ROUTE OF DRUG ADMINISTRATION AND EXTRAHEPATIC DRUG METABOLISM

The decline in plasma concentrations after drug administration results from drug elimination or removal by the body. The elimination of most drugs from the body involves the processes of both metabolism (biotransformation) and renal excretion (see). For many drugs, the principal site of metabolism is the liver. However, other tissues or organs, especially those tissues associated with portals of drug entry into the body, may also be involved in drug metabolism. These sites include the lung, skin, gastrointestinal mucosal cells, microbiological flora in the distal portion of the ileum, and large intestine. The kidney may also be involved in certain drug metabolism reactions.

Knowledge of the fraction of the drug that is eliminated by metabolism and the fraction of drug that is eliminated by excretion is useful information that helps to predict whether a change in drug elimination is likely to be affected by renal disease, hepatic disease, or a drug–drug interaction. Drugs that are highly metabolized (such as phenytoin, theophylline, and lidocaine) demonstrate large intersubject variability in elimination half-lives and are dependent on the intrinsic activity of the biotransformation enzymes, which may be altered by genetic and environmental factors. Intersubject variability in elimination half-lives is less for drugs that are eliminated primarily by renal drug excretion. Renal drug excretion is highly dependent on the *glomerular filtration rate* (GFR). Since GFR is relatively constant among individuals with normal renal function, the elimination of drugs that are primarily excreted unchanged in the urine is less variable.

First-Order Elimination

The rate constant of elimination (k) is the sum of the first-order rate constant for metabolism (k_m) and the first-order rate constant for excretion (k_e):

$$k = k_e + k_m \qquad (11.1)$$

In practice, the excretion rate constant (k_e) is easily evaluated for drugs that are primarily renally excreted. Nonrenal drug elimination is usually assumed to be due for the most part to hepatic metabolism, though metabolism or degradation can occur in any organ or tissue that contains metabolic enzymes or is in a degradative condition. Therefore, the rate constant for metabolism (k_m) is difficult to mea-sure directly and is usually found from the difference between k and k_e.

$$k_m = k - k_e$$

A drug may be biotransformed to several metabolites (metabolite A, metabolite B, metabolite C, etc); thus, the metabolism rate constant (k_m) is the sum of the rate constants for the formation of each metabolite:

$$k_m = k_{mA} + k_{mB} + k_{mC} + \cdots + k_{mI} \qquad (11.2)$$

The relationship in this equation assumes that the process of metabolism is first order and that the substrate (drug) concentration is very low. Drug concentrations at therapeutic plasma levels for most drugs are much lower than the Michaelis–Menten constant, K_M, and do not saturate the enzymes involved in metabolism. Nonlinear Michaelis–Menten kinetics must be used when drug concentrations saturate metabolic enzymes (see also).

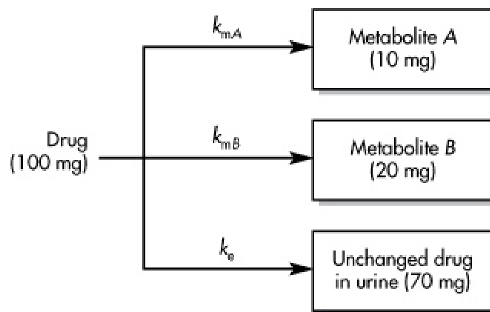
Because these rates of elimination at low drug concentration are considered first-order processes, the percentage of total drug metabolized may be found by the following expression:

$$\%\ \text{drug metabolized} = \frac{k_m}{k} \times 100 \qquad (11.3)$$

Fraction of Drug Excreted Unchanged (f_e) and Fraction of Drug Metabolized ($1 - f_e$)

For most drugs, the *fraction of dose eliminated unchanged* (f_e) and the fraction of dose eliminated as metabolites can be determined. For example, consider a drug that has two major metabolites and is also eliminated by renal excretion (). Assume that 100 µM of the drug were given to a patient and the drug was completely absorbed (bioavailability factor $F = 1$). A complete (cumulative) urine collection was obtained, and the quantities in parentheses in indicate the amounts of each metabolite and unchanged drug that were recovered. The overall elimination half-life ($t_{1/2}$) for this drug was 2.0 hours ($k = 0.347\ \text{hr}^{-1}$).

Figure 11-1.



Model of a drug that has two major metabolites and is also eliminated by renal excretion.

To determine the renal excretion rate constant, the following relationship is used:

$$\frac{k_e}{k} = \frac{\text{total dose excreted in urine}}{\text{total dose absorbed}} = \frac{D_u^\infty}{FD_0} \qquad (11.4)$$

where D^∞_u is the total amount of unchanged drug recovered in the urine. In this example, k_e is found by proper substitution into Equation 11.4:

$$k_e = (0.347)\ \frac{70}{100} = 0.243\ \text{hr}^{-1}$$

To find the percent of drug eliminated by renal excretion, the following approach may be used:

$$\%\ \text{drug excretion} = \frac{k_e}{k} \times 100 = \frac{0.243}{0.347} \times 100 = 70\%$$

Alternatively, because 70 mg of unchanged drug was recovered from a total dose of 100 mg, the percent of drug excretion may be found by

$$\%\ \text{drug excretion} = \frac{70}{100} \times 100 = 70\%$$

Therefore, the percent of drug metabolized is 100% –70%, or 30%.

For many drugs, the literature has approximate values for the fraction of drug (f_e) excreted unchanged in the urine. In this example, the value of k_e may be estimated from the literature values for the elimination half-life of the drug and f_e. Assuming that the elimination half-life of the drug is 2 hours and f_e is 0.7, then k_e is estimated by Equation 11.5.

$$k_e = f_e k \qquad (11.5)$$

Because $t_{1/2}$ is 2 hours, k is 0.693/2 hr = 0.347 hr^{-1}, and k_e is

$$k_e = (0.7)\,(0.347) = 0.243\ \text{hr}^{-1}$$

Practical Focus

The percentages of drug excretion and metabolism are clinically useful information. If the renal excretion pathway becomes impaired, as in certain kidney disorders, then less drug will be excreted renally and hepatic metabolism may become the primary drug elimination route. The reverse is true if liver function declines. For example, if in the above situation renal excretion becomes totally impaired ($k_e \approx 0$), the elimination $t_{1/2}$ can be determined as follows:

$$k = k_m + k_e$$

but

$$k_e \approx 0$$

Therefore,

$$k \approx k_m \approx 0.104\ \text{hr}^{-1}$$

The new $t_{1/2}$ (after complete renal shutdown) is

$$t_{1/2} = \frac{0.693}{0.104} = 6.7\ \text{hr}$$

In this example, renal impairment caused the drug elimination $t_{1/2}$ to be prolonged from 2 to 6.7 hours. Clinically, the dosage of

this drug must be lowered to prevent the accumulation of toxic drug levels. Methods for adjusting the dose for renal impairment are discussed in .

HEPATIC CLEARANCE

The clearance concept may be applied to any organ and is used as a measure of drug elimination drug by the organ (see also). *Hepatic clearance* may be defined as the volume of blood that perfuses the liver and is cleared of drug per unit of time. As discussed in , total body clearance is composed of all the clearances in the body:

$$Cl_T = Cl_{nr} + Cl_r \qquad (11.6)$$

where Cl_T is total body clearance, Cl_{nr} is nonrenal clearance (often equated with hepatic clearance, Cl_h), and Cl_r is renal clearance. Hepatic clearance (Cl_h) is also equal to total body clearance (Cl_T) minus renal clearance (Cl_R) assuming no other organ metabolism, as shown by rearranging Equation 11.6 to

$$Cl_h = Cl_T - Cl_R \qquad (11.6a)$$

Examples

1. The total body clearance for a drug is 15 mL/min/kg. Renal clearance accounts for 10 mL/min/kg. What is the hepatic clearance for the drug?

Solution

$$\text{Hepatic clearance} = 15 - 10 = 5\,\text{mL/min/kg}$$

Sometimes the renal clearance is not known, in which case hepatic clearance and renal clearance may be calculated from the percent of intact drug recovered in the urine.

2. The total body clearance of a drug is 10 mL/min/kg. The renal clearance is not known. From a urinary drug excretion study, 60% of the drug is recovered intact and 40% is recovered as metabolites. What is the hepatic clearance for the drug, assuming that metabolism occurs in the liver?

Solution

$$\text{Hepatic clearance} = \text{total body clearance} \times (1 - f_e) \qquad (11.7)$$

where f_e = percent of intact drug recovered in the urine.

$$\text{Hepatic clearance} = 10 \times (1 - 0.6) = 4\,\text{mL/min/kg}$$

In this example, the metabolites are recovered completely and hepatic clearance may be obtained as total body clearance times the percent of dose recovered as metabolites. Often, the metabolites are not completely recovered, thus precluding the accuracy of this approach. In this case, hepatic clearance is estimated as the difference between body clearance and renal clearance.

Extrahepatic Metabolism

A few drugs (eg, nitroglycerin) are metabolized extensively outside the liver. This is known as *extrahepaticmetabolism*. A simple way to assess extrahepatic metabolism is to calculate hepatic (metabolic) clearance of the drug.

EXAMPLES

1. Morphine clearance, Cl_T, for a 75-kg male patient is 1800 mL/min. After an oral dose, 4% of the drug is excreted unchanged in the urine (f_e = 0.04). The fraction of drug absorbed after an oral dose of morphine sulfate is 24% (F = 0.24). Hepatic blood flow is about 1500 mL/min. Does morphine have any extrahepatic metabolism?

Solution

Since f_e = 0.04, renal clearance $Cl_r = 0.04Cl_T$ and nonrenal clearance $Cl_{nr} = (1 - 0.04)\,Cl_T = 0.96Cl_T$. Therefore, Cl_{nr} = 0.96 x 1800 mL/min = 1728 mL/min. Since hepatic blood flow is about 1500 mL/min, the drug appears to be metabolized faster than the rate of hepatic blood flow. Thus, at least some of the drug must be metabolized outside the liver. The low fraction of drug absorbed after an oral dose indicates that much of the drug is metabolized before reaching the systemic circulation.

2. Flutamide (Eulexin, Schering), used to treat prostate cancer, is rapidly metabolized to an active metabolite, α-hydroxyflutamide in humans. The steady-state level is 51 ng/mL (range 24–78 ng/mL) after oral multiple doses of 250 mg of flutamide given 3 times daily or every 8 hours (manufacturer-supplied information). Calculate the total body clearance and hepatic clearance assuming that flutamide is 90% metabolized, and is completely (100%) absorbed.

Solution

From and , total body clearance, Cl_T, can be calculated by

$$Cl_{\mathrm{T}} = \frac{FD_0}{C_{\mathrm{av}}^{\infty}\tau}$$

$$Cl_{\mathrm{T}} = \frac{250 \times 1{,}000{,}000}{51 \times 8} = 6.127 \times 10^5\ \mathrm{mL/hr} = 10{,}200\ \mathrm{mL/min}$$

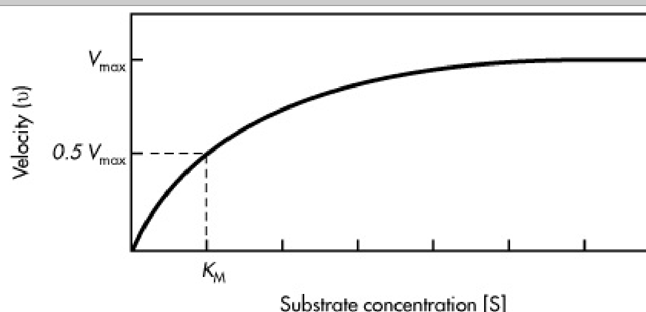
$$Cl_{\mathrm{nr}} = 10{,}200\ \mathrm{mL/min} \times 0.9 = 9180\ \mathrm{mL/min}$$

The Cl_{nr} of flutamide is far greater than the rate of hepatic blood flow (about 1500 mL/min), indicating extensive extrahepatic clearance.

ENZYME KINETICS

The process of *biotransformation* or *metabolism* is the enzymatic conversion of a drug to a metabolite. In the body, the metabolic enzyme concentration is constant at a given site, and the drug (substrate) concentration may vary. When the drug concentration is low relative to the enzyme concentration, there are abundant enzymes to catalyze the reaction, and the rate of metabolism is a first-order process. Saturation of the enzyme occurs when the drug concentration is high, all the enzyme molecules become complexed with drug, and the reaction rate is at a maximum rate; the rate process then becomes a zero-order process (). The *maximum reaction rate* is known as V_{max}, and the substrate or drug concentration at which the reaction occurs at half the maximum rate corresponds to a composite parameter K_M. These two parameters determine the profile of a simple enzyme reaction rate at various drug concentrations. The relationship of these parameters is described by the *Michaelis–Menten* equation.

Figure 11-2.



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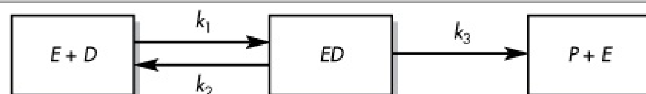
Michaelis–Menten enzyme kinetics. The hyperbolic relationship between enzymatic reaction velocity and the drug substrate concentration is described by Michaelis–Menten enzyme kinetics. The K_M is the substrate concentration when the velocity of the reaction is at $0.5V_{max}$.

Enzyme kinetics generally considers that 1 mole of drug interacts with 1 mole of enzyme to form an enzyme–drug (ie, enzyme–substrate) intermediate. The enzyme–drug intermediate further reacts to yield a reaction product or a drug metabolite (). The rate process for drug metabolism is described by the Michaelis–Menten equation (see), which assumes that the rate of an enzymatic reaction is dependent on the concentrations of both the enzyme and the drug and that an energetically favored drug–enzyme intermediate is initially formed, followed by the formation of the product and regeneration of the enzyme.

Figure 11-3.



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[*D*] = drug; [*E*] = enzyme; [*ED*] = drug–enzyme intermediate; [*P*] = metabolite or product; k_1, k_2, and k_3 = first-order rate constants. Brackets denote concentration.

Each rate constant in is a first-order reaction rate constant. The following rates may be written:

$$\text{Rate of intermediate } [ED] \text{ formation} = k_1[E][D]$$

$$\text{Rate of intermediate } [ED] \text{ decomposition} = k_2[ED] + k_3[ED]$$

$$\frac{d\,[ED]}{dt} = k_1[E][D] - k_2[ED] - k_3[ED]$$

$$\frac{d\,[ED]}{dt} = k_1[E][D] - (k_2 + k_3)[ED] \quad \textbf{(11.8)}$$

By mass balance, the total enzyme concentration $[E_t]$ is the sum of the free enzyme concentration $[E]$ and the enzyme–drug intermediate concentration $[ED]$:

$$[E_t] = [E] + [ED] \quad \textbf{(11.9)}$$

Rearranging,

$$[E] = [E_t] - [ED] \quad \textbf{(11.10)}$$

Substituting for $[E]$ in Equation 11.8,

$$\frac{d[ED]}{dt} = k_1([E_t] - [ED])[D] - (k_2 + k_3)[ED] \quad \textbf{(11.11)}$$

At steady state, the concentration $[ED]$ is constant with respect to time, because the rate of formation of the drug–enzyme intermediate equals the rate of decomposition of the drug–enzyme intermediate. Thus, $d[ED]/dt = 0$, and

$$k_1[E_t][D] = [ED]\{k_1[D] + (k_2 + k_3)\} \quad \textbf{(11.12)}$$

$$[E_t][D] = [ED]\left([D] + \frac{k_2 + k_3}{k_1}\right) \quad \textbf{(11.13)}$$

Let

$$K_M = \frac{k_2 + k_3}{k_1} \quad \textbf{(11.14)}$$

$$[E_t][D] = [ED]([D] + K_M) \quad \textbf{(11.15)}$$

Solving for $[ED]$,

$$[ED] = \frac{[D][E_t]}{[D] + K_M} \quad \textbf{(11.16)}$$

Multiplying by k_3 on both sides,

$$\frac{k_3[E_t][D]}{[D] + K_M} = k_3[ED] \quad \textbf{(11.17)}$$

When all the enzyme is saturated (ie, all the enzyme is in the form of the *ED* intermediate) because of large drug concentration, the reaction is dependent on the availability of free enzyme, and the reaction proceeds at the maximum velocity, V_{max}.

$$V_{max} = k_3[E_t] \quad \textbf{(11.18)}$$

The *velocity* or rate (v) of the reaction is the rate for the formation of the product (metabolite), which is also the forward rate of decomposition of the *ED* intermediate ().

$$v = k_3[ED] \quad \textbf{(11.19)}$$

Therefore, the velocity of metabolism is given by the equation

$$v = \frac{V_{max}[D]}{[D] + K_M} \quad \textbf{(11.20)}$$

Equation 11.20 describes the rate of metabolite formation, or the Michaelis–Menten equation. The maximum velocity (V_{max}) corresponds to the rate when all of the available enzyme is in the form of the drug–enzyme (*ED*) intermediate. At V_{max}, the drug (substrate) concentration is in excess, and the forward reaction, $k_3[ED]$, is dependent on the availability of more free enzyme molecules. The *Michaelis constant,* K_M, is defined as the substrate concentration when the velocity (v) of the reaction is equal to one-half the maximum velocity, or $0.5V_{max}$ (). The K_M is a useful parameter that reveals the concentration of the substrate at which the reaction occurs at half V_{max}. In general, for a drug with a large K_M, a higher concentration will be necessary before saturation is reached.

