clearance of that drug and clearance is used to calculate the maintenance dose, identifying a single nucleotide polymorphism (SNP) related to a given CYP enzyme can aid in "personalizing" an individual's dose. Single nucleotide polymorphisms can result in a patient handling a drug in such a manner that they would be considered to be a particular "type" of metabolizer. Homozygous individuals with a polymorphism resulting in the expression of a "loss-of-function"

(inactive) or "reduced-function" CYP enzyme would be considered a poor metabolizer. These individuals would have a decreased clearance of substrate drugs and would require a lower maintenance dose to achieve the desired therapeutic response. Individuals who are heterozygous, with one allele producing a loss-of-function or decreased-function enzyme and the other producing a normal-function enzyme, are termed intermediate metabolizers. These individuals may require a lower maintenance dose because they would have a decreased clearance. However, the reduction in clearance would not be as great as that seen in a poor metabolizer, and the required maintenance dose would not be as low. Extensive metabolizers are individuals who have two normal function alleles, and would receive the "normal" maintenance dose. The fourth type of individual would be one in whom there is gene duplication with a consequential overexpression of the CYP enzyme, resulting in a high clearance of the drug, necessitating a higher maintenance dose. These individuals are called **ultrarapid metabolizers (UM)**.

Terminology used to describe the types of phenotypic metabolizers insinuates two concepts related to drug metabolism. The first is the extent of metabolism, and the second is the rate of metabolism. These terms are related to pharmacokinetics in that the phenotypic category of a given individual (i.e., poor metabolizer, intermediate metabolizer, extensive metabolizer, or ultrarapid metabolizer) implies the characteristics of specific pharmacokinetic parameters and dosing requirements. As described above, clearance is the primary pharmacokinetic parameter that is affected by an individual's genetic constitution. This will result in a potential alteration in the half-life because it is dependent on the clearance (and the volume of distribution). Also, an altered clearance will impact the maintenance dose, and the half-life will influence the dosing interval. **Table 2–4** describes the impact of **phenotype** on pharmacokinetic parameters related to metabolism and dosing considerations.

It is important to understand that an individual's **genotype** may *not* match their phenotype, in that influences other than genetics can alter the expression of a metabolizing enzyme. For instance, an individual with the *1/*1 genotype for CYP2C19 (CYP2C19*1/*1) would be considered an extensive (or "normal") metabolizer. However, if this individual is receiving a certain proton pump inhibitor (PPI), such as omeprazole, for the treatment of esophageal reflux disease, the PPI may inhibit the function of CYP2C19, thus causing the individual to effectively be a poor metabolizer.[22] Here, due to the drug interaction, the individual has the phenotype of a poor metabolizer. It is always important to consider drug–gene interactions and drug–drug interactions simultaneously.

Table 2-4

Metabolic Phenotypes: Pharmacokinetic and Dosing Consequences[a]

Phenotype	Pharmacokinetic Parameter	Consequence	Dosing	Potential Consequence
Poor metabolizer (PM)	k_e; elimination rate constant/$t_{1/2}$; half-life (related to k_e)	↓↓/↑↑	Dosing frequency	↓↓
	CL; clearance	↓↓	Average concentration	↑↑
Intermediate metabolizer (IM)	k_e; elimination rate constant/$t_{1/2}$; half-life (related to k_e)	↓/↑	Dosing frequency	↓
	CL; clearance	↓	Average concentration	↑
Extensive metabolizer (EM)	—	—	—	—
Ultrarapid metabolizer (UM)	k_e; elimination rate constant/$t_{1/2}$; half-life (related to k_e)	↑↑/↓↓	Dosing frequency	↑↑
	CL; clearance	↑↑	Average concentration	↓↓

[a] Relative to the extensive metabolizer being considered "normal," with the same dose being administered to each individual with a given phenotype: ↓ = decreased, ↑ = increased. The number of arrows indicates the relative magnitude of the consequence.

