Hepatic elimination of drugs
Chapter 11

Relationship between Blood Flow, Intrinsic Clearance, and Hepatic Clearance

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.

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.

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

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:

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

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 -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.**

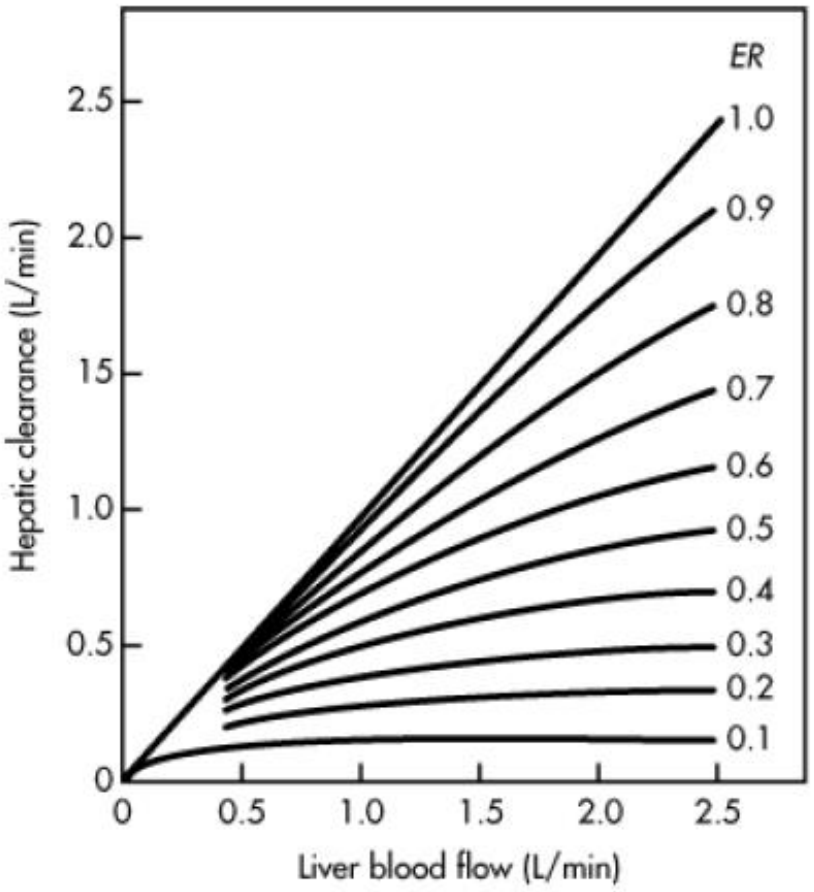
Intrinsic clearance is a distinct characteristic of a particular drug, and as such, it reflects the inherent ability of the liver to metabolize the drug. Intrinsic clearance may be shown to be analogous to the ratio *V*max/*K* M for a drug that follows Michaelis-Menten kinetics.

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.**



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

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

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.

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.