The Michaelis–Menten equation assumes that one drug molecule is catalyzed sequentially by one enzyme at a time. However, enzymes may catalyze more than one drug molecule (multiple sites) at a time, which may be demonstrated *in vitro*. In the body, drug may be eliminated by enzymatic reactions (metabolism) to one or more metabolites and by the excretion of the unchanged drug via the kidney. In , the Michaelis–Menton equation is used for modeling drug conversion in the body.

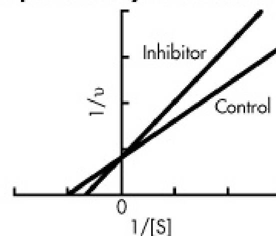
The relationship of the rate of metabolism to the drug concentration is a nonlinear, hyperbolic curve (). To estimate the parameters V_{max} and K_M, the reciprocal of the Michaelis–Menten equation is used to obtain a linear relationship.

$$\frac{1}{v} = \frac{K_M}{V_{max}} \frac{1}{[D]} + \frac{1}{V_{max}} \qquad (11.21)$$

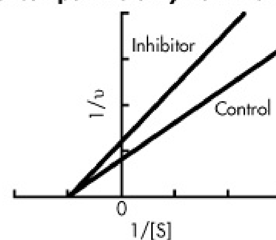
Equation 11.21 is known as the *Lineweaver–Burk equation,* in which K_M and V_{max} may be estimated from a plot of $1/v$ versus $1/[D]$ (). Although the Lineweaver–Burk equation is widely used, other rearrangements of the Michaelis–Menten equation have been used to obtain more accurate estimates of V_{max} and K_M. In , drug concentration $[D]$ is replaced by C, which represents drug concentration in the body.

Figure 11-4.

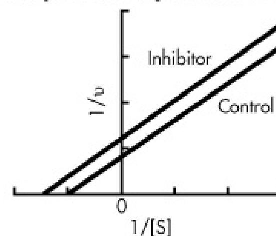
Competitive enzyme inhibition



Noncompetitive enzyme inhibition



Uncompetitive enzyme inhibition



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Lineweaver–Burk plots. The Lineweaver– Burk equation, which is the reciprocal of the Michaelis–Menten equation, is used to obtain estimates of V_{max} and K_M and to distinguish between various types of enzyme inhibition. $[S]$ is the substrate concentration equal to $[D]$ or drug concentration.

Kinetics of Enzyme Inhibition

Many compounds (eg, cimetidine) may inhibit the enzymes that metabolize other drugs in the body. An inhibitor may decrease the rate of drug metabolism by several different mechanisms. The inhibitor may combine with a cofactor such as $NADPH_2$ needed for enzyme activity, interact with the drug or substrate, or interact directly with the enzyme. Enzyme inhibition may be reversible or irreversible. The type of enzyme inhibition is usually classified by enzyme kinetic studies and observing changes in the K_M and V_{max} ().

In the case of *competitive enzyme inhibition*, the inhibitor and drug–substrate compete for the same active center on the enzyme. The drug and the inhibitor may have similar chemical structures. An increase in the drug (substrate) concentration may displace the inhibitor from the enzyme and partially or fully reverse the inhibition. Competitive enzyme inhibition is usually observed by a change in the K_M, but the V_{max} remains the same.

The equation for competitive inhibition is

$$v = \frac{V_{max}[D]}{[D] + K_M\{1 + [I]/k_i\}} \quad (11.22)$$

where $[I]$ is the inhibitor concentration and k_i is the inhibition constant, which is determined experimentally.

In *noncompetitive enzyme inhibition*, the inhibitor may inhibit the enzyme by combining at a site on the enzyme that is different from the active site (ie, an *allostericsite*). In this case, enzyme inhibition depends only on the inhibitor concentration. In noncompetitive enzyme inhibition, K_M is not altered, but V_{max} is lower. Noncompetitive enzyme inhibition cannot be reversed by increasing the drug concentration, because the inhibitor will interact strongly with the enzyme and will not be displaced by the drug.

For a noncompetitive reaction,

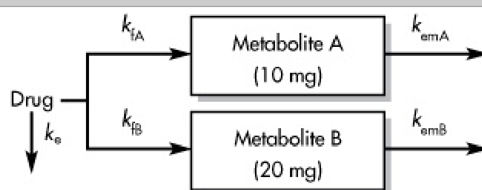
$$v = \frac{V_{max}[D]/\{1 + [I]/k_i\}}{[D] + K_M} \quad (11.23)$$

Other types of enzyme inhibition, such as mixed enzyme inhibition and enzyme uncompetitive inhibition, have been described by observing changes in K_M and V_{max}.

Metabolite Pharmacokinetics for Drugs that Follow a One-Compartment Model

The one-compartment model may be used to estimate simultaneously both metabolite formation and drug decline in the plasma. For example, a drug is given by intravenous bolus injection and the drug is metabolized by more than one parallel pathway (). Assume that both metabolites and parent drug concentrations follow linear (first-order) pharmacokinetics at therapeutic concentrations. The elimination rate constant and the volume of distribution for each metabolite and the parent drug are obtained from curve fitting of the plasma drug concentration–time and each metabolite concentration–time curves. If the metabolites are available, each metabolite should be administered IV separately, to verify the pharmacokinetic parameters independently.

Figure 11-5.



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Parallel pathway for the metabolism of a drug to metabolite *A* and metabolite *B*. Each metabolite may be excreted and/or further metabolized.

The rate of elimination of the metabolite may be faster or slower than the rate of formation of the metabolite from the drug. Generally, metabolites such as glucuronide, sulfate, or glycine conjugates are more polar or more water soluble than the parent drug and will be eliminated more rapidly than the parent drug. Therefore, the rate of elimination of each of these metabolites is more rapid than the rate of formation. In contrast, if the drug is acetylated or metabolized to a less polar or less water-soluble metabolite, then the rate of elimination of the metabolite is slower than the rate of formation of the metabolite. In this case, metabolite accumulation will occur.

Compartment modeling of drug and metabolites is relatively simple and practical. The major shortcoming of compartment modeling is the lack of realistic physiologic information when compared to more sophisticated models that take into account spatial location of enzymes and flow dynamics. However, compartment models are useful for predicting drug and metabolite plasma levels.

For a drug given by IV bolus injection, the metabolite concentration may be predicted from the following equation:

$$C_m = \frac{k_f D_0}{V_m(k_f - k_{em})}\left(e^{-k_{em}t} - e^{-k_f t}\right) \quad (11.24)$$

where C_m is the metabolite concentration in plasma, k_{em} is the metabolite elimination rate constant, k_f is the metabolite formation rate constant, V_m is the metabolite volume of distribution, D_0 is the dose of drug, and V_D is the apparent volume of distribution of drug. All rate constants are first order.

PRACTICE PROBLEM

A drug is eliminated primarily by biotransformation (metabolism) to a glucuronide conjugate and a sulfate conjugate. A single dose (100 mg) of the drug is given by IV bolus injection, and all elimination processes of the drug follow first-order kinetics. The V_D is 10 L and the elimination rate constant for the drug is 0.9 hr^{-1}. The rate constant (k_f) for the formation of the glucuronide

conjugate is 0.6 hr^{-1}, and the rate constant for the formation of the sulfate conjugate is 0.2 hr^{-1}.

a. Predict the drug concentration 1 hour after the dose.

b. Predict the concentration of glucuronide and sulfate metabolites 1 hour after the dose, if the V_m for both metabolites is the same as for the parent drug and the k_{em} for both metabolites is 0.4 hr^{-1}. (*Note:* V_m and k_{em} usually differ between metabolites and parent drug.) In this example, V_m and k_{em} are assumed to be the same, so that the concentration of the two metabolites may be compared by examining the formation constants.

Solution

The plasma drug concentration 1 hour after the dose may be estimated using the following equation for a one-compartment-model, IV bolus administration:

$$C_p = C_p^0 e^{-kt} = \frac{D_0}{V_D} e^{-kt}$$

$$C_m = \frac{100}{10} e^{-(0.9)(1)} = 4.1\,\text{mg/L}$$

The plasma concentrations for the glucuronide and sulfate metabolites 1 hour postdose are estimated after substitution into Equation 11.24.

$$\text{Glucuronide:}\quad C_m = \frac{(0.6)(100)}{10(0.6-0.4)}\left(e^{-(0.4)(1)} - e^{-(0.6)(1)}\right)$$

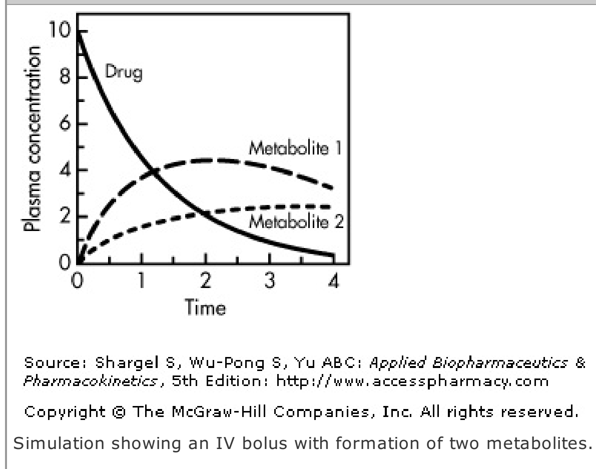
$$C_m = 3.6\,\text{mg/L}$$

$$\text{Sulfate:}\quad C_m = \frac{(0.2)(100)}{10(0.2-0.4)}\left(e^{-(0.4)(1)} - e^{-(0.2)(1)}\right)$$

$$C_m = 1.5\,\text{mg/L}$$

After an IV bolus dose of a drug, the equation describing metabolite concentration formation and elimination by first-order processes is kinetically analogous to drug absorption after oral administration (). Simulated plasma concentration–time curves were generated using Equation 11.24 for the glucuronide and sulfate metabolites, respectively (). The rate constant for the formation of the glucuronide is faster than the rate constant for the formation of the sulfate. Therefore, the time for peak plasma glucuronide concentrations is shorter compared to the time for peak plasma sulfate conjugate concentrations. Equation 11.24 cannot be used if drug metabolism is nonlinear because of enzyme saturation (ie, if metabolism follows Michaelis–Menten kinetics).

Figure 11-6.



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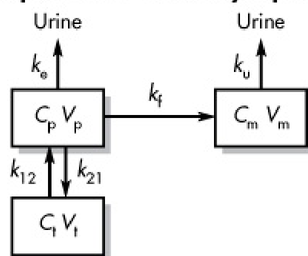
Simulation showing an IV bolus with formation of two metabolites.

Metabolite Pharmacokinetics for Drugs that Follow a Two-Compartment Model

Cephalothin is an antibiotic drug that is metabolized rapidly by hydrolysis in both humans and rabbits. The metabolite desacetylcephalothin has less antibiotic activity than the parent drug. In urine, 18–33% of the drug was recovered as des-acetylcephalothin metabolite in a human. The time course of both the drug and the metabolite may be predicted after a given dose from the distribution kinetics of both the drug and the metabolite. Cephalothin follows a two-compartment model after IV bolus injection in a rabbit, whereas the desacetylcephalothin metabolite follows a one-compartment model (). After a single IV bolus dose of cephalothin (20 mg/kg) to a rabbit, cephalothin declines as a result of excretion and metabolism to desacetylcephalothin. The plasma levels of both cephalothin and desacetylcephalothin may be calculated using equations based on a model with linear metabolism and excretion.

Figure 11-7.



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Pharmacokinetic model of cephalothin and desacetylcephalothin (metabolite) after an IV bolus dose.

The equations for cephalothin plasma and tissue levels are the same as those derived in for a simple two-compartment model, except that the elimination constant k for the drug now consist of $k_e + k_f$, representing excretion and formation constant for metabolite, respectively.

$$C_p = D_0\left[\frac{k_{21} - a}{V_p(b - a)}e^{-at} + \frac{k_{21} - b}{V_p(a - b)}e^{-bt}\right] \quad (11.25)$$

$$C_t = D_0\left[\frac{k_{12}}{V_t(b - a)}e^{-at} + \frac{k_{12}}{V_t(a - b)}e^{-bt}\right] \quad (11.26)$$

$$a + b = k + k_{12} + k_{21} \quad (11.27)$$

$$ab = kk_{21} \quad (11.28)$$

$$k = k_f + k_e \quad (11.29)$$

The equation for metabolite plasma concentration, C_m, is triexponential, with three preexponential coefficients (C_5, C_6, and C_7) calculated from the various kinetic constants, V_m, and the dose of the drug.

$$C_m = C_5e^{-k_u t} + C_6e^{-at} + C_7e^{-bt} \quad (11.30)$$

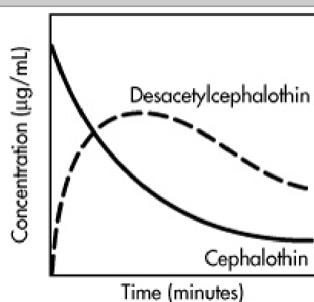
$$C_5 = \frac{k_f D_0 k_{21} - k_f D_0 k_u}{V_m(b - k_u)(a - k_u)} \quad (11.31)$$

$$C_6 = \frac{k_f D_0 k_{21} - k_f D_0 a}{V_m(b - a)(k_u - a)} \quad (11.32)$$

$$C_7 = \frac{k_f D_0 k_{21} - k_f D_0 b}{V_m(k_u - b)(a - b)} \quad (11.33)$$

For example, after the IV administration of cephalothin to a rabbit, both metabolite and plasma cephalothin concentration may be fitted to Equations 11.25 and 11.30 simultaneously (), with the following parameters obtained using a regression computer program (all rate constants in min^{-1}).

Figure 11-8.



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Formation of desacetylcephalothin from cephalothin in the rabbit after an IV bolus dose of cephalothin.

$k_{12} = 0.052$ $k_{21} = 0.009$ $V_m = 285\ \text{mL/kg}$

$k_u = 0.079$ $k = 0.067$ $D_0 = 20\ \text{mg/kg}$

$k_f = 0.045$ $V_p = 548\ \text{mL/kg}$ $k_e = 0.022$

ANATOMY AND PHYSIOLOGY OF THE LIVER

The liver is the major organ responsible for drug metabolism. However, intestinal tissues, lung, kidney, and skin also contain appreciable amounts of biotransformation enzymes, as reflected by animal data ().

Table 11.1 Distribution of Cytochrome P-450 and Glutathione S-Transferase in the Rat

Tissue	CYT P-450[a]	GSH Transferase[b]
Liver	0.73	599
Lung	0.046	61
Kidney	0.135	88
Small intestine	0.042	103
Colon	0.016	_[c]
Skin	0.12	_[c]
Adrenal gland	0.5	308

[a]Cytochrome P-450, nmole/mg microsome protein.

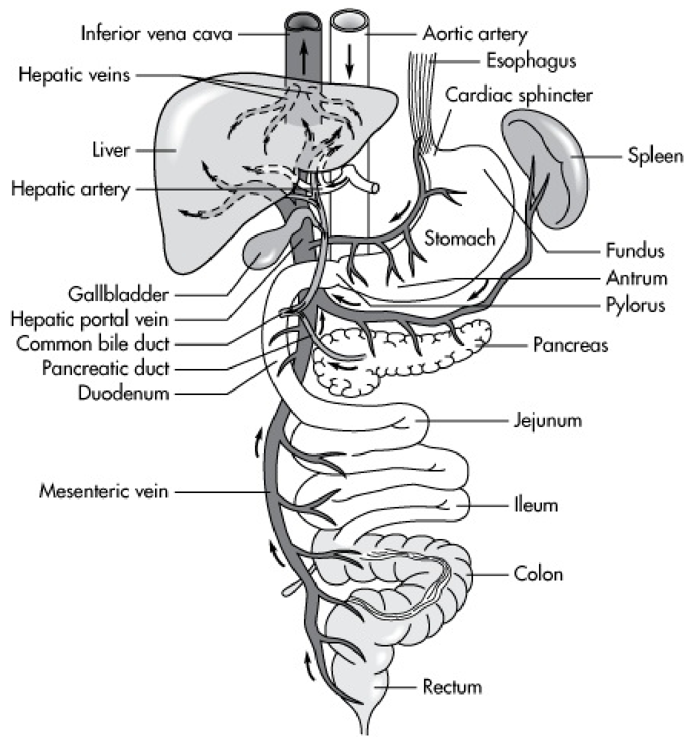
[b]Glutathione S-transferase, nmole conjugate formed/min/mg cytosolic protein.

[c]Values not available.

Adapted from , with permission.

The liver is both a synthesizing and an excreting organ. The basic unit of liver is the liver lobule, which contains parenchymal cells, a network of interconnected lymph and blood vessels. The liver consists of large right and left lobes that merge in the middle. The liver is perfused by blood from the hepatic artery; in addition, the large hepatic portal vein that collects blood from various segments of the GI tract also perfuses the liver (). The hepatic artery carries oxygen to the liver and accounts for about 25% of the liver blood supply. The hepatic portal vein carries nutrients to the liver and accounts for about 75% of liver blood flow. The terminal branches of the hepatic artery and portal vein fuse within the liver and mix with the large vascular capillaries known as *sinusoids* (). Blood leaves the liver via the hepatic vein, which empties into the vena cava (). The liver also secretes bile acids within the liver lobes, which flow through a network of channels and eventually empty into the common bile duct (and). The common bile duct drains bile and biliary excretion products from both lobes into the gallbladder.