Genetic–Kinetic Interface: Drug Metabolism, CL, Dose, and Dosing Interval

An individual with inheritance of alleles resulting in CYP2D6 gene duplication is receiving doxepin for the treatment of depression. Doxepin, a tricyclic antidepressant, is metabolized by CYP2D6. The genetic constitution of this individual results in the individual being an ultrarapid metabolizer, exhibiting a significantly higher clearance of doxepin. This individual has been taking the drug, but has not been responding. This could be due to the increased clearance of the drug, resulting in low concentrations and drug exposure (Equation 9):

$$\downarrow\downarrow C_{ave}^{ss} = \frac{F \cdot Dose}{\uparrow\uparrow CL \cdot \tau}$$

$$\downarrow\downarrow AUC = \frac{Dose}{\uparrow\uparrow CL} \qquad \text{(eq. 9)}$$

The increased clearance will require an increased maintenance dose to achieve the desired concentration that would maximize the probability of a therapeutic response:

$$\uparrow\uparrow D_M = \uparrow\uparrow CL \cdot C_{ave}^{ss}$$

Additionally, the significantly higher clearance seen in an individual who is an ultrarapid metabolizer will result in a shorter half-life:

$$\downarrow\downarrow t_{½} = \frac{0.693 \cdot Vd}{\uparrow\uparrow CL}$$

If the individual is to remain on the drug, the frequency of administration will need to be increased to maintain therapeutic concentrations. The dosing interval **tau (τ)** can be estimated for a rapidly absorbed drug as (Equation 10):

$$\downarrow\downarrow \tau = \frac{\ln \frac{C_{max}}{C_{min}}}{\uparrow\uparrow k} \qquad \text{(eq. 10)}$$

or specifically for an intravenous medication (Equation 10a):

$$\downarrow\downarrow \tau = \frac{\ln \frac{C_{max}}{C_{min}}}{\uparrow\uparrow k} + t_i \qquad \text{(eq. 10a)}$$

where t_i is the infusion time.

Excretion

As previously mentioned, drug influx and efflux transporters are found in many tissues and play a role in the distribution of drugs throughout the body. Not only do these transporters affect distribution, but they can influence the drug's removal from the body through drug excretion.

The renal excretion of a drug, moving the compound from the blood to the urine, can be a consequence of genetically mediated drug transport.[4,23,24] Renal filtration occurs in the glomerulus, and active secretion occurs in the nephron tubules. Both of these sites are "excretory" because drug is moved from the blood to the urine. Relative to tubular secretion, numerous transporters have been identified in kidney tissue, including P-gp (MDR1), OCT1, OAT1, MRP2, cMOAT, and ENT1, among others. **Table 2–5** presents examples of drug transporters in the kidney and their influence on renal drug handling. Transporter distribution among different populations may explain differences in renal excretion of drugs, and SNPs may further delineate drug removal in given individuals.

Table 2-5

Examples of Renal Drug Transporters Responsible for Urinary Excretion

Example Drug	Example Transporter	Renal Drug Process
Cefamandole[a]	OAT1	Renal tubular excretion
Cimetidine[b]	OAT3	Renal tubular excretion
Acyclovir[b]	OCT1	Renal tubular excretion
Amoxicillin[a]	PEPT1	Renal tubular excretion
Zidovudine[b]	OAT4	Renal tubular reabsorption

[a] Inhibitor of transporter.

[b] Substrate of transporter.

Genetic–Kinetic Interface: Renal Drug Excretion

An individual receiving metformin for treatment of type 2 diabetes may have the genetic constitution that results in the expression of a less active form of the drug transporter OCT1 found on the apical side of the proximal and distal tubules in the kidney. This expression results in decreased uptake of metformin from the plasma, resulting in decreased renal clearance, and hence overall clearance because the clearances are additive (Equation 11):

$$\downarrow CL = \downarrow CL_R + CL_{Other} \quad \text{(eq. 11)}$$

However, OCT1 is also found in liver tissue, and the decreased activity in this tissue results in decreased hepatic uptake of metformin, which may alter the drug effect (pharmacodynamics).

