Chapter-11
lecture-21

Hepatic clearance

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.

$$k_m = k - k_e$$

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

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.

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

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?

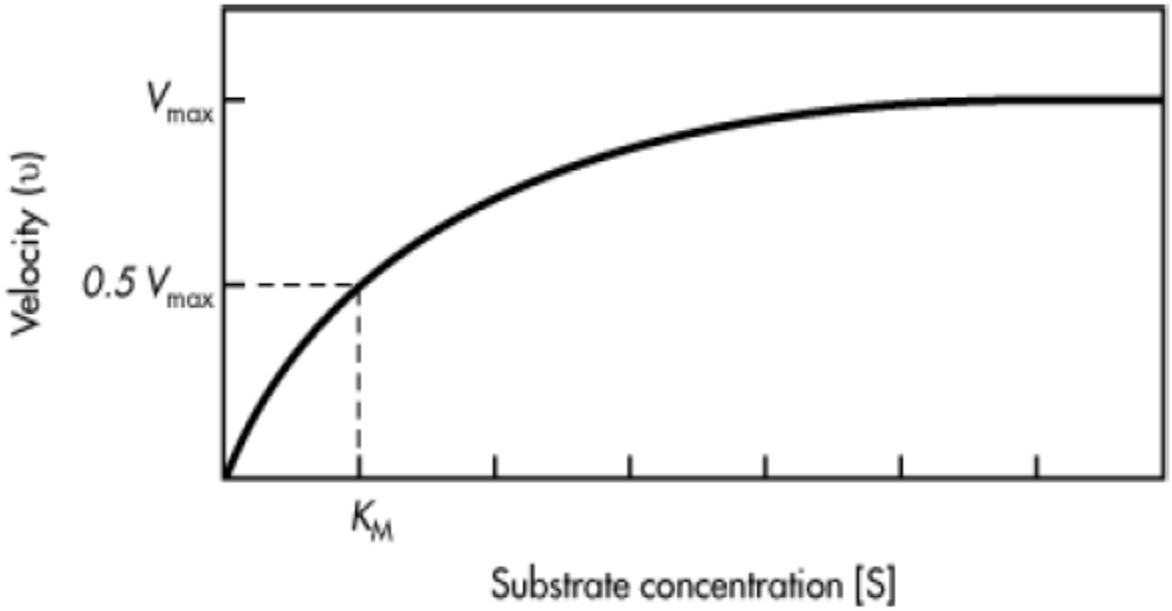
Solution

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, $Cl_{nr} = 0.96 \times 1800$ 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.

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 *Michaelisâ€"Menten* equation.

Figure 11-2.



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

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

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

For drugs that undergo first-pass effects $AUC^{â^}_{0,\,oral}$ is smaller than $AUC^{â^}_{0,\,IV}$ 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.

$$\mathrm{ER} = \frac{C_\mathrm{a} - C_\mathrm{v}}{C_\mathrm{a}} \qquad (11.35)$$

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 0.7â€”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 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.

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

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:

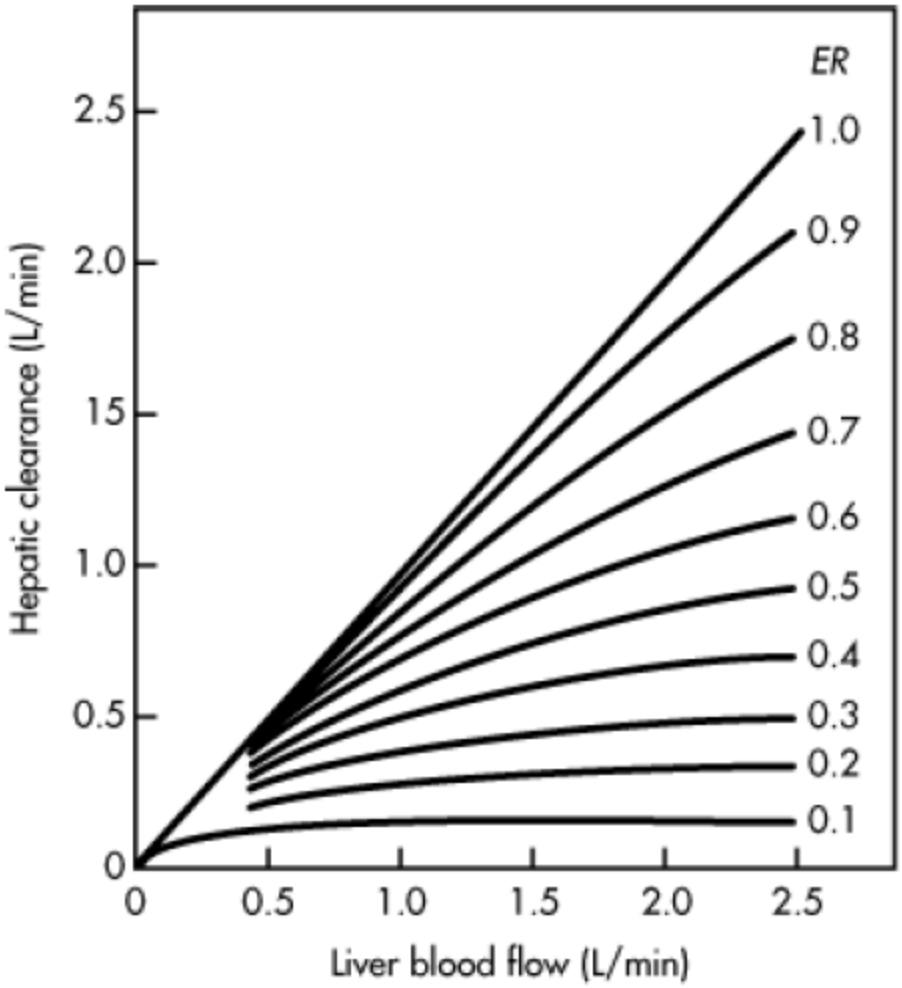
$$Cl_h = \frac{Q\,(C_a - C_v)}{C_a} = Q \times \mathrm{ER} \qquad (11.41)$$

$F' = 1 - Cl_h / Q = 1 - ER \qquad (11.39)$

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 Michaelisâ€"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.

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

Figure 11-17.



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

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

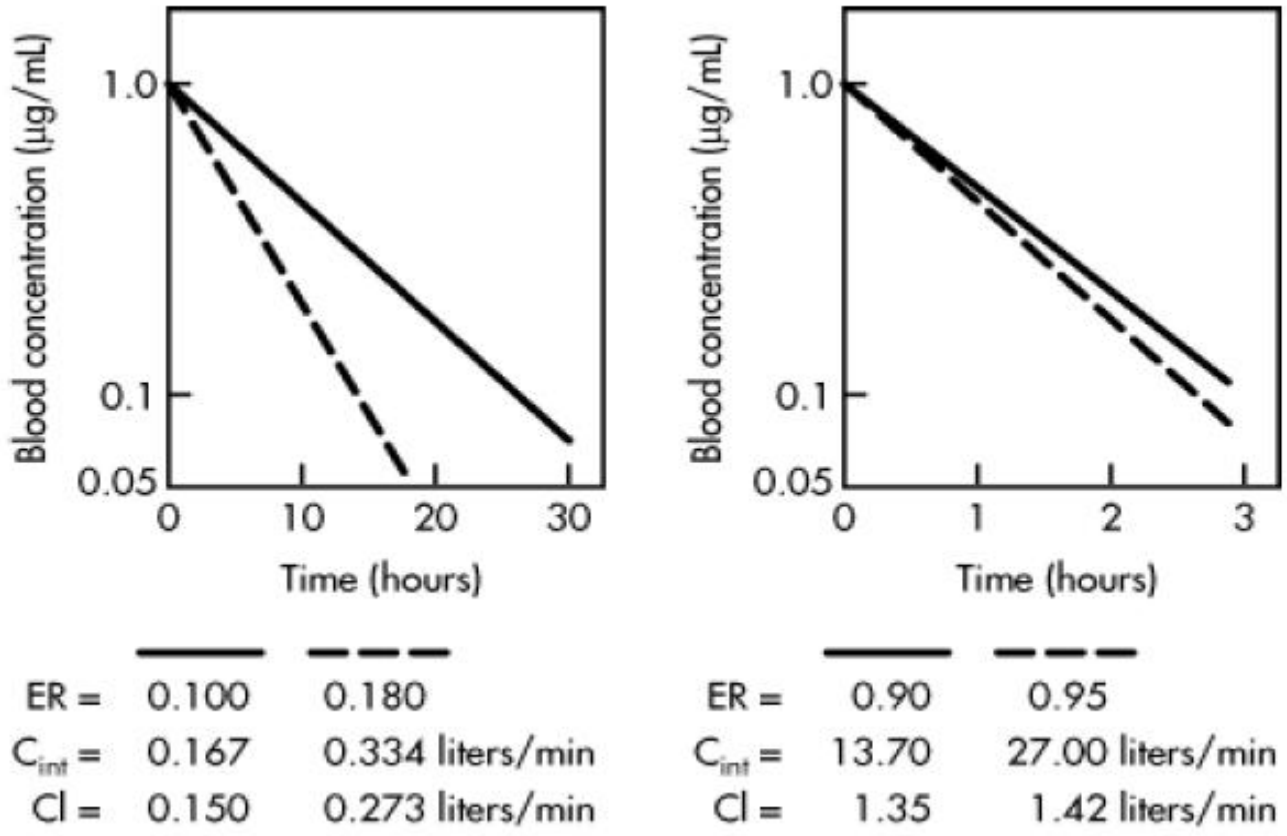
$$Cl_h = \frac{\text{rate of drug removed by the liver}}{C_a} \qquad (11.43)$$