Figure 11-9.



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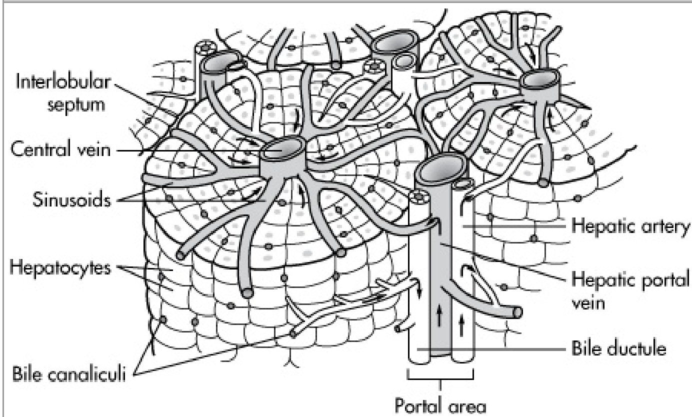
The large hepatic portal vein that collects blood from various segments of the GI tract also perfuses the liver.

Figure 11-10.



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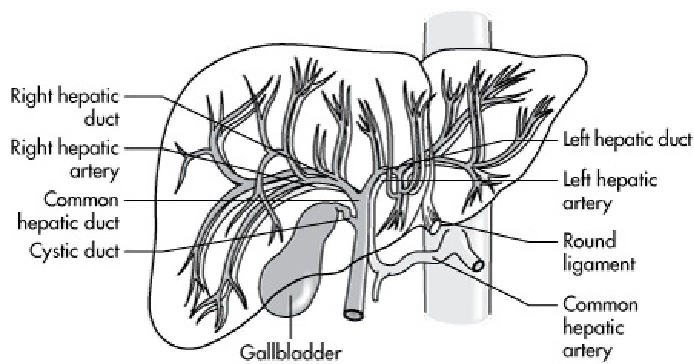
Intrahepatic distribution of the hepatic and portal veins.

Figure 11-11.



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Intrahepatic distribution of the hepatic artery, portal vein, and biliary ducts.

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Sinusoids are blood vessels that form a large reservoir of blood, facilitating drug and nutrient removal before the blood enters the general circulation. The sinusoids are lined with endothelial cells, or *Kupffer cells*. Kupffer cells are phagocytic tissue macrophages that are part of the *reticuloendothelial system* (RES). Kupffer cells engulf worn-out red blood cells and foreign material.

Drug metabolism in the liver has been shown to be *flow* and *site dependent*. Some enzymes are reached only when blood flow travels from a given direction. The quantity of enzyme involved in metabolizing drug is not uniform throughout the liver. Consequently, changes in blood flow can greatly affect the fraction of drug metabolized. Clinically, hepatic diseases, such as cirrhosis, can cause tissue fibrosis, necrosis, and hepatic shunt, resulting in changing blood flow and changing bioavailability of drugs (see). For this reason, and in part because of genetic differences in enzyme levels among different subjects and environmental factors, the half-lives of drugs eliminated by drug metabolism are generally very variable.

A pharmacokinetic model simulating hepatic metabolism should involve several elements, including the heterogenicity of the liver, the hydrodynamics of hepatic blood flow, the nonlinear kinetics of drug metabolism, and any unusual or pathologic condition of the subject. Most models in practical use are simple or incomplete models, however, because insufficient information is available about an individual patient. For example, the average hepatic blood flow is usually cited as 1.3–1.5 L/min. Actually, hepatic arterial blood flow and hepatic venous (portal) blood enter the liver at different flow rates, and their drug concentrations are different. It is possible that a toxic metabolite may be transiently higher in some liver tissues and not in others. The pharmacokinetic challenge is to build models that predict regional (organ) changes from easily accessible data, such as plasma drug concentration.

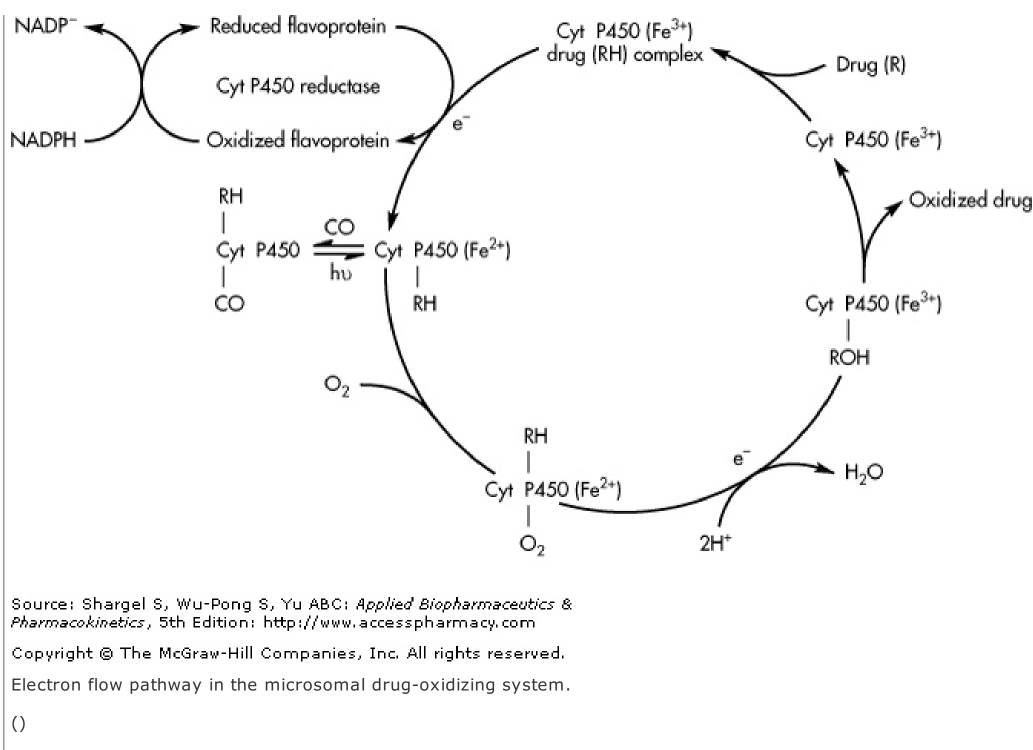
HEPATIC ENZYMES INVOLVED IN THE BIOTRANSFORMATION OF DRUGS

Mixed-Function Oxidases

The liver is the major site of drug metabolism, and the type of metabolism is based on the reaction involved. Oxidation, reduction, hydrolysis, and conjugation are the most common reactions, as discussed under phase I and phase II reactions in the next two sections. The enzymes responsible for oxidation and reduction of drugs (*xenobiotics*) and certain natural metabolites, such as steroids, are monoxygenase enzymes known as *mixed-function oxidases* (MFOs). The hepatic parenchymal cells contain MFOs in association with the *endoplasmic reticulum,* a network of lipoprotein membranes within the cytoplasm and continuous with the cellular and nuclear membranes. If hepatic parenchymal cells are fragmented and differentially centrifuged in an ultracentrifuge, a microsomal fraction, or *microsome*, is obtained from the postmitochondrial supernatant. The microsomal fraction contains fragments of the endoplasmic reticulum.

The mixed-function oxidase enzymes are structural enzymes that constitute an electron-transport system that requires reduced NADPH ($NADPH_2$), molecular oxygen, cytochrome P-450, NADPH–cytochrome P-450 reductase, and phospholipid. The phospholipid is involved in the binding of the drug molecule to the cytochrome P-450 and coupling the NADPH–cytochrome P-450 reductase to the cytochrome P-450. Cytochrome P-450 is a heme protein with iron protoporphyrin IX as the prosthetic group. Cytochrome P-450 is the terminal component of an electron-transfer system in the endoplasmic reticulum and acts as both an oxygen- and a substrate-binding locus for drugs and endogenous substrates in conjunction with a flavoprotein reductase, NADPH–cytochrome P-450 reductase. Many lipid-soluble drugs bind to cytochrome P-450, resulting in oxidation (or reduction) of the drug. Cytochrome P-450 consists of closely related isoenzymes (*isozymes*) that differ somewhat in amino acid sequence and drug specificity (see). A general scheme for MFO drug oxidation is described in .

Figure 11-12.



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Electron flow pathway in the microsomal drug-oxidizing system.

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DRUG BIOTRANSFORMATION REACTIONS

The hepatic biotransformation enzymes play an important role in the inactivation and subsequent elimination of drugs that are not easily cleared through the kidney. For these drugs—theophylline, phenytoin, acetaminophen, and others—there is a direct relationship between the rate of drug metabolism (*biotransformation*) and the elimination half-life for the drug.

For most biotransformation reactions, the metabolite of the drug is more polar than the parent compound. The conversion of a drug to a more polar metabolite enables the drug to be eliminated more quickly than if the drug remained lipid soluble. A lipid-soluble drug crosses cell membranes and is easily reabsorbed by the renal tubular cells, exhibiting a consequent tendency to remain in the body. In contrast, the more polar metabolite does not cross cell membranes easily, is filtered through the glomerulus, is not readily reabsorbed, and is more rapidly excreted in the urine.

Both the nature of the drug and the route of administration may influence the type of drug metabolite formed. For example, isoproterenol given orally forms a sulfate conjugate in the gastrointestinal mucosal cells, whereas after IV administration, it forms the 3-O-methylated metabolite due to S-adenosylmethionine and catechol-O-methyltransferase. Azo drugs such as sulfasalazine are poorly absorbed after oral administration. However, the azo group of sulfasalazine is cleaved by the intestinal microflora, producing 5-aminosalicylic acid and sulfapyridine, which is absorbed in the lower bowel.

The biotransformation of drugs may be classified according to the pharmacologic activity of the metabolite or according to the biochemical mechanism for each biotransformation reaction. For most drugs, biotransformation results in the formation of a more polar metabolite that is pharmacologically inactive and is eliminated more rapidly than the parent drug ().

Table 11.2 Biotransformation Reactions and Pharmacologic Activity of the Metabolite

Reaction		Example
Active Drug to Inactive Metabolite		
Amphetamine	Deamination →	Phenylacetone
Phenobarbital	Hydroxylation →	Hydroxyphenobarbital
Active Drug to Active Metabolite		
Codeine	Demethylation →	Morphine
Procainamide	Acetylation →	N-acetylprocainamide
Phenylbutazone	Hydroxylation →	Oxyphenbutazone
Inactive Drug to Active Metabolite		
Hetacillin	Hydrolysis →	Ampicillin
Sulfasalazine	Azoreduction →	Sulfapyridine + 5-aminosalicylic acid
Active Drug to Reactive Intermediate		
Acetaminophen	Aromatic Hydroxylation →	Reactive metabolite (hepatic necrosis)

Benzo[a]pyrene		Reactive metabolite (carcinogenic)

For some drugs the metabolite may be pharmacologically active or produce toxic effects. *Prodrugs* are inactive and must be biotransformed in the body to metabolites that have pharmacologic activity. Initially, prodrugs were discovered by serendipity, as in the case of prontosil, which is reduced to the antibacterial agent sulfanilamide. More recently, prodrugs have been intentionally designed to improve drug stability, increase systemic drug absorption, or to prolong the duration of activity. For example, the antiparkinsonian agent levodopa, crosses the blood–brain barrier and is then decarboxylated in the brain to L-dopamine, an active neurotransmitter. L-Dopamine does not easily penetrate the blood–brain barrier into the brain and therefore cannot be used as a therapeutic agent.

PATHWAYS OF DRUG BIOTRANSFORMATION

Pathways of drug biotransformation may be divided into two major groups of reactions, phase I and phase II reactions. *Phase I,* or *asyntheticreactions*, include oxidation, reduction, and hydrolysis. *Phase II*, or *synthetic* reactions, include conjugations. A partial list of these reactions is presented in . In addition, a number of drugs that resemble natural biochemical molecules are able to utilize the metabolic pathways for normal body compounds. For example, isoproterenol is methylated by catechol O-methyl transferase (COMT), and amphetamine is deaminated by monamine oxidase (MAO). Both COMT and MAO are enzymes involved in the metabolism of noradrenaline.

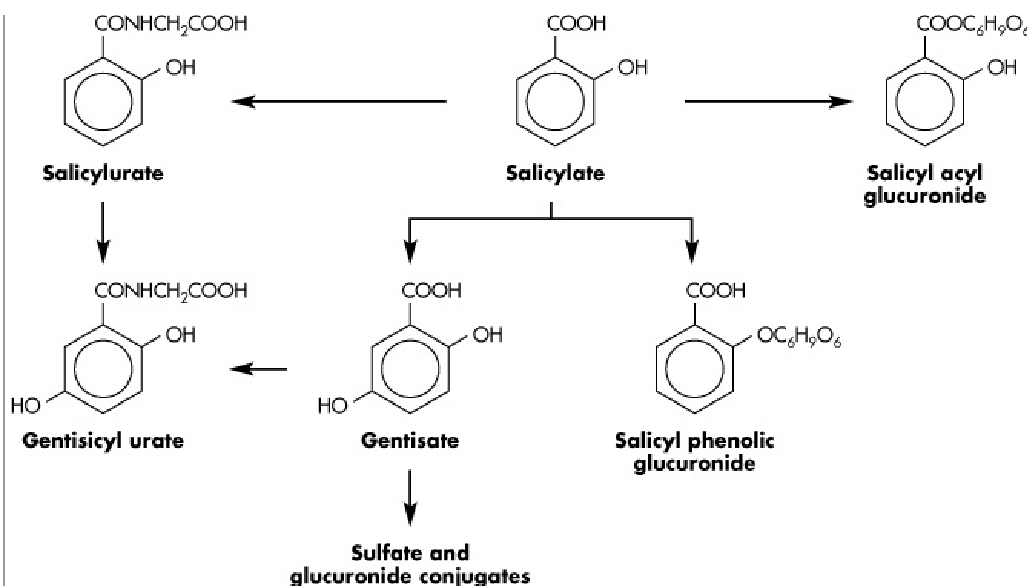
Table 11.3 Some Common Drug Biotransformation Reactions

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

Phase I Reactions

Usually, phase I biotransformation reactions occur first and introduce or expose a functional group on the drug molecules. For example, oxygen is introduced into the phenyl group on phenylbutazone by aromatic hydroxylation to form oxyphenbutazone, a more polar metabolite. Codeine is demethylated to form morphine. In addition, the hydrolysis of esters, such as aspirin or benzocaine, will yield more polar products, such as salicylic acid and *p*-aminobenzoic acid, respectively. For some compounds, such as acetaminophen, benzo[a]pyrene, and other drugs containing aromatic rings, reactive intermediates, such as epoxides, are formed during the hydroxylation reaction. These aromatic epoxides are highly reactive and will react with macromolecules, possibly causing liver necrosis (acetaminophen) or cancer (benzo[a]pyrene). The biotransformation of salicylic acid () demonstrates the variety of possible metabolites that may be formed. It should be noted that salicylic acid is also conjugated directly (phase II reaction) without a preceding Phase I reaction.

Figure 11-13.



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Biotransformation of salicylic acid.

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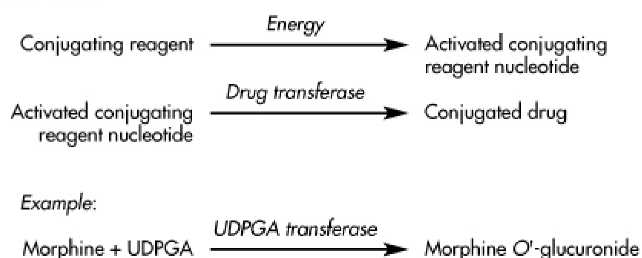
Conjugation (Phase II) Reactions

Once a polar constituent is revealed or placed into the molecule, a phase II or conjugation reaction may occur. Common examples include the conjugation of salicyclic acid with glycine to form salicyluric acid or glucuronic acid to form salicylglucuronide ().

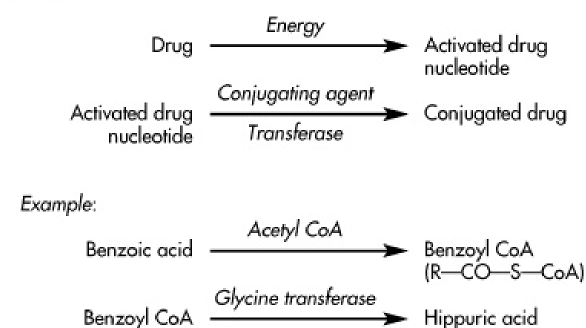
Conjugation reactions use conjugating reagents, which are derived from biochemical compounds involved in carbohydrate, fat, and protein metabolism. These reactions may include an active, high-energy form of the conjugating agent, such as uridine diphosphoglucuronic acid (UDPGA), acetyl CoA, 3'-phosphoadenosine-5'-phosphosulfate (PAPS), or S-adenosylmethionine (SAM), which, in the presence of the appropriate transferase enzyme, combines with the drug to form the conjugate. Conversely, the drug may be activated to a high-energy compound that then reacts with the conjugating agent in the presence of a transferase enzyme (). The major conjugation (phase II) reactions are listed in and .