Similar to renal drug excretion, biliary excretion is another mechanism of drug elimination. Efflux transporters (MDR1, MDR3, and others) move drug from the hepatocyte into the biliary canaliculi. The drug/metabolite then is moved to the small intestine, where it may be reabsorbed through enterohepatic cycling or excreted from the body in the feces. Therefore, changes in the level of expression/activity of these transporters within the hepatocytes would be expected to impact biliary drug excretion.

Chapter Summary

The pharmacokinetics of a drug are determined by evaluating the concentration of drug in biologic fluids over time. Drug metabolizing enzymes and drug transporters may influence all aspects of the concentration–time profile, including transporters affecting the volume of distribution, which is used in calculating the loading dose and metabolizing enzymes influencing the clearance, which is used in calculating the maintenance dose. Both the volume of distribution and the clearance influence the elimination rate constant, and hence the half-life, which is used to calculate the dosing interval. It is clear that genetic variation in transporters and metabolizing enzymes are responsible for the varied dosing regimens of the same drug required by different individuals.

Review Questions

1. The study of a gene involved in response to a drug is referred to as:
   a. pharmacokinetics.
   b. pharmacodynamics.
   c. pharmacogenetics.
   d. pharmacogenomics.

2. The _____ is the main site of drug absorption due to its large surface area, membrane permeability, and capillary blood flow.
   a. liver
   b. large intestine
   c. small intestine
   d. stomach

3. If an individual is an extensive metabolizer of a drug relative to an intermediate metabolizer or a poor metabolizer, what happens to the k_e and T_{max} of that drug?
   a. k_e is decreased and the drug is eliminated more slowly; therefore, the T_{max} will occur later.
   b. k_e is decreased and the drug is eliminated faster; therefore, the T_{max} will occur sooner.
   c. k_e is increased and the drug is eliminated more slowly; therefore, the T_{max} will occur later.
   d. k_e is increased and the drug is eliminated faster; therefore, the T_{max} will occur sooner.

4. The _____ of drug absorption is expressed by T_{max}, and the _____ of drug absorption is defined by C_{max} and AUC.
   a. rate; extent
   b. extent; rate
   c. concentration; time
   d. time; concentration

5. With respect to drug metabolism, which individual, relative to metabolizer status, may be at risk of experiencing toxicity from a standard dose of a particular drug (not referring to a prodrug)?
   a. Poor metabolizer
   b. Intermediate metabolizer
   c. Extensive metabolizer
   d. Ultrarapid metabolizer

6. Compared to an extensive metabolizer, an ultrarapid metabolizer will need _____ dosing frequency.
   a. a decreased
   b. an increased
   c. the same
   d. Not enough information has been provided to answer this question.

7. If an individual has a genetic constitution that results in the decreased production of gastrointestinal influx transporters, what will happen to the bioavailability and concentration of a drug that is a substrate for the transporters?
   a. Bioavailability will increase; the concentration will decrease.
   b. Bioavailability will increase; the concentration will increase.
   c. Bioavailability will decrease; the concentration will decrease.
   d. Bioavailability will decrease; the concentration will increase.

8. How might treatment outcome be affected if less of a dose of drug avoids gastrointestinal wall metabolism in a patient?
   a. The patient may be at risk of treatment failure due to low drug concentrations.
   b. The patient may be at risk of toxicity due to high drug concentrations.
   c. The patient may be at risk of treatment failure due to increased bioavailability.
   d. The patient may be at risk of toxicity due to increased bioavailability.

