Hepatic Elimination of Drugs

The elimination of most drugs from the body involves the processes of both metabolism (biotransformation) and renal excretion.

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.

First-Order Elimination

The rate constant of elimination (k) is the sum of the first-order rate constant for metabolism (k\textsubscript{m}) and the first-order rate constant for excretion (k\textsubscript{e}):

\[ k = k_e + k_m \quad \text{....1} \]

In practice, the excretion rate constant (k\textsubscript{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\textsubscript{m}) is difficult to measure directly and is usually found from the difference between k and k\textsubscript{e}.

\[ k_m = k - k_e \]
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:

\[
\text{% drug metabolized} = \frac{k_m}{k} \times 100
\]

\[\text{……2}\]

**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 (figure 1). 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 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 hr⁻¹).

To determine the renal excretion rate constant, the following relationship is used:
Where $D_u^\infty$ is the total amount of unchanged drug recovered in the urine. In this example, $k_e$ is found by proper substitution into Equation

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

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

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

**HEPATIC CLEARANCE**

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:

$$Cl_T = Cl_{nr} + Cl_r \quad \text{.....4}$$

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 4.
\[ Cl_h = Cl_T - Cl_R \]  

**Examples 1**

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**

\[
\text{Hepatic clearance} = 15 - 10 = 5 \text{ mL/min/kg}
\]

**Example 2**

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**

\[
\text{Hepatic clearance} = \text{total body clearance} \times (1 - f_e) \]

Where \( f_e \) = percent of intact drug recovered in the urine.

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

**Extrahepatic Metabolism**

A few drugs (e.g., nitroglycerin) are metabolized extensively outside the liver. This is known as extra-hepatic metabolism. A simple way to assess extra-hepatic metabolism is to calculate hepatic (metabolic) clearance of the drug.

**EXAMPLE 3**

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 $Cl_r = 0.04 Cl_T$ and nonrenal clearance $Cl_{nr} = (1-0.04) Cl_T = 0.96 Cl_T$.

Therefore, $Cl_{nr} = 0.96 \times 1800\ mL/min = 1728\ mL/min$. 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.

**ENZYMES KINETICS**

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 (figure 2).

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.
The Michaelis-Menten equation 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.

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

Rate of intermediate \([ED]\) formation = \(k_1[E][D]\)

Rate of intermediate \([ED]\) decomposition = \(k_2[ED] + k_3[ED]\)

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

\[
\frac{d[ED]}{dt} = k_1[E][D] - (k_2 + k_3)[ED]
\]

By mass balance, the total enzyme concentration \([E_t]\) is the sum of the free enzyme concentration \([E]\) and the enzyme-drug intermediate concentration \([ED]\):

\[
[E_t] = [E] + [ED]
\]
Substituting for \([E]\) in Equation 7

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

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, \(\frac{d[ED]}{dt} = 0\), and

\[k_1[E_t][D] = [ED]\{k_1[D] + (k_2 + k_3)\}
\]

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

Let

\[K_M = \frac{k_2 + k_3}{k_1}\]

\[\frac{[E_t]}{[D]} = [ED]^2 \left(\frac{[D]}{K_M + [D]}\right)
\]

Solving for \([ED]\),

\[\[ED\] = \frac{[D][E_t]}{[D] + K_M}
\]

Multiplying by \(k_3\) on both sides,
When all the enzyme is saturated (i.e., 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, $V_{\text{max}}$.

\[
V_{\text{max}} = k_3[E_t]
\]

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.

\[
v = k_3[ED]
\]

Therefore, the velocity of metabolism is given by the equation

\[
v = \frac{V_{\text{max}}[D]}{[D] + K_M}
\]

Equation 19 describes the rate of metabolite formation, or the Michaelis-Menten equation. The maximum velocity ($V_{\text{max}}$) corresponds to the rate when all of the available enzyme is in the form of the drug-enzyme (ED) intermediate. At $V_{\text{max}}$, 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 $0.5V_{\text{max}}$. The $K_M$ is a useful parameter that reveals the concentration of the substrate at which the reaction occurs at half $V_{\text{max}}$. In general, for a drug with a large $K_M$, a higher concentration will be necessary before saturation is reached.
The relationship of the rate of metabolism to the drug concentration is a nonlinear, hyperbolic curve. To estimate the parameters $V_{\text{max}}$ and $K_M$, the reciprocal of the Michaelis-Menten equation is used to obtain a linear relationship.

$$\frac{1}{v} = \frac{K_M}{V_{\text{max}}} \frac{1}{[D]} + \frac{1}{V_{\text{max}}}$$

Equation 20 is known as the Lineweaver-Burk equation, in which $K_M$ and $V_{\text{max}}$ 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 $V_{\text{max}}$ and $K_M$. In, drug concentration $[D]$ is replaced by $C$, which represents drug concentration in the body.

**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 NADPH2 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 $V_{\text{max}}$ (figure 2).
Figure 2: 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.

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.

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.

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 (figure 3). 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.

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

\[
C_m = \frac{k_f D_0}{V_m (k_f - k_{em})} \left( e^{-k_{em} t} - e^{-k_f t} \right)
\]

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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.