Figure 11-14.

Scheme A



Scheme B



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General scheme for phase II reactions.

Table 11.4 Phase II Conjugation Reactions

Conjugation Reaction	Conjugating Agent	High-Energy Intermediate	Functional Groups Combined with
Glucuronidation	Glucuronic acid	UDPGA[a]	—OH, —COOH, $—NH_2$, SH
Sulfation	Sulfate	PAPS[b]	—OH, $—NH_2$
Amino acid conjugation	Glycine [c]	Coenzyme A thioesters	—COOH
Acetylation	Acetyl CoA	Acetyl CoA	—OH, $—NH_2$
Methylation	CH_3 from S-adenosylmethionine	S-adenosylmethionine	—OH, $—NH_2$
Glutathione (mercapturine acid conjugation)	Glutathione	Arene oxides, epoxides	Aryl halides, epoxides, arene oxides

[a]UDPGA = uridine diphosphoglucuronic acid.

[b]PAPS = 3'-phosphoadenosine-5'-phosphosulfate.

[c] Glycine conjugates are also known as hippurates.

Some of the conjugation reactions may have limited capacity at high drug concentrations, leading to nonlinear drug metabolism. In most cases, enzyme activity follows first-order kinetics with low drug (substrate) concentrations. At high doses, the drug concentration may rise above the Michaelis–Menten rate constant (K_M), and the reaction rate approaches zero order (V_{max}). Glucuronidation reactions have a high capacity and may demonstrate nonlinear (saturation) kinetics at very high drug concentrations. In contrast, glycine, sulfate, and glutathione conjugations show lesser capacity and demonstrate nonlinear kinetics at therapeutic drug concentrations (). The limited capacity of certain conjugation pathways may be due to several factors, including (1) limited amount of the conjugate transferase, (2) limited ability to synthesize the active nucleotide intermediate, or (3) limited amount of conjugating agent, such as glycine.

In addition, the N-acetylated conjugation reaction shows genetic polymorphism: for certain drugs, the human population may be divided into fast and slow acetylators. Finally, some of these conjugation reactions may be diminished or defective in cases of inborn errors of metabolism.

Glucuronidation and sulfate conjugation are very common Phase II reactions that result in water-soluble metabolites being rapidly excreted in bile (for some high-molecular-weight glucuronides) and/or urine. Acetylation and mercapturic acid synthesis are conjugation reactions that are often implicated in the toxicity of the drug; they will now be discussed more fully.

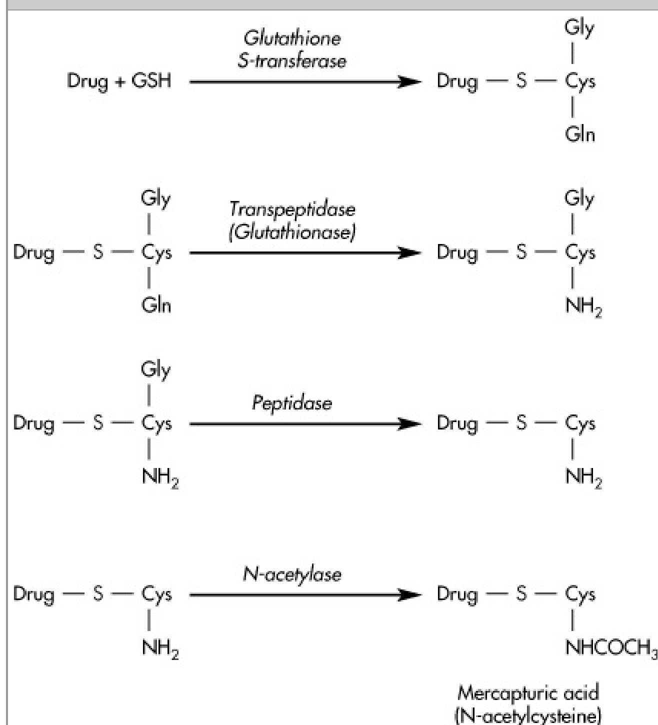
Acetylation

The acetylation reaction is an important conjugation reaction for several reasons. First, the acetylated product is usually less polar than the parent drug. The acetylation of such drugs as sulfanilamide, sulfadiazine, and sulfisoxazole produces metabolites that are less water soluble and that in sufficient concentration precipitate in the kidney tubules, causing kidney damage and crystaluria. In addition, a less polar metabolite is reabsorbed in the renal tubule and has a longer elimination half-life. For example, procainamide (elimination half-life of 3 to 4 hours) has an acetylated metabolite, N-acetylprocainamide, which is biologically active and has an elimination half-life of 6 to 7 hours. Lastly, the N-acetyltransferase enzyme responsible for catalyzing the acetylation of isoniazid and other drugs demonstrates a genetic polymorphism. Two distinct subpopulations have been observed to inactivate isoniazid, including the "slow inactivators" and the "rapid inactivators" (). Therefore, the former group may demonstrate an adverse effect of isoniazide, such as peripheral neuritis, due to the longer elimination half-life and accumulation of the drug.

Glutathione and Mercapturic Acid Conjugation

Glutathione (GSH) is a tripeptide of glutamyl-cysteine-glycine that is involved in many important biochemical reactions. GSH is important in the detoxification of reactive oxygen intermediates into nonreactive metabolites and is the main intracellular molecule for protection of the cell against reactive electrophilic compounds. Through the nucleophilic sulfhydryl group of the cysteine residue, GSH reacts nonenzymatically and enzymatically via the enzyme glutathione S-transferase, with reactive electrophilic oxygen intermediates of certain drugs, particularly aromatic hydrocarbons formed during oxidative biotransformation. The resulting GSH conjugates are precursors for a group of drug conjugates known as mercapturic acid (N-acetylcysteine) derivatives. The formation of a mercapturic acid conjugate is shown in .

Figure 11-15.



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Mercapturic acid conjugation.

The enzymatic formation of GSH conjugates is saturable. High doses of drugs such as acetaminophen (APAP) may form electrophilic intermediates and deplete GSH in the cell. The reactive intermediate covalently bonds to hepatic cellular macromolecules, resulting in cellular injury and necrosis. The suggested antidote for intoxication (overdose) of acetaminophen is the administration of N-acetylcysteine (Mucomyst), a drug molecule that contains available sulfhydryl (R–SH) groups.

Metabolism of Enantiomers

Many drugs are given as mixtures of stereoisomers. Each isomeric form may have different pharmacologic actions and different side effects. For example, the natural thyroid hormone is *l*-thyroxine; whereas the synthetic *d* enantiomer, *d*-thyroxine, lowers cholesterol but does not stimulate basal metabolic rate like the *l* form. Since enzymes as well as drug receptors demonstrate

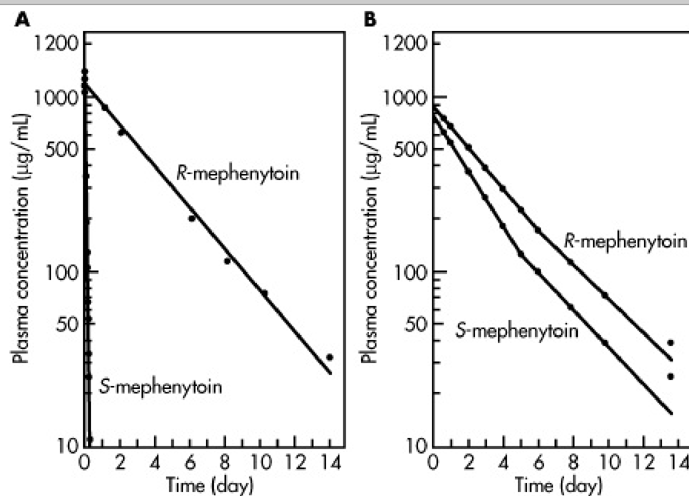
stereoselectivity, isomers of drugs may show differences in biotransformation and pharmacokinetics (). With improved techniques for isolating mixtures of enantiomers, many drugs are now available as pure enantiomers. The rate of drug metabolism and the extent of drug protein binding are often different for each stereoisomer. For example, (S)-(+)disopyramide is more highly bound in humans than (R)-(−)disopyramide. Carprofen, a nonsteroidal anti-inflammatory drug, also exists in both an S and an R configuration. The predominate activity lies in the S configuration. The clearance of the S-carprofen glucuronide through the kidney was found to be faster than that of the R form, 36 versus 26 mL/min (). A list of some common drugs with enantiomers is given in . A review () shows that of 475 semisynthetic drugs derived from natural sources, 469 were enantiomers, indicating that the biologic systems are very stereospecific.

Table 11.5 Common Drug Enantiomers

Atropine	Brompheniramine	Cocaine
Disopyramide	Doxylamine	Ephedrine
Propranolol	Nadolol	Verapamil
Tocainide	Propoxyphene	Morphine
Warfarin	Thyroxine	Flecainide
Ibuprofen	Atenolol	Subutamol
Metoprolol	Terbutaline	

The anticonvulsant drug mephenytoin is another example of a drug that exists as R and S enantiomers. Both enantiomers are metabolized by hydroxylation in humans (). After an oral dose of 300 mg of the racemic or mixed form, the plasma concentration of the S form in most subjects was only about 25% of that of the R form. The elimination half-life of the S form (2.13 hours) was much faster than that of the R form (76 hours) in these subjects (). The severity of the sedative side effect of this drug was also less in subjects with rapid metabolism. Hydroxylation reduces the lipophilicity of the metabolite and may reduce the partition of the metabolite into the CNS. Interestingly, some subjects do not metabolize the S form of mephenytoin well, and the severity of sedation in these subjects was increased. The plasma level of the S form was much higher in these subjects (). The variation in metabolic rate was attributed to genetically controlled enzymatic differences within the population.

Figure 11-16.



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Plasma level of mephenytoin after 300-mg oral dose of the recemic drug. **A.** Efficient metabolizer. **B.** Poor metabolizer. The plasma levels of the *R* and *S* form are different due to different rates of metabolism of the two isomers.

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Regioselectivity

In addition to stereoselectivity, biotransformation enzymes may also be regioselective. In this case, the enzymes catalyze a reaction that is specific for a particular region in the drug molecule. For example, isoproterenol is methylated via catechol-O-methyltransferase and S-adenosylmethionine primarily in the meta position, resulting in a 3-O-methylated metabolite. Very little methylation occurs at the hydroxyl group in the para position.

Species Differences in Hepatic Biotransformation Enzymes

The biotransformation activity of hepatic enzymes can be affected by a variety of factors (). During the early preclinical phase of drug development, drug metabolism studies attempt to identify the major metabolic pathways of a new drug through the use of animal models. For most drugs, different animal species may have different metabolic pathways. For example, amphetamine is

mainly hydroxylated in rats, whereas in humans and dogs it is largely deaminated. In many cases, the rates of metabolism may differ among different animal species even though the biotransformation pathways are the same. In other cases, a specific pathway may be absent in a particular species. Generally, the researcher tries to find the best animal model that will be predictive of the metabolic profile in humans.

Table 11.6 Sources of Variation in Intrinsic Clearance
Genetic factors
Genetic differences within population
Racial differences among different populations
Environmental factors and drug interactions
Enzyme induction
Enzyme inhibition
Physiologic conditions
Age
Gender
Diet/nutrition
Pathophysiology
Drug dosage regimen
Route of drug administration
Dose dependent (nonlinear) pharmacokinetics

Variation of Biotransformation Enzymes

Variation in metabolism may be caused by a number of biologic and environmental variables (). *Pharmacogenetics* is the study of genetic differences in drug elimination (). For example, the N-acetylation of isoniazid has been found to be genetically determined, with at least two identifiable groups, including rapid and slow acetylators (). The difference is referred to as *genetic polymorphism*. Individuals with slow acetylation are prone to isoniazid-induced neurotoxicity. Procainamide and hydralazine are other drugs that are acetylated and demonstrate genetic polymorphism.

Another example of genetic differences in drug metabolism is glucose 6-phosphate-dehydrogenase deficiency, which is observed in approximately 10% of African Americans. A well-documented example of genetic polymorphism occurred with phenytoin (). Two phenotypes, EM (efficient metabolizer) and PM (poor metabolizer), were identified in the study population. The PM frequency in Caucasians was about 4% and among Japanese was about 16%. Variation in metabolic rate was also observed with mephobarbital. The incidence of side effects was higher in Japanese subjects, possibly due to a slower oxidative metabolism. Metabolism difference of propranolol due to genetic difference among Chinese populations was also reported (). Some variations in metabolism may be also related to geographic differences rather than racial differences ().

Besides genetic influence, the basal level of enzyme activity may be altered by environmental factors and exposure to chemicals. Shorter theophylline elimination half-life due to smoking was observed in smoking subjects. Apparently, the aromatic hydrocarbons, such as benzpyrene, that are released during smoking stimulate the enzymes involved in theophylline metabolism. Young children are also known to eliminate theophylline more quickly. Phenobarbital is a potent inducer of a wider variety of hepatic enzymes. Polycyclic hydrocarbons such as 3-methylcholanthrene and benzpyrene also induce hepatic enzyme formation. These compounds are carcinogenic.

Hepatic enzyme activity may also be inhibited by a variety of agents including carbon monoxide, heavy metals, and certain imidazole drugs such as cimetidine. Enzyme inhibition by cimetidine may lead to higher plasma levels and longer elimination of co-administered phenytoin or theophylline. The physiologic condition of the host—including age, gender, nutrition, diet, and pathophysiology—also affects the level of hepatic enzyme activities.

Genetic Variation of Cytochrome P-450 (CYP) Isozymes

The most important enzymes accounting for variation in phase I metabolism of drugs is the cytochrome P-450 enzyme group, which exists in many forms among individuals because of genetic differences (; ; ; see also). Initially, the cytochrome P-450 enzymes were identified according to the substrate that was biotransformed. More recently, the genes encoding many of these enzymes have been identified. Multiforms of cytochrome P-450 are referred to as *isozymes,* and are classified into families (originally denoted by Roman numerals: I, II, III, etc) and subfamilies (denoted by A, B, C, etc) based on the similarity of the amino acid sequences of the isozymes. If an isozyme amino acid sequence is 60% similar or more, it is placed within a family. Within the family, isozymes with amino acid sequences of 70% or more similarity are placed into a subfamily, and an Arabic number follows for further classification.

The substrate specificities of the P-450 enzymes appear to be due to the nature of the amino acid residues, the size of the amino acid side chain, and the polarity and charge of the amino acids (). The individual gene is denoted by an Arabic number (last number) after the subfamily. For example, cytochrome P-450IA2 is involved in the oxidation of caffeine and cytochrome; P-450IID6 is involved in the oxidation of drugs, such as codeine, propranolol, and dextromethorphan. The well-known cytochrome P-450IID6 is responsible for debrisoquine metabolism among individuals showing genetic polymorphism. The vinca alkaloids used in cancer treatment have shown great inter- and intraindividual variabilities. P-450IIIA cytochromes are known to be involved in

the metabolism of vindesine, vinblastine, and other vinca alkaloids (). Failing to recognize variations in drug clearance in cancer chemotherapy may result in greater toxicity or even therapeutic failure.

There are now at least eight families of cytochrome isozymes known in humans and animals. Cytochrome P-450 I–III (CYP 1–3) is best known for metabolizing clinically useful drugs in humans. Variation in isozyme distribution and content in the hepatocytes may affect intrinsic hepatic clearance of a drug. The levels and activities of the cytochrome P-450 isozymes differ among individuals as a result of genetic and environmental factors. Clinically, it is important to look for evidence of unusual metabolic profiles in patients before dosing. Pharmacokinetic experiments using a "marker" drug such as the antipyrine or dextromethorphan may be used to determine if the intrinsic hepatic clearance of the patient is significantly different from that of an average subject.

and have reviewed the nomenclature of the P-450 family of enzymes. A new nomenclature starting with CYP as the root denoting cytochrome P-450, and an Arabic number now replaces the Roman numeral (). The CYP3A subfamily of CYP3 appears to be responsible for the metabolism of a large number of structurally diverse endogenous agents (eg, testosterone, cortisol, progesterone, estradiol) and xenobiotics (eg, nifedipine, lovastatin, midazolam, terfenadine, erythromycin).

Table 11.7 Comparison of P-450 Nomenclatures Currently in Use

P-450 Gene Family/Subfamily	New Nomenclature
P-450I	CYP1
P-450IIA	CYP2A
P-450IIB	CYP2B
P-450IIC	CYP2C
P-450IID	CYP2D
P-450IIE	CYP2E
P-450III	CYP3
P-450IV	CYP4

Sources: and .

The metabolism of debrisoquin is polymorphic in the population, with some individuals having extensive metabolism (EM) and other individuals having poor metabolism (PM). Those individuals who are PM lack functional CYP2D6 (P-450IID6). In EM individuals, quinidine will block CYP2D6 so that genotypic EM individuals appear to be phenotypic PM individuals (). Some drugs metabolized by CYP2D6 (P-450IID6) are codeine, flecainide, dextromethorphan, imipramine, and other cyclic antidepressants that undergo ring hydroxylation. The inability to metabolize substrates for CYP2D6 results in increased plasma concentrations of the parent drug in PM individuals.

