**HEPATIC ELIMINATION OF DRUGS**

Hepatic clearance \((CL_H)\) may be defined as the volume of blood perfusing the liver that is cleared of drug per unit time. Usually, hepatic clearance is equated with nonrenal clearance and is calculated as total body clearance \((CL_E)\) minus renal clearance \((CL_R)\).

\[
CL_H = CL_E - CL_R \tag{Equation 1}
\]

Accordingly, these estimates may include a component of extrahepatic nonrenal clearance.

The factors that affect hepatic clearance include blood flow to the liver \((Q)\), the fraction of drug not bound to plasma proteins \((f_u)\), and intrinsic clearance \((CL_{int})\) \((1, 2)\). Intrinsic clearance is simply the clearance that would be observed in the absence of blood flow and protein binding restrictions. As discussed in Lecture 2, hepatic clearance usually can be considered to be a first-order process. In those cases, intrinsic clearance represents the ratio of \(V_{max}/K_m\), and this relationship has been used as the basis for correlating *in vitro* studies of drug metabolism with *in vivo* results \((3)\). However, for phenytoin and several other drugs the Michaelis-Menten equation is needed to characterize intrinsic clearance.

The well-stirred model, shown in Figure 1 is the model of hepatic clearance that is used most commonly in pharmacokinetics.

**Blood Flow \((Q)\)**

\[
\begin{align*}
C_a & \quad C_v \\
V, C_v & \quad f_u CL_{int}
\end{align*}
\]

**Figure 1**: The well-stirred model of hepatic clearance in which the liver is viewed as a single compartment having a volume \((V)\) and blood flow \((Q)\). Drug concentrations reaching the liver via the hepatic artery and portal vein are designated by \(C_a\), and those in emergent hepatic venous blood by \(C_v\). Drug concentrations within the liver are considered to be in equilibrium with those in emergent venous blood. Intrinsic clearance \((CL_{int})\) acts to eliminate the fraction of drug not bound to plasma proteins \((f_u)\).
If we apply the Fick Equation (see Lecture 6) to this model, hepatic clearance can be defined as follows (2):

$$CL = Q \left[ \frac{C_a - C_v}{C_a} \right]$$  \hspace{1cm} \text{Equation 2}

The ratio of concentrations defined by the terms within the brackets is termed the extraction ratio ($ER$). An expression for the extraction ratio also can be obtained by applying the following mass balance equation to the model shown in Figure 1:

$$V \frac{dC}{dt} = QC_a - QC_v - f_u CL_{int} C_v$$

At steady state:

$$Q \left( C_a - C_v \right) = f_u CL_{int} C_v$$  \hspace{1cm} \text{Equation 3}

Also:

$$QC_a = \left( Q + f_u CL_{int} \right) C_v$$  \hspace{1cm} \text{Equation 4}

Since:

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

Equation 3 can be divided by Equation 4 to define extraction ratio in terms of $Q$, $f_u$, and $CL_{int}$:

$$ER = \frac{f_u CL_{int}}{Q + f_u CL_{int}}$$  \hspace{1cm} \text{Equation 5}

By substituting this expression for extraction ratio into Equation 2, hepatic clearance can be expressed as:

$$CL = Q \left[ \frac{f_u CL_{int}}{Q + f_u CL_{int}} \right]$$  \hspace{1cm} \text{Equation 6}

Two limiting cases arise when $f_u CL_{int} << Q$ and when $f_u CL_{int} >> Q$ (2). In the former instance Equation 5 can be simplified to

$$CL = f_u CL_{int}$$  \hspace{1cm} \text{Equation 7}

Hepatic clearance is termed restrictive in this case, since it is limited by protein binding. This situation is analogous to the elimination of drugs by glomerular filtration. Drugs that are restrictively eliminated have extraction ratios < 0.3.
When \( f_u \) \( CL_{int} \gg Q \), Equation 5 can be reduced to:

\[
CL_H = Q
\]

Equation 8

In this case, hepatic clearance is \textit{flow limited}, similar to the renal tubular excretion of para-aminohippurate. Since protein binding does not affect their clearance, drugs whose hepatic clearance is flow limited are said to be \textit{nonrestrictively} eliminated and have extraction ratios \( > 0.7 \).

In addition to the well-stirred model that is the basis for Equation 6, several other kinetic models of hepatic clearance have been developed (4). However, the following discussion will be based on the relationships defined by Equation 6, and the limiting cases represented by Equations 7 and 8.