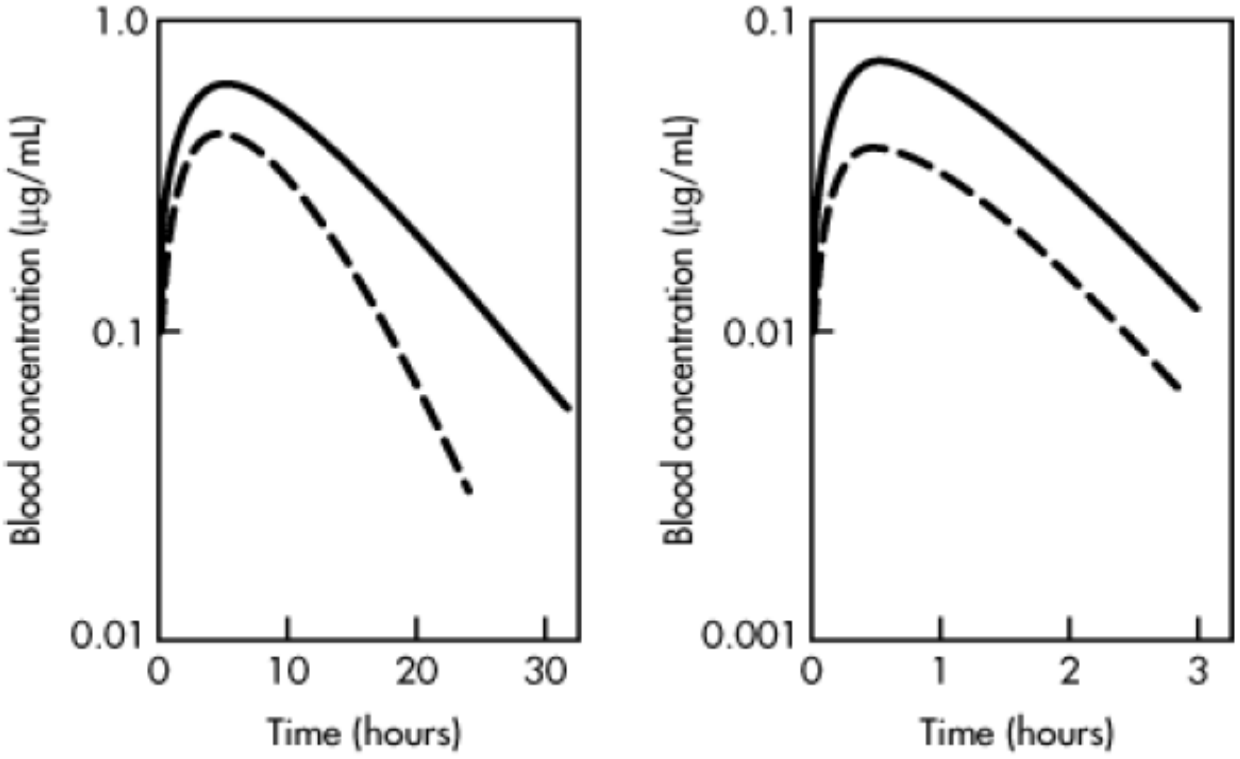
Because the rate of drug removal by the liver is usually the rate of drug metabolism, Equation 11.43 may be expressed in terms of hepatic clearance and drug concentration entering the liver (C_a):

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

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

Figure 11-18.