Drug Interactions Involving Drug Metabolism

The enzymes involved in the metabolism of drugs may be altered by diet and the co-administration of other drugs and chemicals. *Enzyme induction* is a drug- or chemical-stimulated increase in enzyme activity, usually due to an increase in the amount of enzyme present. Enzyme induction usually requires some onset time for the synthesis of enzyme protein. For example, rifampin induction occurs within 2 days, while phenobarbital induction takes about 1 week to occur. Enzyme induction for carbmazepine begins after 3 to 5 days and is not complete for approximately 1 month or longer. Smoking can change the rate of metabolism of many cyclic antidepressant drugs (CAD) through enzyme induction (). Agents that induce enzymes include aromatic hydrocarbons (such as benzopyrene, found in cigarette smoke), insecticides (such as chlordane), and drugs such as carbamazepine, rifampin, and phenobarbital (see also). *Enzyme inhibition* may be due to substrate competition or due to direct inhibition of drug-metabolizing enzymes, particularly one of several of the cytochrome P-450 enzymes. Many widely prescribed antidepressants generally known as selective serotonin reuptake inhibitors (SSRIs) have been reported to inhibit the CYP2D6 system, resulting in significantly elevated plasma concentration of co-administered psychotropic drugs. Fluoxetine causes a 10-fold decrease in the clearance of imipramine and desipramine because of its inhibitory effect on hydroxyl-ation ().

A few clinical examples of enzyme inhibitors and inducers are listed in . Diet also affects drug-metabolizing enzymes. For example, plasma theophylline concentrations and theophylline clearance in patients on a high-protein diet are lower than in subjects whose diets are high in carbohydrates. Sucrose or glucose plus fructose decrease the activity of mixed-function oxidases, an effect related to a slower metabolism rate and a prolongation in hexobarbital sleeping time in rats. Chronic administration of 5% glucose was suggested to affect sleeping time in subjects receiving barbiturates. A decreased intake of fatty acids may lead to decreased basal MFO activities () and affect the rate of drug metabolism.

Table 11.8 Examples of Drug Interactions Affecting Mixed Function Oxidase Enzymes

Inhibitors of Drug Metabolism	Example	Result
Acetaminophen	Ethanol	Increased hepatotoxicity in chronic alcoholics
Cimetidine	Warfarin	Prolongation of prothrombin time
Erythromycin	Carbamazepine	Decreased carbazepine clearance
Fluoxetine	Imipramine (IMI)	Decreased clearance of CAD

Fluoxetine	Desipramine (DMI)	Decreased clearance of CAD
Inducers of Drug Metabolism	**Example**	**Result**
Carbamazepine	Acetaminophen	Increased acetaminophen metabolism
Rifampin	Methadone	Increased methadone metabolism, may precipitate opiate withdrawal
Phenobarbital	Dexamethasone	Decreased dexamethasone elimination half-life
Rifampin	Prednisolone	Increased elimination of prednisolone

The protease inhibitor saquinavir mesylate (Invirase, Roche), has very low bioavailability—only about 4%. In studies conducted by Hoffmann-La Roche, the area under the curve (AUC) of saquinavir was increased to 150% when the volunteers took a 150-mL glass of grapefruit juice with the saquinavir, and then another 150-mL glass an hour later. Concentrated grapefruit juice increased the AUC up to 220%. Naringin, a bioflavonoid in grapefruit juice, was found to be at least partially responsible for the inhibition of the enzyme CYP3A4, present in the liver and the intestinal wall, which metabolizes saquinavir, resulting in an increase in its AUC. Ketoconazole and ranitidine (Zantac) may also increase the AUC of saquinavir by inhibition of the cytochrome P-450 enzymes. In contrast, rifampin greatly reduces the AUC of saquinavir, apparently due to enzymatic stimulation. Other drugs recently shown to have increased bioavailability when taken with grapefruit juice include several sedatives and the anticoagulant coumarin (). Increases in drug levels may be dangerous, and the pharmacokinetics of drugs with potential interactions should be closely monitored. More complete tabulations of the cytochrome P-450s are available (; ;); some examples are given in

Table 11.9 Change in Drug Availability Due to Oral Coadministration of Grapefruit Juice

Drug	Study
Triazolam	
Midazolam	
Cyclosporine	
Coumarin	
Nisoldipine	
Felodipine	

Table 11.10 Cytochrome P450 Isoforms and Examples

CYP1A2	Substrates—amitriptyline, imipramine, theophylline (other enzymes also involved); induced by smoking
	Fluvoxamine, some quinolones and grapefruit juice are inhibitors
CYP2B6	Substrates—cyclophosphamide, methadone
CYP2C9	Metabolism of S-warfarin and tolbutamide by CYP2C9
	Substrates—NSAIDs—ibuprofen, diclofenac
CYP2C19	Omeprazole, S-mephenytoin, and Propranolol
	Diazepam (mixed), and imipramine (mixed)
	Inhibitors: cimetidine, fluoxetine, and ketoconazole.
CYP2D6	Many antidepressants, β-blockers are metabolized by CYP2D6
	SRIIs, cimetidine are inhibitors
	Substrates—amitriptyline, imipramine, fluoxetine, antipsychotics (haloperidol, thioridazine)
	Inhibitors—paroxetine, fluoxetine, sertraline, fluvoxamine, cimetidine, haloperidol
CYP2E1	Substrates—acetaminophen, ethanol, halothane
	Induced by INH and disulfiram
CYP3A4, 5, 6	CYP3A subfamilies are the most abundant cytochrome enzymes in humans and include many key therapeutic and miscellaneous groups:
	Ketoconazole, atorvastatin, lovastatin.
	Azithromycin, clarithromycins, amitriptyline
	Benzodiazepines—alprazolam, triazolam, midazolam
	Calcium blockers—verapamil, diltiazam
	Protease inhibitors—ritonavir, saquinavir, indinavir

Examples based on , , and .

For new drugs, the potential for drug metabolism/interaction is studied *in vitro* and/or *in vivo* by identifying whether the drug is a substrate for the common CYP450 subfamilies (). Examples of substrates include, but are not limited to, (1) midazolam, buspirone, felodipine, simvastatin, or lovastatin for CYP3A4; (2) theophylline for CYP1A2; (3) S-warfarin for CYP2C9; and (4)

desipramine for CYP2D6.

Other substrates mentioned for further study of a CYP3A4-interacting investigational drug include dihydropyridine calcium channel blockers and triazolobenzodiazepines. For CYP2D6 inhibiting, the investigational drug might include metoprolol.

Since metabolism usually occurs in the liver (some enzymes such as CYP3A4 are also important in gut metabolism), human liver microsomes provide a convenient way to study CYP450 metabolism. Microsomes are a subcellular fraction of tissue obtained by differential high-speed centrifugation. The key CYP450 enzymes are collected in the microsomal fraction. The CYP450 enzymes retain their activity for many years in microsomes or whole liver stored at low temperature. Hepatic microsomes can be obtained commercially, with or without prior phenotyping, for most important CYP450 enzymes. The cDNAs for the common CYP450s have been cloned, and the recombinant human enzymatic proteins have been expressed in a variety of cells. These recombinant enzymes provides an excellent way to confirm results using microsomes. Pharmacokinetic endpoints recommended for assessment of the substrate are (1) exposure measures such as AUC, C_{max}, time to C_{max} (T_{max}), and others as appropriate; and (2) pharmacokinetic parameters such as clearance, volumes of distribution, and half-lives (). For metabolism induction studies, *in-vivo* studies are more relied upon because enzyme induction may not be well predicted from *in-vitro* results. Considerations in drug-metabolizing/interaction studies include: (1) acute or chronic use of the substrate and/or interacting drug; (2) safety considerations, including whether a drug is likely to be an NTR (narrow therapeutic range) or non-NTR drug; (3) pharmacokinetic and pharmacodynamic characteristics of the substrate and interacting drugs; and (4) the need to assess induction as well as inhibition. The inhibiting/inducing drugs and the substrates should be dosed so that the exposures of both drugs are relevant to their clinical use.

FIRST-PASS EFFECTS

For some drugs, the route of administration affects the metabolic rate of the compound. For example, a drug given parenterally, transdermally, or by inhalation may distribute within the body prior to metabolism by the liver. In contrast, drugs given orally are normally absorbed in the duodenal segment of the small intestine and transported via the mesenteric vessels to the hepatic portal vein and then to the liver before entering the systemic circulation. Drugs that are highly metabolized by the liver or by the intestinal mucosal cells demonstrate poor systemic availability when given orally. This rapid metabolism of an orally administered drug before reaching the general circulation is termed *first-pass effect* or *presystemic elimination*.

Evidence of First-Pass Effects

First-pass effects may be suspected when there is a lack of parent (or intact) drug in the systemic circulation after oral administration. In such a case, the AUC for a drug given orally is less than the AUC for the same dose of drug given intravenously. From experimental findings in animals, first-pass effects may be assumed if the intact drug appears in a cannulated hepatic portal vein but not in general circulation.

For an orally administered drug that is chemically stable in the gastrointestinal tract and is 100% systemically absorbed (F = 1), the area under the plasma drug concentration curve, $\text{AUC}^{\infty}_{0,\text{ oral}}$, should be the same when the same drug dose is given intravenously, $\text{AUC}^{\infty}_{0,\text{ IV}}$. Therefore, the absolute bioavailability (F) may reveal evidence of drug being removed by the liver due to first-pass effects as follows:

$$F = \frac{[\text{AUC}]^{\infty}_{0,\text{ oral}} / D_{0,\text{ oral}}}{[\text{AUC}]^{\infty}_{0,\text{ IV}} / D_{0,\text{ IV}}} \qquad (11.34)$$

For drugs that undergo first-pass effects $\text{AUC}^{\infty}_{0,\text{ oral}}$ is smaller than $\text{AUC}^{\infty}_{0,\text{ IV}}$ and $F < 1$. Drugs such as propranolol, morphine, and nitroglycerin have F values less than 1 because these drugs undergo significant first-pass effects.

Liver Extraction Ratio

Because there are many other reasons for a drug to have a reduced F value, the extent of first-pass effects is not very precisely measured from the F value. The liver extraction ratio (ER) provides a direct measurement of drug removal from the liver after oral administration of a drug.

$$\text{ER} = \frac{C_a - C_v}{C_a} \qquad (11.35)$$

where C_a is the drug concentration in the blood entering the liver and C_v is the drug concentration leaving the liver.

Because C_a is usually greater than C_v, ER is usually less than 1. For example, for propranolol, ER or [E] is about 0.7—that is, about 70% of the drug is actually removed by the liver before it is available for general distribution to the body. By contrast, if the drug is injected intravenously, most of the drug would be distributed before reaching the liver, and less of the drug would be metabolized.

Relationship between Absolute Bioavailability and Liver Extraction

Liver ER provides a measurement of liver extraction of a drug orally administered. Unfortunately, sampling of drug from the hepatic portal vein and artery is difficult and performed mainly in animals. Animal ER values may be quite different from those in humans. The following relationship between bioavailability and liver extraction enables a rough estimate of the extent of liver extraction:

$$F = 1 - \text{ER} - F'' \qquad (11.36)$$

where F is the fraction of bioavailable drug, ER is the drug fraction extracted by the liver, and F'' is the fraction of drug removed by nonhepatic process.

If F'' is assumed to be negligible—that is, there is no loss of drug due to chemical degradation, gut metabolism, and incomplete absorption—ER may be estimated from

$$F = 1 - \text{ER} \qquad (11.37)$$

After substitution of Equation 11.34 into Equation 11.37,

$$\text{ER} = 1 - \frac{[\text{AUC}]_{0,\text{oral}}^{\infty} / \text{D}_{0,\text{oral}}}{[\text{AUC}]_{0,\text{IV}}^{\infty} / \text{D}_{0,\text{IV}}} \qquad (11.38)$$

ER is a rough estimation of liver extraction for a drug. Many other factors may alter this estimation: the size of the dose, the formulation of the drug, and the pathophysiologic condition of the patient all may affect the ER value obtained.

Liver ER provides valuable information in determining the oral dose of a drug when the intravenous dose is known. For example, propranolol requires a much higher oral dose compared to an IV dose to produce equivalent therapeutic blood levels, because of oral drug extraction by the liver. Because liver extraction is affected by blood flow to the liver, dosing of drug with extensive liver metabolism may produce erratic plasma drug levels. Formulation of this drug into an oral dosage form requires extensive, careful testing.

Estimation of Reduced Bioavailability Due to Liver Metabolism and Variable Blood Flow

Blood flow to the liver plays an important role in the amount of drug metabolized after oral administration. Changes in blood flow to the liver may substantially alter the percentage of drug metabolized and therefore alter the percentage of bioavailable drug. The relationship between blood flow, hepatic clearance, and percent of drug bioavailable is

$$F' = 1 - \frac{Cl_{\text{h}}}{Q} = 1 - \text{ER} \qquad (11.39)$$

where Cl_{h} is the hepatic clearance of the drug and Q is the effective hepatic blood flow. F' is the bioavailability factor obtained from estimates of liver blood flow and hepatic clearance, ER.

This equation provides a reasonable approach for evaluating the reduced bioavailability due to first-pass effect. The usual effective hepatic blood flow is 1.5 L/min, but it may vary from 1 to 2 L/min depending on diet, food intake, physical activity or drug intake (). For the drug propoxyphene hydrochloride, F' has been calculated from hepatic clearance (990 mL/min) and an assumed liver blood flow of 1.53 L/min:

$$F' = 1 - \frac{0.99}{1.53} = 0.35$$

The results, showing that 35% of the drug is systemically absorbed after liver extraction, are reasonable compared with the experimental values for propranolol.

Presystemic elimination or *first-pass effect* is a very important consideration for drugs that have a high extraction ratio (). Drugs with low extraction ratios, such as theophylline, have very little presystemic elimination, as demonstrated by complete systemic absorption after oral administration. In contrast, drugs with high extraction ratios have poor bioavailability when given orally. Therefore, the oral dose must be higher than the intravenous dose to achieve the same therapeutic response. In some cases, oral administration of a drug with high presystemic elimination, such as nitroglycerin, may be impractical due to very poor oral bioavailability, and thus a sublingual, transdermal, or nasal route of administration may be preferred.

Table 11.11 Hepatic and Renal Extraction Ratios of Representative Drugs

Extraction Ratios		
Low (<0.3)	**Intermediate (0.3–0.7)**	**High (>0.7)**
Hepatic Extraction		
Amobarbital	Aspirin	Arabinosyl-cytosine
Antipyrine	Quinidine	Encainide
Chloramphenicol	Desipramine	Isoproterenol
Chlordiazepoxide	Nortriptyline	Meperidine
Diazepam		Morphine
Digitoxin		Nitroglycerin
Erythromycin		Pentazocine
Isoniazid		Propoxyphene
Phenobarbital		Propranolol
Phenylbutazone		Salicylamide
Phenytoin		Tocainide

Procainamide		Verapamil
Salicylic acid		
Theophylline		
Tolbutamide		
Warfarin		

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Furthermore, if an oral drug product has slow dissolution characteristics or release rate, then more of the drug will be subject to first-pass effect compared to doses of drug given in a more bioavailable form (such as a solution). In addition, drugs with high presystemic elimination tend to demonstrate more variability in drug bioavailability between and within individuals. Finally, the quantity and quality of the metabolites formed may vary according to the route of drug administration, which may be clinically important if one or more of the metabolites has pharmacologic or toxic activity.

To overcome first-pass effect, the route of administration of the drug may be changed. For example, nitroglycerin may be given sublingually or topically, and xylocaine may be given parenterally to avoid the first-pass effects. Another way to overcome first-pass effects is to either enlarge the dose or change the drug product to a more rapidly absorbable dosage form. In either case, a large amount of drug is presented rapidly to the liver, and some of the drug will reach the general circulation in the intact state.

Although Equation 11.39 seems to provide a convenient way of estimating the effect of liver blood flow on bioavailability, this estimation is actually more complicated. A change in liver blood flow may alter hepatic clearance and *F*'. A large blood flow may deliver enough drug to the liver to alter the rate of metabolism. In contrast, a small blood flow may decrease the delivery of drug to the liver and become the rate-limiting step for metabolism. The hepatic clearance of a drug is usually calculated from plasma drug data rather than whole-blood data. Significant nonlinearity may be the result of drug equilibration due to partitioning into the red blood cells.

EXAMPLES

1. A new propranolol 5-mg tablet was developed and tested in volunteers. The bioavailability of propranolol from the tablet was 70% compared to an oral solution of propranolol, and 21.6%, compared to an intravenous dose of propranolol. Calculate the relative and absolute bioavailability of the propranolol tablet. Comment on the feasibility of further improving the absolute bioavailability of the propranolol tablet.