9. _____ or _____ activity of gastrointestinal efflux transporters results in decreased bioavailability and potentially lower systemic drug concentrations.
   a. Underexpression; decreased
   b. Underexpression; increased
   c. Overexpression; decreased
   d. Overexpression; increased

10. With regards to the following equation, if the fraction of a drug that avoids gastrointestinal wall efflux decreases, what would happen to the resultant concentration of the drug in the blood?

$$C_{ave}^{ss} = \frac{F \cdot Dose}{CL \cdot \tau}$$

   a. Decreased
   b. Increased
   c. No change
   d. Not enough information has been provided to answer the question.

11. An individual has the genetic constitution that shows "loss-of-function" of the drug metabolizing enzyme CYP2C19, and this individual is taking a drug that is metabolized by this isozyme. With regards to hepatic first-pass metabolism, _____ of the given drug avoids metabolism, resulting in _____ bioavailability of the drug.
    a. more; increased
    b. more; decreased
    c. less; increased
    d. less; decreased

12. On average, which cytochrome P450 enzyme has the highest percentage of presence in both the gut wall and the liver?
    a. CYP2C9
    b. CYP3A4/5
    c. CYP2C19
    d. CYP2D6

13. An individual overexpresses the efflux protein P-gp and also is an ultrarapid metabolizer, overexpressing CYP2C19. If a drug is a metabolic substrate for CYP2C19 and is subject to efflux by P-gp, what would be the effect on bioavailability? Consider that:

$$F = (ff \cdot fg) \cdot ffp$$

    a. Bioavailability would decrease.
    b. Bioavailability would increase.
    c. Bioavailability would not change.
    d. Not enough information has been provided to answer the question.

14. Influx and efflux transporters in the gastrointestinal epithelium can influence _____ and _____.
    a. distribution of a drug; bioavailability
    b. distribution of a drug; drug absorption
    c. drug absorption; bioavailability
    d. volume of distribution; bioavailability

15. The volume of distribution influences the half-life and is used to calculate a drug's:
    a. maintenance dose.
    b. loading dose.
    c. dosing interval.
    d. a and c

16. _____ is a primary pharmacokinetic parameter that is affected by an individual's genetic constitution.
    a. k_a
    b. $t_{1/2}$
    c. k_e
    d. CL

17. If a patient has underexpression of the influx transporter OATP1B1 in the liver, and the volume of distribution and clearance are decreased by the same magnitude, what change would need to be made to the dosing interval of the drug?
    a. The dosing interval would need to be decreased.
    b. The dosing interval would need to be increased.
    c. The drug would need to be discontinued.
    d. The dosing interval would not need to be changed.

18. A homozygous individual with a polymorphism resulting in a loss-of-function CYP enzyme would be considered a (n) _____ and would have _____ clearance requiring a _____ maintenance dose.
    a. poor metabolizer; increased; higher
    b. extensive metabolizer; increased; higher
    c. poor metabolizer; decreased; lower
    d. extensive metabolizer; decreased; lower

19. An individual with depression has CYP2D6 gene duplication and is considered to be an ultrarapid metabolizer. If this individual is taking the antidepressant doxepin, a CYP2D6 metabolic substrate, what would be the likely treatment outcome and what could be done to correct this?
    a. The individual would likely experience adverse drug reactions due to the relatively high clearance and would require an increased maintenance dose or the use of another drug.
    b. The individual would likely experience adverse drug reactions due to the relatively low clearance and would require a decreased maintenance dose.
    c. The individual would likely experience treatment failure due to the relatively high clearance and would require an increased maintenance dose or the use of another drug.
    d. The individual would likely experience treatment failure due to the decreased clearance and would require a decreased maintenance dose.

20. With regards to renal excretion, if an individual has overexpression of the ABCB1 gene coding for the P-gp (MDR1) transporter in the kidney, what effect would this have on clearance and the drug concentration?
    a. Increased clearance and increased drug concentration.
    b. Decreased clearance and decreased drug concentration.
    c. Increased clearance and decreased drug concentration.
    d. Decreased clearance and increased drug concentration.

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