ER =	0.100	0.180	ER =	0.90	0.95
C_{int} =	0.167	0.334 liters/min	C_{int} =	13.70	27.00 liters/min
Cl =	0.150	0.273 liters/min	Cl =	1.35	1.42 liters/min

The effect of increasing hepatic total intrinsic clearance (Cl_{int}) on the total blood concentrationâ€"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}.

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 .

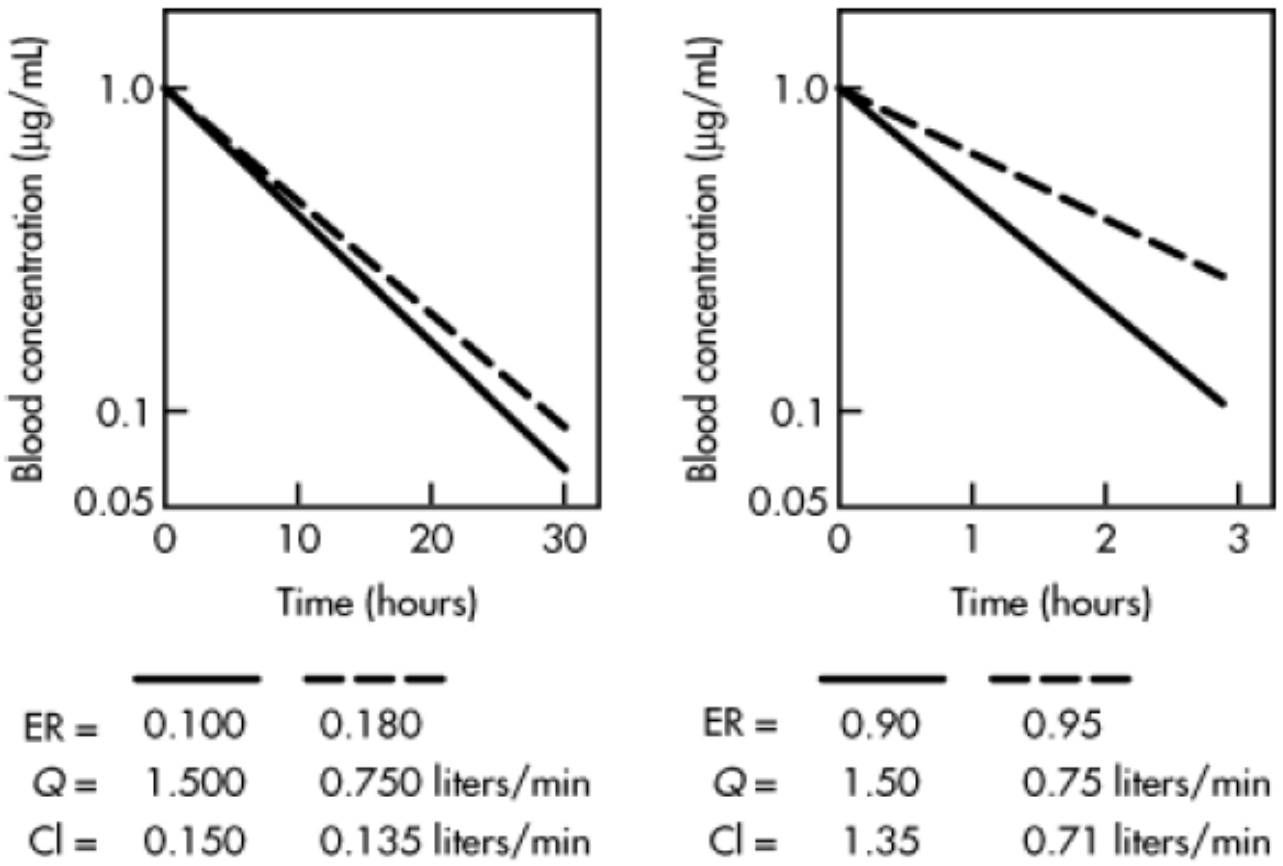