Solution

The relative bioavailability of propranolol from the tablet compared to the solution is 70% or 0.7. The absolute bioailability, *F*, of propranolol from the tablet compared to the IV dose is 21.6%, or *F* = 0.216. From the table of ER values (), the ER for propranolol is 0.6 to 0.8. If the product is perfectly formulated, ie, the tablet dissolves completely and all the drug is released from the tablet, the fraction of drug absorbed after deducting for the fraction of drug extracted by the liver is

$$F' = 1 - \text{ER}$$

$$F' = 1 - 0.7 \qquad (\text{mean ER} = 0.7)$$

$$F' = 0.3$$

Table 11.12 Pharmacokinetic Classification of Drugs Eliminated Primarily by Hepatic Metabolism

Drug Class	Extraction Ratio (approx.)	Percent Bound
Flow Limited		
Lidocaine	0.83	45–80[a]
Propranolol	0.6–0.8	93
Pethidine (meperidine)	0.60–0.95	60
Pentazocine	0.8	—
Propoxyphene	0.95	—
Nortriptyline	0.5	95
Morphine	0.5–0.75	35
Capacity Limited, Binding Sensitive		
Phenytoin	0.03	90
Diazepam	0.03	98
Tolbutamide	0.02	98
Warfarin	0.003	99
Chlorpromazine	0.22	91–99
Clindamycin	0.23	94
Quinidine	0.27	82

Digitoxin	0.005	97
Capacity Limited, Binding Insensitive		
Theophylline	0.09	59
Hexobarbital	0.16	—
Amobarbital	0.03	61
Antipyrine	0.07	10
Chloramphenicol	0.28	60–80
Thiopental	0.28	72
Acetaminophen	0.43	5[a]

[a]Concentration dependent in part.

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Thus, under normal conditions, total systemic absorption of propranolol from an oral tablet would be about 30% (F = 0.3). The measurement of relative bioavailability for propranolol is always performed against a reference standard given by the same route of administration and can have a value greater than 100%.

The following shows a method for calculating the absolute bioavailability from the relative bioavailability provided the ER is accurately known. Using the above example,

Absolute availability of the solution = 1–ER = 1–0.7 = 0.3 = 30%

Relative availability of the solution = 100%

Absolute availability of the tablet = x%

Relative availability of the tablet = 70%

$$x = \frac{30 \times 70}{100} = 21\%$$

Therefore, this product has a theoretical absolute bioavailability of 21%. The small difference of calculated and actual (the difference between 21.6% and 21%) absolute bioavailability is due largely to liver extraction fluctuation. All calculations are performed with the assumption of linear pharmacokinetics, which is generally a good approximation. ER may deviate significantly with changes in blood flow or other factors.

2. Fluvastatin sodium (Lescol, Novartis) is a drug used to lower cholesterol. The absolute bioavailability after an oral dose is reported to be 19–29%. The drug is rapidly and completely absorbed (manufacturer's product information). What are the reasons for the low oral bioavailability in spite of reportedly good absorption? What is the extraction ratio of fluvastatin? (The absolute bioavailability, F, is 46%, according to values reported in the literature.)

Solution

Assuming the drug to be completely absorbed as reported, using Equation 11.37,

$$\text{ER} = 1 - 0.46 = 0.54$$

Thus, 54% of the drug is lost due to first-pass effect because of a relatively large extraction ratio. Since bioavailability is only 19–29%, there is probably some nonhepatic loss according to Equation 11.36. Fluvastatin sodium was reported to be extensively metabolized, with some drug excreted in feces.

Relationship between Blood Flow, Intrinsic Clearance, and Hepatic Clearance

Although Equation 11.39 seems to provide a convenient way of estimating the effect of liver blood flow on bioavailability, this estimation is actually more complicated. For example, factors that affect the hepatic clearance of a drug include (1) blood flow to the liver, (2) intrinsic clearance, and (3) the fraction of drug bound to protein.

A change in liver blood flow may alter hepatic clearance and F'. A large blood flow may deliver enough drug to the liver to alter the rate of metabolism. In contrast, a small blood flow may decrease the delivery of drug to the liver and become the rate-limiting step for metabolism. The hepatic clearance of a drug is usually calculated from plasma drug data rather than whole-blood data. Significant nonlinearity may be the result of drug equilibration due to partitioning into the red blood cells.

In experimental animals, the blood flow (Q) to the liver, the drug concentration in the artery (C_a), and the drug concentration in the vein (C_v) may be measured. As the arterial blood containing drug perfuses the liver, a certain portion of the drug is removed by metabolism and/or biliary excretion. Therefore, the drug concentration in the vein is less than the drug concentration in the artery. An extraction ratio may be expressed as 100% of the drug entering the liver less the relative concentration (C_v/C_a) of drug that is removed by the liver.

$$\text{ER} = \frac{C_a - C_v}{C_a} \qquad \textbf{(11.40)}$$

The ER may vary from 0 to 1.0. An ER of 0.25 means that 25% of the drug was removed by the liver. If both the ER for the liver

and the blood flow to the liver are known, then hepatic clearance may be calculated by the following expression:

$$Cl_h = \frac{Q\,(C_a - C_v)}{C_a} = Q \times \text{ER} \qquad (11.41)$$

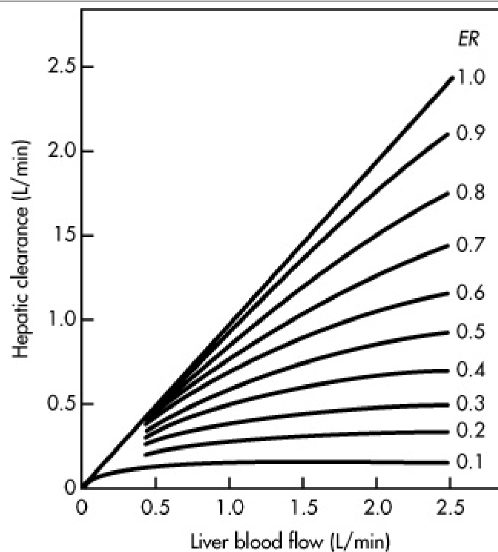
For some drugs (such as isoproterenol, lidocaine, and nitroglycerin), the extraction ratio is high (greater than 0.7), and the drug is removed by the liver almost as rapidly as the organ is perfused by blood in which the drug is contained. For drugs with very high extraction ratios, the rate of drug metabolism is sensitive to changes in hepatic blood flow. Thus, an increase in blood flow to the liver will increase the rate of drug removal by the organ. Propranolol, a β-adrenergic blocking agent, decreases hepatic blood flow by decreasing cardiac output. In such a case, the drug decreases its own clearance through the liver when given orally. Many drugs that demonstrate first-pass effects are drugs that have high extraction ratios with respect to the liver.

Intrinsic clearance (Cl_{int}) is used to describe the total ability of the liver to metabolize a drug in the absence of flow limitations, reflecting the inherent activities of the mixed-function oxidases and all other enzymes. Intrinsic clearance is a distinct characteristic of a particular drug, and as such, it reflects the inherent ability of the liver to metabolize the drug. Intrinsic clearance may be shown to be analogous to the ratio V_{max}/K_M for a drug that follows Michaelis–Menten kinetics. Hepatic clearance is a concept for characterizing drug elimination based on both blood flow and the intrinsic clearance of the liver, as shown in Equation 11.42.

$$Cl_h = Q\frac{Cl_{int}}{Q + Cl_{int}} \qquad (11.42)$$

When the blood flow to the liver is constant, hepatic clearance is equal to the product of blood flow (*Q*) and the extraction ratio (*ER*) Equation 11.41. However, the hepatic clearance of a drug is not constant. Hepatic clearance changes with blood flow () and the intrinsic clearance of the drug, as described in Equation 11.42. For drugs with low extraction ratios (eg, theophylline, phenylbutazone, and procainamide), the hepatic clearance is less affected by hepatic blood flow. Instead, these drugs are more affected by the intrinsic activity of the mixed-function oxidases. Describing clearance in terms of all the factors in a physiologic model allow drug clearance to be estimated when physiologic or disease condition causes changes in blood flow or intrinsic enzyme activity. Smoking, for example, can increase the intrinsic clearance for the metabolism of many drugs.

Figure 11-17.



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

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The relationship between liver blood flow and total hepatic clearance for drugs with varying extraction rates (*ER*).

Changes or alterations in mixed-function oxidase activity or biliary secretion can affect the intrinsic clearance and thus the rate of drug removal by the liver. Drugs that show low extraction ratios and are eliminated primarily by metabolism demonstrate marked variation in overall elimination half-lives within a given population. For example, the elimination half-life of theophylline varies from 3 to 9 hours. This variation in $t_{1/2}$ is thought to be due to genetic differences in intrinsic hepatic enzyme activity. Moreover, the elimination half-lives of these same drugs are also affected by enzyme induction, enzyme inhibition, age of the individual, nutritional, and pathologic factors.

Clearance may also be expressed as the rate of drug removal divided by plasma drug concentration:

$$Cl_h = \frac{\text{rate of drug removed by the liver}}{C_a} \qquad (11.43)$$

Because the rate of drug removal by the liver is usually the rate of drug metabolism, Equation 11.43 may be expressed in terms of hepatic clearance and drug concentration entering the liver (C_a):

$$\text{Rate of liver drug metabolism} = Cl_h C_a \qquad (11.44)$$

HEPATIC CLEARANCE OF A PROTEIN-BOUND DRUG: RESTRICTIVE AND NONRESTRICTIVE CLEARANCE FROM BINDING

It is generally assumed that protein-bound drugs are not easily metabolized (*restrictive clearance*), while free (unbound) drugs are subject to metabolism. Protein-bound drugs do not easily diffuse through cell membranes, while free drugs can reach the site of the mixed-function oxidase enzymes easily. Therefore, an increase in the free drug concentration in the blood will make more drug available for hepatic extraction. The concept is discussed under restrictive and nonrestrictive clearance () of protein-bound drugs (see).

Most drugs are *restrictively* cleared—for example, diazepam, quinidine, tolbutamide, and warfarin. The clearance of these drugs is proportional to the fraction of unbound drug (f_u). However, some drugs, such as propranolol, morphine, and verapamil, are *nonrestrictively* extracted by the liver regardless of drug bound to protein or free. Kinetically, a drug is nonrestrictively cleared if its hepatic extraction ratio (ER) is greater than the fraction of free drug (f_u), and the rate of drug clearance is unchanged when the drug is displaced from binding. Mechanistically, the protein binding of a drug is a reversible process and for a nonrestrictively bound drug, the free drug gets "stripped" from the protein during the process of drug metabolism. The elimination half-life of a nonrestrictively cleared drug is not significantly affected by a change in the degree of protein binding. This is an analogous situation to a protein-bound drug that is actively secreted by the kidney.

For a drug with restrictive clearance, the relationship of blood flow, intrinsic clearance, and protein binding is

$$Cl_h = Q\left(\frac{f_u Cl'_{int}}{Q + f_u Cl'_{int}}\right) \qquad (11.45)$$

where f_u is the fraction of drug unbound in the blood and Cl'_{int} is the intrinsic clearance of free drug. Equation 11.45 is derived by substituting $f_u Cl'_{int}$ for Cl_{int} in Equation 11.42.

From Equation 11.45, when Cl'_{int} is very small in comparison to hepatic blood flow (ie, $Q > Cl'_{int}$), then Equation 11.46 reduces to Equation 11.47.

$$Cl_h = \frac{Q f_u Cl'_{int}}{Q} \qquad (11.46)$$

$$Cl_h = f_u Cl'_{int} \qquad (11.47)$$

As shown in Equation 11.47, a change in Cl'_{int} or f_u will cause a proportional change in Cl_h for drugs with protein binding.

In the case where Cl'_{int} for a drug is very large in comparison to flow ($Cl'_{int} >> Q$), Equation 11.48 reduces to Equation 11.49.

$$Cl_h = \frac{Q f_u Cl'_{int}}{f_u Cl'_{int}} \qquad (11.48)$$

$$Cl_h \approx Q \qquad (11.49)$$

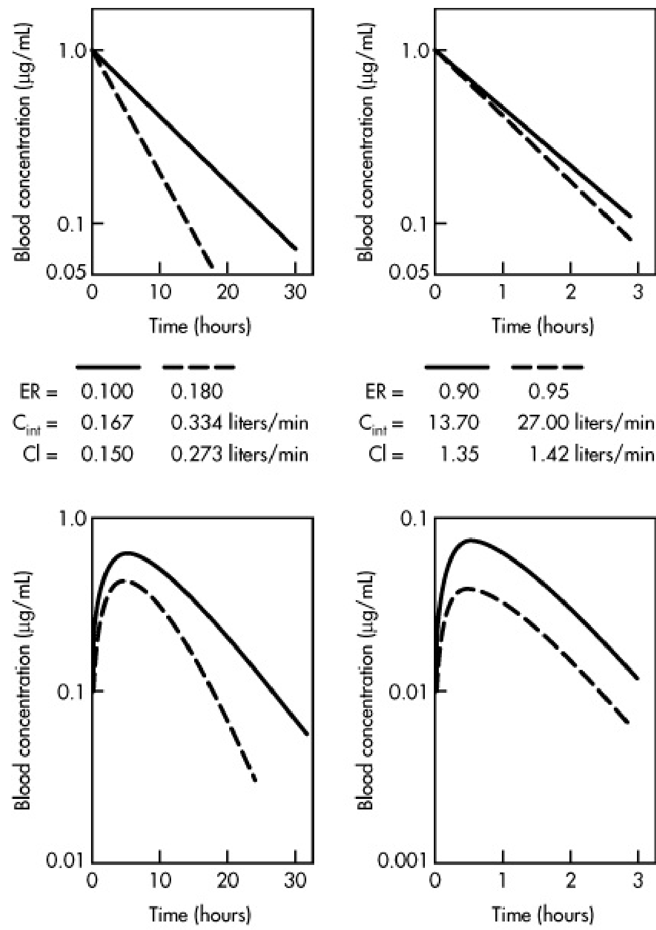
Thus, for drugs with a very high Cl'_{int}, Cl_h is dependent on hepatic blood flow, and independent of protein binding.

For restrictively cleared drugs, change in binding generally alters drug clearance. For a drug with low hepatic extraction ratio and low plasma binding, clearance will increase, but not significantly, when the drug is displaced from binding. For a drug highly bound to plasma proteins (more than 90%), a displacement from these binding sites will significantly increase the free concentration of the drug, and clearance (both hepatic and renal clearance) will increase (). There are some drugs that are exceptional and show a paradoxical increase in hepatic clearance despite an increase in protein binding. In one case, increased binding to AAG (α_1 acid glycoprotein) was found to concentrate drug in the liver, leading to an increased rate of metabolism because the drug was nonrestrictively cleared in the liver.

Effect of Changing Intrinsic Clearance and/or Blood Flow on Hepatic Extraction and Elimination Half-Life after IV and Oral Dosing

The effects of altered hepatic intrinsic clearance and liver blood flow on the blood level–time curve have been described by after both IV and oral dosing (and). These illustrations show how changes in intrinsic clearance and blood flow affect the elimination half-life, first-pass effects, and bioavailability of the drug as represented by the area under the curve.

Figure 11-18.



The effect of increasing hepatic total intrinsic clearance (Cl_{int}) on the total blood concentration–time curves after intravenous (upper panels) and oral (lower panels) administration of equal doses of two totally metabolized drugs. The left panels refer to a drug with an initial Cl_{int} equivalent to an extraction ratio of 0.1 at a liver blood flow of 1.5 L/min and the right panels to one with an initial extraction ratio of 0.9. The AUCs after oral administration are inversely proportional to Cl_{int}.

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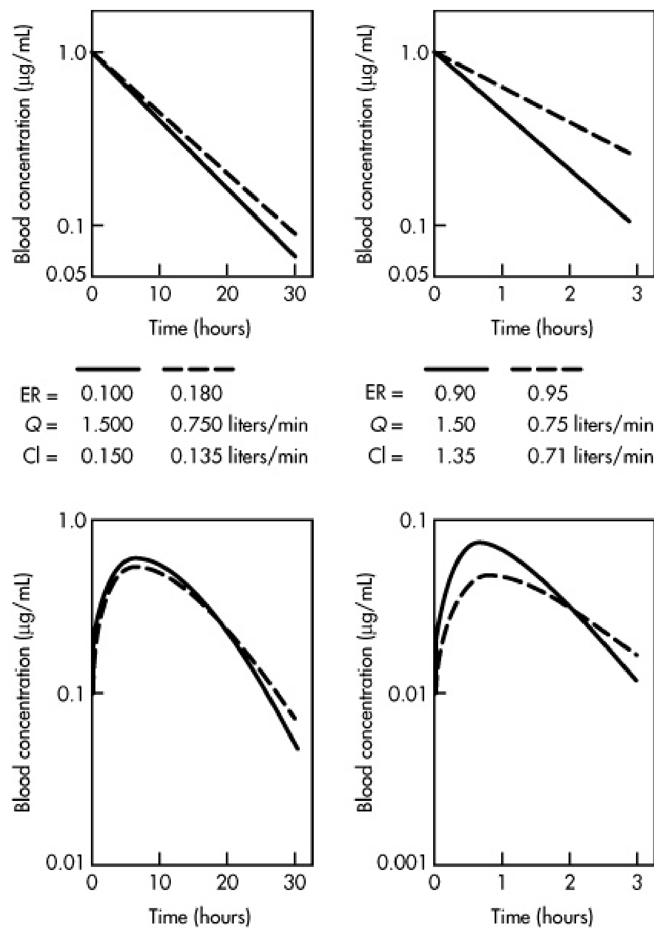
Figure 11-19.