Example:

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 kem for both metabolites is 0.4 hr⁻¹. (Note: V m and kem usually differ between metabolites and parent drug.) In this example, V m and kem 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

Glucuronide: \[ C_m = \frac{(0.6)(100)}{10(0.6 - 0.4)} \left( e^{-0.4(1)} - e^{-0.6(1)} \right) \]
\[ C_m = 3.6 \text{ mg/L} \]

Sulfate: \[ C_m = \frac{(0.2)(100)}{10(0.2 - 0.4)} \left( e^{-0.4(1)} - e^{-0.2(1)} \right) \]
\[ C_m = 1.5 \text{ mg/L} \]
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.

**FIRST-PASS EFFECTS**

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.

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, $\text{AUC}_{0-\infty}^\text{oral}$, should be the same when the same drug dose is given intravenously, $\text{AUC}_{0-\infty}^\text{IV}$. Therefore, the absolute bioavailability (F) may reveal evidence of drug being removed by the liver due to first-pass effects as follows:
For drugs that undergo first-pass effects $AUC_0\infty$, oral is smaller than $AUC_0\infty$, 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.

$$ER = \frac{C_a - C_v}{C_a}$$

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.

**Relationship between Absolute Bioavailability and Liver Extraction**

The following relationship between bioavailability and liver extraction enables a rough estimate of the extent of liver extraction:

$$F = 1 - ER - F''$$

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.
After substitution of Equation 22 into Equation 24

$$ER = 1 - \frac{[\text{AUC}]_{0, \text{oral}}^{\infty} / D_{0, \text{oral}}}{[\text{AUC}]_{0, \text{IV}}^{\infty} / D_{0, \text{IV}}} \quad \ldots \ldots 25$$

**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

$$F' = 1 - \frac{Cl_h}{Q} = 1 - ER \quad \ldots \ldots 26$$

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:

$$F' = 1 - \frac{0.99}{1.53} = 0.35$$
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 bioavailability, \( F \), of propranolol from the tablet compared to the IV dose is 21.6%, or \( F = 0.216 \). 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

\[
F' = 1 - ER \\
F' = 1 - 0.7 \quad (\text{mean ER} = 0.7) \\
F' = 0.3
\]

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.

**Relationship between Blood Flow, Intrinsic Clearance, and Hepatic Clearance**

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.

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.

\[
\text{ER} = \frac{C_a - C_v}{C_a}
\]

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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:

\[
C_{l_h} = \frac{Q}{C_a} \left( C_a - C_v \right) = Q \times \text{ER}
\]

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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 \( \beta \)-adrenergic blocking agent, decreases hepatic blood flow by decreasing cardiac output.
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

\[ Cl_h = Q \frac{Cl_{int}}{Q + Cl_{int}} \]

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

\[ Cl_h = \frac{\text{rate of drug removed by the liver}}{C_a} \]

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Because the rate of drug removal by the liver is usually the rate of drug metabolism, Equation 30 may be expressed in terms of hepatic clearance and drug concentration entering the liver (C_a):

\[ \text{Rate of liver drug metabolism} = Cl_h C_a \]

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FREQUENTLY ASKED QUESTIONS

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

Most orally administered drugs pass through the liver prior to systemic absorption. The rate of blood flow can greatly affect the extent of drug that reaches the systemic circulation. Also, intrinsic metabolism may differ among individuals and
may be genetically determined. These factors may cause drug levels to be more erratic for drugs that undergo extensive metabolism compared to drugs that are excreted renally.

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

Protein synthesis may be altered by liver dysfunction. In general, when drug protein binding is reduced, the free drug may be metabolized more easily. However, some drugs may be metabolized regardless of whether the drug is bound or free (for discussion of nonrestrictive binding, see ). In such cases, there is little change in pharmacodynamic activity due to changes in drug protein binding.

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?

\[
k = 0.347 \text{ hr}^{-1}
\]

\[
k_e = (0.9)(0.347) = 0.312 \text{ hr}^{-1}
\]

b. Renal excretion, 90% of the drug is excreted unchanged.

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?
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.

\[ Cl_H = Q \left( \frac{Cl_{int}}{Q + Cl_{int}} \right) \quad Q = 1.5 \text{ L/min} \quad Cl_{int} = 0.040 \text{ L/min} \]

\[ Cl_H = 1.5 \left( \frac{0.040}{1.5 + 0.040} \right) = 0.039 \text{ L/min} \]

Congestive heart failure:

\[ Cl_H = 1.0 \left( \frac{0.040}{1.0 + 0.040} \right) = 0.038 \text{ L/min} \]

\[ Cl_H = 1.5 \left( \frac{12}{1.5 + 12} \right) = 1.33 \text{ L/min} \]

Congestive heart failure (CHF):

\[ Cl_H = 1.0 \left( \frac{12}{1.0 + 12} \right) = 0.923 \text{ L/min} \]

a. \[ Cl_H = Q(ER) = Q \left( \frac{Cl_{int}}{Q + Cl_{int}} \right) \]

\[ ER = \frac{Cl_{int}}{Q + Cl_{int}} \]

Normal ER = \[ \frac{12}{1.5 + 12} = 0.89 \text{ L/min} \]

CHF ER = \[ \frac{12}{1.0 + 12} = 0.92 \text{ L/min} \]

b. \[ F = 1 - ER = 1 - 0.89 \]

\[ F = 0.11 \text{ or 11%} \]

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