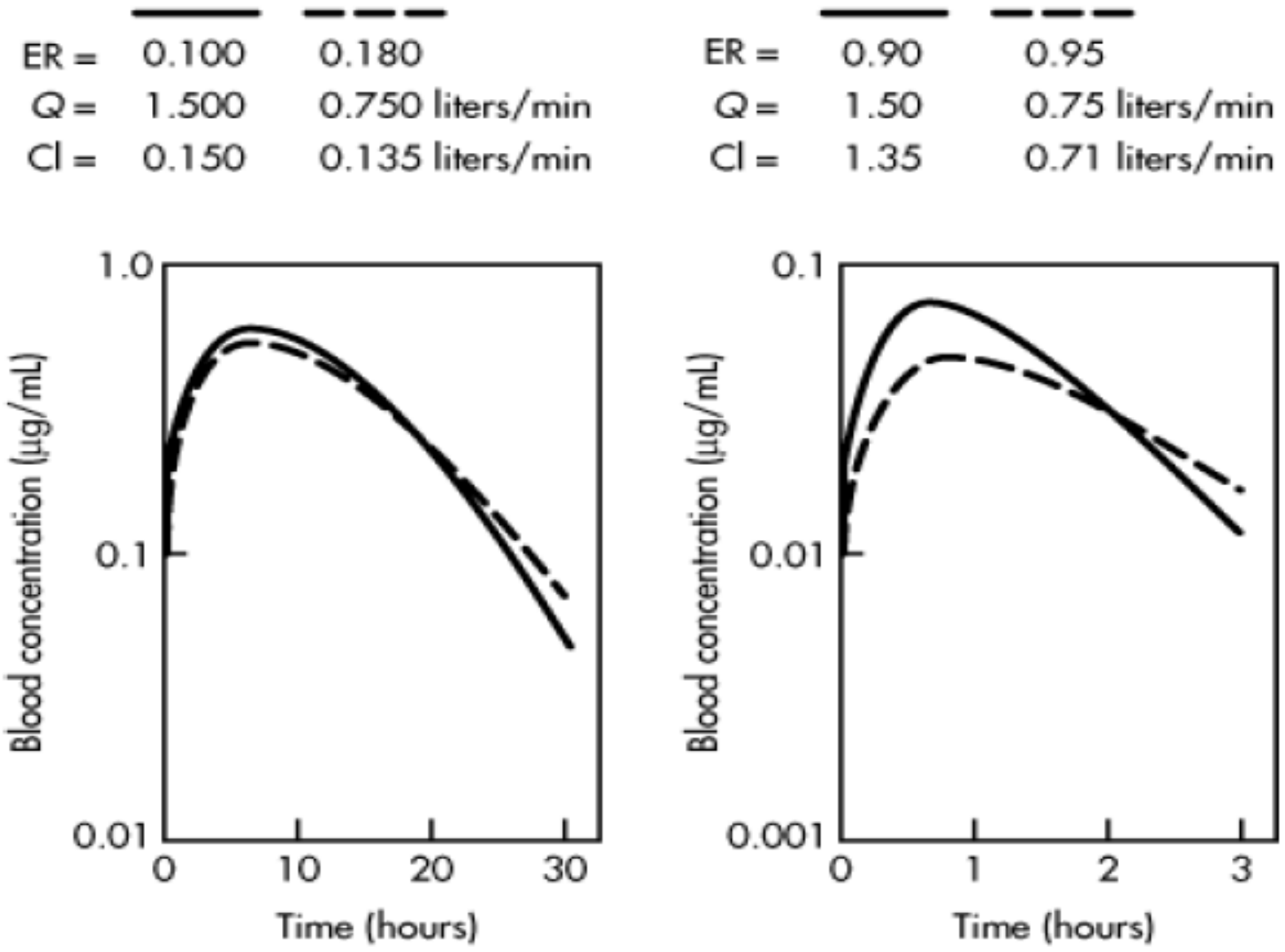


Figure 11-19.

Effects of decreasing liver blood flow in the total blood concentrationâ€“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.


ER = 0.100 0.180
Q = 1.500 0.750 liters/min
Cl = 0.150 0.135 liters/min
Blood concentration (µg/mL)
1.0
0.1
0.01
0
10
20
30
Time (hours)
ER = 0.90 0.95
Q = 1.50 0.75 liters/min
Cl = 1.35 0.71 liters/min
Blood concentration (µg/mL)
0.1
0.01
0.001
0
1
2
3
Time (hours)