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

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Effects of decreasing liver blood flow in the total blood concentration–time curves after intravenous (upper panels) and oral (lower panels) administration of equal doses of two totally metabolized drugs. The left panels refer to a drug with a total intrinsic clearance equivalent to an extraction ratio of 0.1 when blood flow equals 1.5 L/min, and the right panels to a drug with an intrinsic clearance equivalent to an extraction ratio of 0.9.

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EFFECT OF CHANGING INTRINSIC CLEARANCE

For drugs with low ER, the effect of doubling Cl_{int} (see) from 0.167 to 0.334 L/min increases both the extraction ratio (*ER*) and clearance (*Cl*) of the drug, leading to a steeper slope (dotted line) or shorter $t_{1/2}$. The elimination half-life decreases about 50% due to the increase in intrinsic clearance. (bottom left) shows the change in drug concentrations after oral administration when Cl_{int} doubles. In this case, there is a decrease in both AUC and $t_{1/2}$ (dashed line) due the increase in clearance of the drug.

For drugs with high ER, the effect of doubling Cl_{int} (see) from 13.70 to 27.00 L/min increases both the extraction ratio and clearance only moderately, leading to a slightly steeper slope. The elimination half-life decreases only marginally. (bottom right) shows the change in drug levels after oral administration. Some decrease in AUC is observed and the $t_{1/2}$ is shortened moderately.

The elimination half-life of a drug with a low extraction ratio is decreased significantly by an increase in hepatic enzyme activity. In contrast, the elimination half-life of a drug with a high extraction ratio is not markedly affected by an increase in hepatic enzyme activity because enzyme activity is already quite high. In both cases, an orally administered drug with a higher extraction ratio results in a greater first-pass effect as shown by a reduction in the AUC ().

EFFECT OF CHANGING BLOOD FLOW ON DRUGS WITH HIGH OR LOW EXTRACTION RATIO

Drug clearance and elimination half-life are both affected by changing blood flow to the liver. For drugs with low extraction (E = 0.1), a decrease in hepatic blood flow from normal (1.5 L/min) to one-half decreases clearance only slightly, and blood level is slightly higher (, top left, dashed line). In contrast, for a drug with high extraction ratio (E = 0.9), decreasing the blood flow to one-half of normal greatly decreases clearance, and the blood level is much higher (, top right, dashed line).

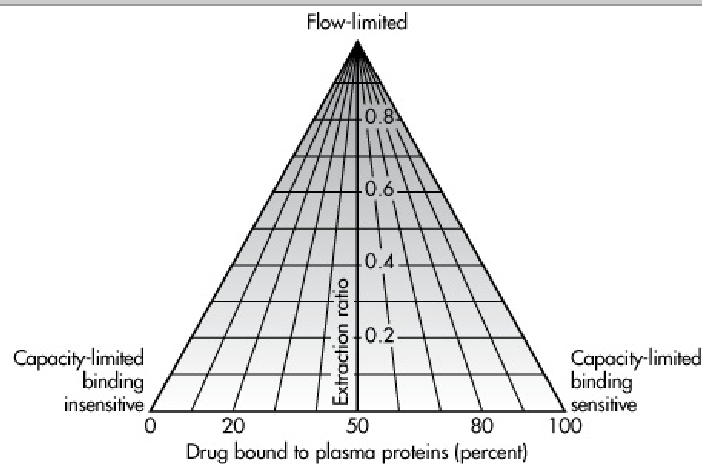
Alterations in hepatic blood flow significantly affect the elimination of drugs with high extraction ratios (eg, propranolol) and have very little effect on the elimination of drugs with low extraction ratios (eg, theophylline). For drugs with low extraction ratios, any concentration of drug in the blood that perfuses the liver is more than the liver can eliminate. Consequently, small changes in hepatic blood flow do not affect the removal rate of such drugs. In contrast, drugs with high extraction ratios are removed from

the blood as rapidly as they are presented to the liver. If the blood flow to the liver decreases, then the elimination of these drugs is prolonged. Therefore, drugs with high extraction ratios are considered to be *flow dependent*. A number of drugs have been investigated and classified according to their extraction by the liver, as shown in . The relationship between hepatic clearance and blood flow for drugs with different extraction ratio is shown in .

EFFECT OF CHANGING PROTEIN BINDING ON HEPATIC CLEARANCE

The effect of protein binding on hepatic clearance is often difficult to quantitate precisely, because it is not always known whether the bound drug is restrictively or nonrestrictively cleared. For example, animal tissue levels of imipramine, a nonrestrictively cleared drug, was shown to change as the degree of plasma protein binding changes (see). As discussed, drug protein binding is not a factor in hepatic clearance for drugs that have high extraction ratios. These drugs are considered to be *flow limited*. In contrast, drugs that have low extraction ratios may be affected by plasma protein binding depending on the fraction of drug bound. For a drug that has a low extraction ratio and is less than 75–80% bound, small changes in protein binding will not produce significant changes in hepatic clearance. These drugs are considered *capacity-limited*, *binding-insensitive drugs* () and are listed in . Drugs that are highly bound to plasma protein but with low extraction ratios are considered *capacity limited and binding sensitive,* because a small displacement in the protein binding of these drugs will cause a very large increase in the free drug concentration. These drugs are good examples of restrictively cleared drugs. A large increase in free drug concentration will cause an increase in the rate of drug metabolism, resulting in an overall increase in hepatic clearance. illustrates the relationship of protein binding, blood flow, and extraction.

Figure 11-20.



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

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This diagram illustrates the way in which two pharmacokinetic parameters (hepatic extraction ratio and percent plasma protein binding) are used to assign a drug into one of three classes of hepatic clearance (flow limited; capacity limited, binding sensitive; and capacity limited, binding insensitive). Any drug metabolized by the liver can be plotted on the triangular graph, but the classification is important only for those eliminated primarily by hepatic processes. The closer a drug falls to a corner of the triangle (shaded areas), the more likely it is to have the characteristic changes in disposition in liver disease as described for the three drug classes in the text.

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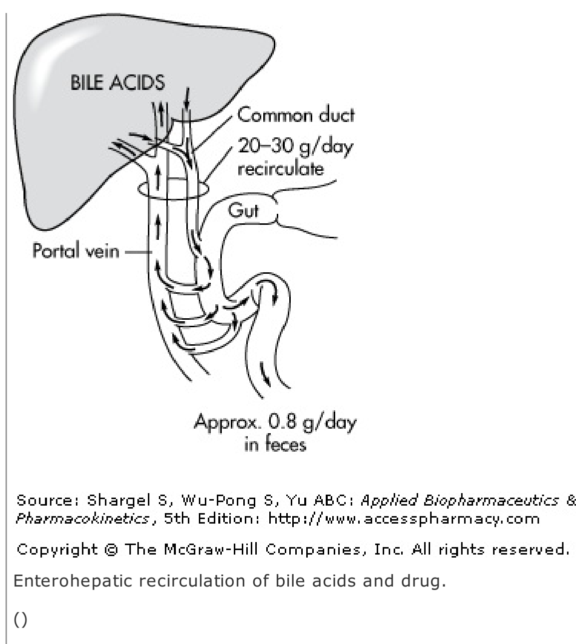
BILIARY EXCRETION OF DRUGS

The biliary system of the liver is an important system for the secretion of bile and the excretion of drugs. Anatomically, the intrahepatic bile ducts join outside the liver to form the common hepatic duct (). The bile that enters the gallbladder becomes highly concentrated. The hepatic duct, containing hepatic bile, joins the cystic duct that drains the gallbladder to form the common bile duct. The common bile duct then empties into the duodenum. Bile consists primarily of water, bile salts, bile pigments, electrolytes, and, to a lesser extent, cholesterol and fatty acids. The hepatic cells lining the bile canaliculi are responsible for the production of bile. The production of bile appears to be an active secretion process. Separate active biliary secretion processes have been reported for organic anions, organic cations, and for polar, uncharged molecules.

Figure 11-21.



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Enterohepatic recirculation of bile acids and drug.

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Drugs that are excreted mainly in the bile have molecular weights in excess of 500. Drugs with molecular weights between 300 and 500 are excreted both in urine and in bile. For these drugs, a decrease in one excretory route results in a compensatory increase in excretion via the other route. Compounds with molecular weights of less than 300 are excreted almost exclusively via the kidneys into urine.

In addition to relatively high molecular weight, drugs excreted into bile usually require a strongly polar group. Many drugs excreted into bile are metabolites, very often glucuronide conjugates. Most metabolites are more polar than the parent drug. In addition, the formation of a glucuronide increases the molecular weight of the compound by nearly 200, as well as increasing the polarity.

Drugs excreted into the bile include the digitalis glycosides, bile salts, cholesterol, steroids, and indomethacin (). Compounds that enhance bile production stimulate the biliary excretion of drugs normally eliminated by this route. Furthermore, phenobarbital, which induces many mixed-function oxidase activities, may stimulate the biliary excretion of drugs by two mechanisms: by an increase in the formation of the glucuronide metabolite and by an increase in bile flow. In contrast, compounds that decrease bile flow or pathophysiologic conditions that cause cholestasis decrease biliary drug excretion. The route of administration may also influence the amount of the drug excreted into bile. For example, drugs given orally may be extracted by the liver into the bile to a greater extent than the same drugs given intravenously.

Table 11.13 Examples of Drugs Undergoing Enterohepatic Circulation and Biliary Excretion
Enterohepatic Circulation
Imipramine
Indomethacin
Morphine
Pregnenolone
Biliary Excretion (intact or as metabolites)
Cefamandole
Cefoperazone
Chloramphenicol
Diazepam
Digoxin
Doxorubicin
Doxycycline
Estradiol
Fluvastatin
Lovastatin
Moxalactam
Practolol
Spironolactone
Testosterone

Tetracycline
Vincristine

Estimation of Biliary Clearance

The rate of drug elimination may be measured by monitoring the amount of drug secreted into the GI perfusate using a special intubation technique that blocks off a segment of the gut with an inflating balloon. In animals, bile duct cannulation allows both the volume of the bile and the concentration of drug in the bile to be measured directly.

Assuming an average bile flow of 0.5–0.8 mL/min in humans, biliary clearance can be calculated if the bile concentration, C_{bile}, is known.

$$Cl_{\text{biliary}} = \frac{\text{bile flow} \times C_{\text{bile}}}{C_{\text{p}}} \quad (11.50)$$

Alternatively, using the perfusion technique, the amount of drug eliminated in bile is determined from the GI perfusate, and Cl_{biliary} may be calculated without the bile flow rate, as follows.

$$Cl_{\text{biliary}} = \frac{\text{amount of drug secreted from bile per minute}}{C_{\text{p}}} \quad (11.51)$$

To avoid any complication of unabsorbed drug in the feces, the drug should be given by parenteral administration (eg, IV) during biliary determination experiments. The amount of drug in the GI perfusate recovered periodically may be determined. The extent of biliary elimination of digoxin has been determined in humans using this approach.

Enterohepatic Circulation

A drug or its metabolite is secreted into bile and upon contraction of the gallbladder is excreted into the duodenum via the common bile duct. Subsequently, the drug or its metabolite may be excreted into the feces or the drug may be reabsorbed and become systemically available. The cycle in which the drug is absorbed, excreted into the bile, and reabsorbed is known as *enterohepatic circulation*. Some drugs excreted as a glucuronide conjugate become hydrolyzed in the gut back to the parent drug by the action of a β-glucuronidase enzyme present in the intestinal bacteria. In this case, the parent drug becomes available for reabsorption.

Significance of Biliary Excretion

When a drug appears in the feces after oral administration, it is difficult to determine whether this presence of drug is due to biliary excretion or incomplete absorption. If the drug is given parenterally and then observed in the feces, one can assess that some of the drug was excreted in the bile. Because drug secretion into bile is an active process, this process can be saturated with high drug concentrations. Moreover, other drugs may compete for the same carrier system.

Enterohepatic circulation after a single dose of drug is not as important as after multiple doses or a very high dose of drug. With a large dose or multiple doses, a larger amount of drug is secreted in the bile, from which drug is then reabsorbed. This reabsorption process may affect the absorption and elimination rate constants. Furthermore, the biliary secretion process may become saturated, thus altering the plasma level–time curve.

Drugs that undergo enterohepatic circulation sometimes show a small secondary peak in the plasma drug–concentration curve. The first peak occurs as the drug in the GI tract is depleted; a small secondary peak then emerges as biliary-excreted drug is reabsorbed. In experimental studies involving animals, bile duct cannulation provides a means of estimating the amount of drug excreted through the bile. In humans, a less accurate estimation of biliary excretion may be made from the recovery of drug excreted through the feces. However, if the drug were given orally, some of the fecal drug excretion could represent unabsorbed drug.

Clinical Example

Leflunomide, an immunomodulator for rheumatoid arthritis, is metabolized to a major active metabolite and several minor metabolites. Approximately 48% of the dose is eliminated in the feces due to high biliary excretion. The active metabolite is slowly eliminated from the plasma. In the case of serious adverse toxicity, the manufacture recommends giving orally, cholestyramine or activated charcoal to bind the active metabolite in the GI tract to prevent its reabsorption and to facilitate its elimination. The use of cholestyramine or activated charcoal reduces the plasma levels of the active metabolite by approximately 40% in 24 hrs and by about 50% in 48 hrs.

FREQUENTLY ASKED QUESTIONS

1. Why do we use the term *hepatic drug clearance* to describe drug metabolism in the liver?

2. Please explain why many drugs with significant metabolism often have variable bioavailability.

3. The metabolism of some drugs is affected more than others when there is a change in protein binding. Why?

4. Give some examples that explain why the metabolic pharmacokinetics of drugs are important in patient care.

LEARNING QUESTIONS

1. A drug fitting a one-compartment model was found to be eliminated from the plasma by the following pathways with the

corresponding elimination rate constants.

Metabolism: $k_m = 0.200\ hr^{-1}$

Kidney excretion: $k_e = 0.250\ hr^{-1}$

Biliary excretion: $k_b = 0.150\ hr^{-1}$

a. What is the elimination half-life of this drug?

b. What would be the half-life of this drug if biliary secretion were completely blocked?

c. What would be the half-life of this drug if drug excretion through the kidney were completely impaired?

d. If drug-metabolizing enzymes were induced so that the rate of metabolism of this drug doubled, what would be the new elimination half-life?

2. A new broad-spectrum antibiotic was administered by rapid intravenous injection to a 50-kg woman at a dose of 3 mg/kg. The apparent volume of distribution of this drug was equivalent to 5% of body weight. The elimination half-life for this drug is 2 hours.

a. If 90% of the unchanged drug was recovered in the urine, what is the renal excretion rate constant?

b. Which is more important for the elimination of the drugs, renal excretion or biotransformation? Why?

3. Explain briefly:

a. Why does a drug that has a high extraction ratio (eg, propranolol) demonstrate greater differences between individuals after oral administration than after intravenous administration?

b. Why does a drug with a low hepatic extraction ratio (eg, theophylline) demonstrate greater differences between individuals after hepatic enzyme induction than a drug with a high hepatic extraction ratio?

4. A drug is being screened for antihypertensive activity. After oral administration, the onset time is 0.5–1 hour. However, after intravenous administration, the onset time is 6–8 hours.

a. What reasons would you give for the differences in the onset times for oral and intravenous drug administration?

b. Devise an experiment that would prove the validity of your reasoning.

5. Calculate the hepatic clearance for a drug with an intrinsic clearance of 40 mL/min in a normal adult patient whose hepatic blood flow is 1.5 L/min.

a. If the patient develops congestive heart failure that reduces hepatic blood flow to 1.0 L/min but does not affect the intrinsic clearance, what is the hepatic drug clearance in this patient?

b. If the patient is concurrently receiving medication, such as phenobarbital, which increases the Cl_{int} to 90 mL/min but does not alter the hepatic blood flow (1.5 L/min), what is the hepatic clearance for the drug in this patient?

6. Calculate the hepatic clearance for a drug with an intrinsic clearance of 12 L/min in a normal adult patient whose hepatic blood flow is 1.5 L/min. If this same patient develops congestive heart failure that reduces his hepatic blood flow to 1.0 L/min but does not affect intrinsic clearance, what is the hepatic drug clearance in this patient?

a. Calculate the extraction ratio for the liver in this patient before and after congestive heart failure develops.

b. From the above information, estimate the fraction of bioavailable drug, assuming the drug is given orally and absorption is complete.

7. Why do elimination half-lives of drugs eliminated primarily by hepatic biotransformation demonstrate greater intersubject variability than those drugs eliminated primarily by glomerular filtration?

8. A new drug demonstrates high presystemic elimination when taken orally. From which of the following drug products would the drug be most bioavailable? Why?

a. Aqueous solution

b. Suspension

c. Capsule (hard gelatin)

d. Tablet

e. Sustained release

9. For a drug that demonstrated presystemic elimination, would you expect qualitative and/or quantitative differences in the formation of metabolites from this drug given orally compared to intravenous injection? Why?

10. The bioavailability of propranolol is 26%. Propranolol is 87% bound to plasma proteins and has an elimination half-life of 3.9 hours. The apparent volume of distribution of propranolol is 4.3 L/kg. Less than 0.5% of the unchanged drug is excreted in the urine.

a. Calculate the hepatic clearance for propranolol in an adult male patient (43 years old, 80 kg).

b. Assuming the hepatic blood flow is 1500 mL/min, estimate the hepatic extraction ratio for propranolol.

c. Explain why hepatic clearance is more important than renal clearance for the elimination of propranolol.

d. What would be the effect of hepatic disease such as cirrhosis on the (1) bioavailability of propranolol and (2) hepatic clearance of propranolol?

e. Explain how a change in (1) hepatic blood flow, (2) intrinsic clearance, or (3) plasma protein binding would affect hepatic clearance of propranolol.

f. What is meant by first-pass effects? From the data above, why is propranolol a drug with first-pass effects?

11. The following pharmacokinetic information for erythromycin was reported by , p. 1679):

Bioavailability: 35%

Urinary excretion: 12%

Bound in plasma: 84%

Volume of distribution: 0.78 L/kg

Elimination half-life: 1.6 hours

An adult male patient (41 years old, 81 kg) was prescribed 250 mg of erythromycin base every 6 hours for 10 days. From the data above, calculate the following:

a. Total body clearance

b. Renal clearance

c. Hepatic clearance

12. Why would you expect hepatic clearance of theophylline in identical twins to be less variable compared to hepatic clearance in fraternal twins?

13. Which of the following statements describe(s) correctly the properties of a drug that follows nonlinear or capacity-limited pharmacokinetics?

a. The elimination half-life will remain constant when the dose changes.

b. The area under the plasma curve (AUC) will increase proportionately with an increase in dose.

c. The rate of drug elimination = $C_p \times K_M$.

d. At maximum saturation of the enzyme by the substrate, the reaction velocity is at V_{max}.

e. At very low substrate concentrations, the reaction rate approximates a zero-order rate.

14. The V_{max} for metabolizing a drug is 10 µm/hr. The rate of metabolism (v) is 5 µm/hr when drug concentration is 4 µm. Which of the following statements is/are true?

a.K_M is 5 µm for this drug.

b.K_M cannot be determined from the information given.

c.K_M is 4 µm for this drug.

15. Which of the following statements is/are true regarding the pharmacokinetics of diazepam (98% protein bound) and propranolol (87% protein bound)?

a. Diazepam has a long elimination half-life due to its lack of metabolism and its extensive plasma protein binding.

b. Propranolol is a drug with high protein binding but unrestricted (unaffected) metabolic clearance.

c. Diazepam exhibits low hepatic extraction.

16. The hepatic intrinsic clearance of two drugs are as follows:

Drug A: 1300 mL/min

Drug B: 26 mL/min

Which drug is likely to show the greatest increase in hepatic clearance when hepatic blood flow is increased from 1 L/min to 1.5 mL/min? Which drug will likely be blood-flow limited?

REFERENCES

Alvares AP, Pratt WB: Pathways of drug metabolism. In Pratt WB, Taylor P (eds): *Principles of Drug Action*, 3rd ed. New York, Churchill Livingstone, 1990, chap 5

Ariens EJ, Wuis EW: Commentary: Bias in pharmacokinetics and clinical pharmacology. *Clin Pharm Ther* **42:**361–363, 1987 [PMID: 3665335]

Baily DG, Arnold JMO, Munoz C, Spence JD: Grapefruit juice–felodipine interaction: Mechanism, predictability, and effect of naringin. *Clin Pharm Ther* **53:**637–642, 1993b

Baily DG, Arnold JMO, Strong HA, Munoz C, Spence JD: Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. *Clin Pharm Ther* **54:**589–593, 1993a

Bertilsson L: Geographic/interracial differences in polymorphic drug oxidation. *Clin Pharmacokinet* **29**(4)**:**192–209, 1995

Blaschke TF: Protein binding and kinetics of drugs in liver diseases. *Clin Pharmacokinet* **2:**32–44, 1977 [PMID: 322909]

Brosen K: Recent developments in hepatic drug oxidation. *Clin Pharmacokinet* **18:**220, 1990 [PMID: 2182263]

Brouwer KL, Dukes GE, Powell JR: Influence of liver function on drug disposition. Applied pharmacokinetics. In Evans WE, Schentag JJ, Jusko WJ, et al (eds); *Principles of Therapeutic Drug Monitoring*. Vancouver, WA, Applied Therapeutics, 1992, chap 6

Caldwell J: Conjugation reactions. In Jenner P, Testa B (eds), *Concepts in Drug Metabolism*. New York, Marcel Dekker, 1980, chap 4

Campbell TC: Nutrition and drug-metabolizing enzymes. *Clin Pharm Ther* **22:**699–706, 1977 [PMID: 334439]

Caraco Y, Sheller J, Wood AJJ: Pharmacogenetic determination of the effects of codeine and prediction of drug interactions. *J Pharmacol Exp Ther* **278:**1165–1174, 1996 [PMID: 8819499]

Cupp MJ, Tracy TS: Cytochrome P-450: New nomenclature and clinical implications. *Am Family Physician*, January 1, 1998 (http://www.aafp.org/afp/980101ap/cupp.html).

Desta Z, Xiaox, Shin JG, et al: Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet* **41**(12):913–958, 2002

Dow P: *Handbook of Physiology*, vol 2, Circulation. Washington, DC, American Physiology Society, 1963, p 1406

Evans DAP: Genetic variations in the acetylation of isoniazid and other drugs. Ann N Y Acad Sci **151:**723, 1968 [PMID: 5263687]

Evans DAP, Manley KA, McKusik VC: Genetic control of isoniazid metabolism in man. *Br Med J* **2:**485, 1968

FDA Guidance for Industry: *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies in vitro,* issued 4/1997

FDA Guidance for Industry: *In Vivo Drug Metabolism/Drug Interaction Studies—Study Design, Data Analysis, and Recommendations for Dosing and Labeling*, issued 11/24/1999 (www.fda.gov/cder/guidance.htm)

Flockhart: http://medicine.iupui.edu/flockhart/ Drug interaction table maintained by David Flockhart. Division of clinical pharmacology, Indiana University

Gilman AG, Rall TW, Nies AS, Taylor (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. Elmsford, NY, Pergamon Press, 1990

Gray H: *Anatomy of the Human Body*, 30th ed. Philadelphia, Lea & Febiger, 1985, p 1495

Hansch C, Zhang L: Quantitative structure-activity relationships of cytochrome P-450. *Drug Metab Rev* **25:**1–48, 1993 [PMID: 8449144]

Harder S, Baas H, Rietbrock S: Concentration effect relationship of levodopa in patients with Parkinson's disease. *Clin Pharmacokinet* **29:**243–256, 1995 [PMID: 8549026]

Hucker HB, Kwan KC, Duggan DE: Pharmacokinetics and metabolism of nonsteroidal antiinflammatory agents. In Bridges JW, Chasseaud LF (eds), *Progress in Drug Research*, vol 5. New York, Wiley, 1980, chap 3

Hukkinen SK, Varhe A, Olkkola KT, Neuvonen PJ: Plasma concentrations of triazolam are increased by concomitant ingestion of grapefruit juice. *Clin Pharm Ther* **58:**127–131, 1995 [PMID: 7648762]

Iwakawa S, Suganuma T, Lee S, et al: Direct determination of diastereomeric carprofen glucuronides in human plasma and urine and preliminary measurements of stereoselective metabolic and renal elimination after oral administration of carprofen in man. *Drug Metab Disp* **17:**414–419, 1989 [PMID: 2571482]

Kupferschmidt HH, Ha HR, Ziegler WH, Meier PJ, Krahenbuhl S: Interaction between grapefruit juice and midazolam in humans. *Clin Pharm Ther* **58:**20–28, 1995 [PMID: 7628179]

Lai ML, Wang SL, Lai MD, Lin ET, Tse M, Huang JD: Propranolol disposition in Chinese subjects of different CYT2D6 genotypes. *Clin Pharm Ther* **58:**264–268, 1995 [PMID: 7554699]

Levy RH, Boddy AV: Stereoselectivity in pharmacokinetics: A general theory. *Pharm Res* **8:**551–556, 1991 [PMID: 1866367]

Lanctot KL, Naranjo CA: Comparison of the Bayesian approach and a simple algorithm for assessment of adverse drug events. *Clin Pharm Ther* **58:**692–698, 1995 [PMID: 8529335]

Lindner HH: *Clinical Anatomy.* Norwalk, CT, Appleton & Lange, 1989

May GD: Genetic differences in drug disposition. *J Clin Pharmacol* **34:**881–897, 1994 [PMID: 7983231]

Merkel U, Sigusch H, Hoffmann A: Grapefruit juice inhibits 7-hydroxylation of coumarin in healthy volunteers. *Eur J Clin Pharm* **46:**175–177, 1994 [PMID: 8039540]

Nebert DW, Nelson DR, Adesnik M, et al: The P-450 superfamily: Updated listing of all genes and recommended nomenclature for the chromosomal loci. *DNA***8:**1, 1989 [PMID: 2651058]

Negishi M, Tomohide U, Darden TA, Sueyoshi T, Pedersen LG: Structural flexibility and functional versatility of mammalian P-450 enzymes. *FASEB J* **10:**683–689, 1996 [PMID: 8635685]

Parkinson A: Biotransformation of xenobiotics. In Klaassen, CD (ed), *Casarett & Doull's Toxicology*, 5th ed. McGraw-Hill, New York, 1996, chap 6

Rahmani R, Zhou XJ: Pharmacokinetics and metabolism of vinca alkaloids. *Cancer Surv* **17:**269–281, 1993 [PMID: 8137344]

Rowland M: Drug administration and regimens. In Melmon K, Morelli HF (eds), *Clinical Pharmacology*. New York, Macmillan, 1978

Rowland M: Effect of some physiologic factors on bioavailability of oral dosage forms. In Swarbrick J (ed), *Current Concepts in the Pharmaceutical Sciences: Dosage Form Design and Bioavailability*. Philadelphia, Lea & Febiger, 1973, chap 6

Toney GB, Ereshefsky L: Cyclic antidepressants. In Schumacher GE (ed), *Therapeutic Drug Monitoring*. Norwalk, CT, Appleton & Lange, 1995, chap 13

Tucker GT: Clinical implications of genetic polymorphism in drug metabolism. *J Pharm Pharmacol* **46**(suppl):417–424, 1994

Tucker GT, Lennard MS: Enantiomer-specific pharmacokinetics. *Pharmacol Ther* **45:**309–329, 1990 [PMID: 2405439]

Wilkinson GR, Guengerich FP, Branch RA: Genetic polymorphism of S-mephenytoin hydroxylation. *Pharmacol Ther* **43:**53–76, 1989 [PMID: 2675129]

Wilkinson GR, Shand DG: A physiological approach to hepatic drug clearance. *Clin Pharmacol Ther* **18:**377–390, 1975 [PMID: 1164821]

Wolf CR: Distribution and regulation of drug-metabolizing enzymes in mammalian tissues. In Caldwell J, Paulson GD (eds), *Foreign Compound Metabolism*. London, Taylor & Francis, 1984

Yee GC, Stanley DL, Pessa LJ, et al: Effect of grapefruit juice on blood cyclosporin concentration. *Lancet* **345:**955–956, 1995 [PMID: 7715295]

BIBLIOGRAPHY

Anders MW: *Bioactivation of Foreign Compounds*. New York, Academic Press, 1985

Balant LP, McAinsh JM: Use of metabolite data in the evaluation of pharmacokinetics and drug action. In Jenner P, Testa B (eds), *Concepts in Drug Metabolism*. New York, Marcel Dekker, 1980, chap 7

Benet LZ: Effect of route of administration and distribution on drug action. *J Pharm Biopharm* **6:**559–585, 1978 [PMID: 731418]

Brown C (ed): Chirality in Drug Design and Synthesis: Racemic Therapeutics—Problems All Along the Line (EJ Ariens), New York, Academic Press, 1990

Ducharme MP, Warbasse LH, Edwards DJ: Disposition of intravenous and oral cyclosporine after administration with grapefruit juice. *Clin Pharm Ther* **57:**485–491, 1995 [PMID: 7768070]

Geroge CF, Shand DG, Renwick AG (eds): *Presystemic Drug Elimination*. Boston, Butterworth, 1982

Gibaldi M, Perrier D: Route of administration and drug disposition. *Drug Metab Rev* **3:**185–199, 1974 [PMID: 4607867]

Gibson GG, Skett P: *Introduction to Drug Metabolism*, 2nd ed. New York, Chapman & Hall, 1994

Glocklin VC: General considerations for studies of the metabolism of drugs and other chemicals. *Drug Metab Rev* **13:**929–939, 1982 [PMID: 6754317]

Gorrod JW, Damani LA: *Biological Oxidation of Nitrogen in Organic Molecules: Chemistry, Toxicology and Pharmacology*. Deerfield Beach, FL, Ellis Horwood, 1985

Hildebrandt A, Estabrook RW: Evidence for the participation of cytochrome b5 in hepatic microsomal mixed-function oxidation reactions. *Arch Biochem Biophys* **143:**66–79, 1971 [PMID: 4397839]

Houston JB: Drug metabolite kinetics. *Pharmacol Ther* **15:**521–552, 1982

Jakoby WB: *Enzymatic Basis of Detoxification*. New York, Academic Press, 1980

Jenner P, Testa B: *Concepts in Drug Metabolism*. New York, Marcel Dekker, 1980–1981

Kaplan SA, Jack ML: Physiologic and metabolic variables in bioavailability studies. In Garrett ER, Hirtz JL (eds), *Drug Fate and Metabolism*, vol 3. New York, Marcel Dekker, 1979

LaDu BL, Mandel HG, Way EL: *Fundamentals of Drug Metabolism and Drug Disposition*. Baltimore, Williams & Wilkins, 1971

Levine WG: Biliary excretion of drugs and other xenobiotics. *Prog Drug Res* **25:**361–420, 1981 [PMID: 6273968]

Morris ME, Pang KS: Competition between two enzymes for substrate removal in liver: Modulating effects due to substrate recruitment of hepatocyte activity. *J Pharm Biopharm* **15:**473–496, 1987 [PMID: 3694493]

Nies AS, Shand DG, Wilkinson GR: Altered hepatic blood flow and drug disposition. *Clin Pharmacokinet* **1:**135–156, 1976 [PMID: 13954]

Pang KS, Rowland M: Hepatic clearance of drugs, 1. Theoretical considerations of a "well-stirred" model and a "parallel tube" model. Influence of hepatic blood flow, plasma, and blood cell binding and the hepatocellular enzymatic activity on hepatic drug clearance. *J Pharmacokinet Biopharmacol* **5:**625, 1977 [PMID: 599411]

Perrier D, Gibaldi M: Clearance and biologic half-life as indices of intrinsic hepatic metabolism. *J Pharmacol Exp Therapeut*, **191:**17–24, 1974 [PMID: 4423599]

Plaa GL: The enterohepatic circulation. In Gillette JR, Mitchell JR (eds), *Concepts in Biochemical Pharmacology*. New York, Springer-Verlag, 1975, chap 63

Pratt WB, Taylor P: *Principles of Drug Action: The Basis of Pharmacology*, 3rd ed. New York, Churchill Livingstone, 1990

Roberts MS, Donaldson JD, Rowland M: Models of hepatic elimination: Comparison of stochastic models to describe residence time distributions and to predict the influence of drug distribution, enzyme heterogeneity, and systemic recycling on hepatic elimination. *J Pharm Biopharm* **16:**41–83, 1988 [PMID: 3373419]

Routledge PA, Shand DG: Presystemic drug elimination. *Annu Rev Pharmacol Toxicol* **19:**447–468, 1979 [PMID: 378106]

Semple HA, Tam YK, Coutts RT: A computer simulation of the food effect: Transient changes in hepatic blood flow and Michaelis–Menten parameters as mediators of hepatic first-pass metabolism and bioavailability of propranolol. *Biopharm Drug Disp* **11:**61–76, 1990 [PMID: 2322637]

Shand DG, Kornhauser DM, Wilkinson GR: Effects of route administration and blood flow on hepatic drug elimination. *J Pharmacol Exp Therapeut*, **195:**425–432, 1975

Stoltenborg JK, Puglisi CV, Rubio F, Vane FM: High performance liquid chromatographic determination of stereoselective disposition of carprofen in humans. *J Pharm Sci* **70:**1207–1212, 1981 [PMID: 6975367]

Testa B, Jenner B: *Drug Metabolism: Chemical and Biochemical Aspects*. New York, Marcel Dekker, 1976

Venot A, Walter E, Lecourtier Y, et al: Structural identifiability of "first-pass" models. *J Pharm Biopharm* **15:**179–189, 1987 [PMID: 3612500]

Wilkinson GR: Pharmacodynamics of drug disposition: Hemodynamic considerations. *Annu Rev Pharmacol* **15:**11–27, 1975 [PMID: 1096786]

Wilkinson GR: Pharmacodynamics in disease states modifying body perfusion. In Benet LZ (ed), *The Effect of Disease States on Drug Pharmacokinetics*. Washington, DC, American Pharmaceutical Association, 1976

Wilkinson GR, Rawlins MD: *Drug Metabolism and Disposition: Considerations in Clinical Pharmacology*. Boston, MTP Press, 1985

Williams RT: Hepatic metabolism of drugs. *Gut* **13:**579–585, 1972 [PMID: 4403576]

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