**Restrictively Metabolized Drugs (ER < 0.3):**

The product of \( f_u \) and \( CL_{int} \) is small relative to liver blood flow (usually about 1500 mL/min) for drugs that are restrictively metabolized. Although the extraction ratio of these drugs is less than 0.3, hepatic metabolism often constitutes their principle pathway of elimination and they frequently have long elimination-phase half lives (e.g. diazepam: \( t_{1/2} = 43 \) hr). The hepatic clearance of these drugs is affected by changes in their binding to plasma proteins, by induction or inhibition of hepatic drug metabolizing enzymes, and by age, nutrition and pathological factors. However, as indicated by Equation 7, their hepatic clearance is not affected significantly by changes in hepatic blood flow.

**Effect of changes in protein binding on hepatic clearance:** It usually is assumed that the free drug concentration in blood is equal to the drug concentration to which hepatic drug metabolizing enzymes are exposed. Although protein binding would not be anticipated to change hepatic clearance significantly for restrictively metabolized drugs that have \( f_u > 80\% \), displacement of highly bound (\( f_u < 20\% \)) drugs from their plasma protein binding sites will result in a significant increase in their hepatic clearance. However, steady state concentrations of unbound drug will be unchanged as long as there is no change in \( CL_{int} \). This occurs in some drug interactions, as diagrammed in Figure 2.

**Figure 2:** Time course of an interaction in which warfarin, a restrictively metabolized drug, is displaced from its plasma protein binding sites. Although free warfarin concentrations rise initially as a result of the interaction, they subsequently return to pre-interaction levels. As a result, the increase in prothrombin time is only transient. Because \( f_u \) is increased, total (bound plus free) warfarin levels remain depressed as long as treatment with the displacing drug is continued (from Atkinson AJ Jr, Reidenberg MM, Thompson WL. Clinical Pharmacology. In: Greenberger N, editor, MKSAP VI Syllabus, Philadelphia, Am Col Phys; 1982. p.
This situation also is encountered in pathological conditions in which plasma proteins or plasma protein binding are decreased, as described in Lecture 5 for phenytoin kinetics in patients with impaired renal function. Since pharmacological effects are related to concentrations of unbound drug, pure displacement-type drug interactions put patients at risk for only a brief period of time. Similarly, dose adjustments are not needed for patients whose protein binding is impaired. In fact, as pointed out in Lecture 5, measurement of total rather than unbound drug levels in these patients actually may lead to inappropriate dose increases.

Effect of changes in intrinsic clearance on hepatic drug clearance: Both hepatic disease and drug interactions can alter the intrinsic clearance of restrictively eliminated drugs. Drug interactions will be considered in more detail in Lecture 14. The effects of liver disease on drug elimination will be discussed below. Although a number of probe drugs have been used to characterize hepatic clearance, analysis of the factors influencing the intrinsic clearance of drugs is hampered by the fact that, in contrast to the use of creatinine clearance to assess renal function, there are no simple measures that can be applied on a routine clinical basis to assess hepatic clearance.

Drugs with an Intermediate Extraction Ratio (0.3 < ER < 0.7):

Few drugs exhibit an intermediate extraction ratio. Evaluation of the hepatic clearance of these drugs requires consideration of all of the parameters included in Equation 6. Disease-associated or drug-induced alterations in protein binding, hepatic blood flow or intrinsic clearance may alter hepatic clearance significantly.

Nonrestrictively Metabolized Drugs (ER > 0.70):

The product of $f_u$ and $CL_{int}$ is large relative to liver blood flow for drugs that are nonrestrictively metabolized. These drugs characteristically have short elimination-phase half lives (e.g. propranolol: $t_{1/2} = 3.9$ hr), and changes in hepatic blood flow have a major effect on their hepatic clearance (Equation 8). Accordingly, hemodynamic changes, such as congestive heart failure, that reduce liver blood flow will reduce the hepatic clearance of these drugs and may necessitate appropriate adjustments in intravenous dosage. Changes in hepatic blood flow will also affect the first-pass metabolism of oral doses of nonrestrictively metabolized drugs but the effects of this on patient exposure are not intuitively obvious.

First-pass metabolism: Because nonrestrictively metabolized drugs have an extraction ratio that exceeds 0.7, they undergo extensive first-pass metabolism which reduces their bioavailability after oral administration (Lecture 4). If there is no loss of drug due to degradation or metabolism within the gastrointestinal tract or to incomplete absorption, the relationship between bioavailability ($F$) and extraction ratio is given by the following equation:

$$F = 1 - ER$$

Equation 9
Because Equation 8 implies that $ER = 1$ for nonrestrictively metabolized drugs, yet the oral route of administration can be used for many drugs in this category (e.g. $F > 0$ for morphine and propranolol), it is apparent that Equation 9 represents only a rough approximation. By using Equation 5 to substitute for $ER$ in Equation 9, we obtain a more precise estimate of the impact of first pass metabolism on bioavailability:

$$F = \frac{Q}{Q + f_u CL_{int}}$$  \hspace{1cm} \text{Equation 10}

Considering the case in which a drug is eliminated only by hepatic metabolism, Equation 2 from Lecture 4 can be re-written as follows:

$$D_{oral} \cdot F = CL_H \cdot AUC_{oral}$$

Using Equations 6 and 10 to substitute respectively for $CL_H$ and $F$, yields the result that:

$$D_{oral} = f_u CL_{int} \cdot AUC_{oral}$$  \hspace{1cm} \text{Equation 11}

It can be seen from Equation 11 that oral doses of nonrestrictively metabolized drugs should not need to be adjusted in response to changes in hepatic blood flow. Equation 11 also forms the basis for using $AUC_{oral}$ measurements to calculate so-called “oral clearance” as an estimate of $f_u CL_{int}$. However, if renal excretion contributes to drug elimination it will reduce $AUC_{oral}$ and lead to overestimation of $f_u CL_{int}$ unless the contribution of renal clearance is accounted for (2).

**Biliary Excretion of Drugs:**

Very few drugs are taken up by the liver and without further metabolism excreted into bile. On the other hand, many polar drug metabolites, such as glucuronide conjugates, are eliminated by biliary excretion. In order for compounds to be excreted in bile they must first pass the fenestrated endothelium that lines the hepatic sinusoids, then cross both the luminal and canalicular membrane surfaces of hepatocytes. Passage across these two hepatocyte membrane surfaces often is facilitated by active transport systems that will be discussed in Lecture 16. Consequently, chemical structure, polarity and molecular weight are important determinants of the extent to which compounds are excreted in bile (5). In general, polar compounds with a molecular weight greater than 400 Da are excreted in bile, whereas those with a lower molecular weight tend to be eliminated preferentially by renal excretion. However, 5-fluorouracil has a molecular weight of only 130 Da, yet is excreted in bile with a bile/plasma concentration ratio of 2.0 (5). Nonetheless, total biliary excretion of parent drug and metabolites represents only 2 to 3% of an administered 5-fluorouracil dose, and renal excretion of this drug predominates in patients with normal kidney function (6).

Compounds that enhance bile production stimulate biliary excretion of drugs normally eliminated by this route, whereas biliary excretion of drugs will be decreased by
compounds that decrease bile flow or pathophysiologic conditions that cause cholestasis (7). Route of administration may also influence the extent of drug excretion into bile. Oral administration may cause a drug to be extracted by the liver and excreted into bile to a greater degree than if the intravenous route were used.

**Enterohepatic circulation:** Drugs excreted into bile traverse the biliary tract to reach the small intestine where they may be reabsorbed. Drug metabolites which reach the intestine also may be converted back to the parent drug and be reabsorbed. This is particularly true for some glucuronide conjugates that are hydrolyzed by β-glucuronidase present in intestinal bacteria. The term *enterohepatic circulation* refers to this cycle in which a drug or metabolite is excreted in bile and then reabsorbed from the intestine as the parent drug.

Studies in animals have demonstrated that biliary clearance actually may exceed plasma clearance for some drugs and species with extensive enterohepatic circulation (8). Interruption of enterohepatic circulation reduces both the area under the plasma level-vs.-time curve and the elimination-phase half life. Enterohepatic circulation also increases the total exposure of the intestinal mucosa to potentially toxic drugs. Thus the intestinal toxicity of indomethacin is most marked in those species that have a high ratio of biliary to renal drug excretion (8).

Enterohepatic circulation may result in a second peak in the plasma level-vs.-time curve. In one study of cyclosporine pharmacokinetics, patients exhibited an initial peak in this curve 3.1 ± 2.0 hours after an oral dose was administered (9). In addition, a second peak was observed in 36% of the patients 5.6 ± 1.8 hours after the dose. In one patient with an ileostomy, it was shown that there was a peak in indomethacin concentrations in ileostomy drainage that occurred shortly before the second peak. The occurrence of this large peak of drug concentrations in intestinal fluid appears to reflect intermittent gallbladder contraction and pulsatile delivery of bile to the intestine since this double peak phenomenon is not encountered in species that lack a gallbladder (8).

**EFFECTS OF LIVER DISEASE ON PHARMACOKINETICS**

Liver disease in humans encompasses a wide range of pathological disturbances that can lead to a reduction in liver blood flow, extrahepatic or intrahepatic shunting of blood, hepatocyte dysfunction, quantitative and qualitative changes in serum proteins, and changes in bile flow. Different forms of hepatic disease may produce different alterations in drug absorption, disposition and pharmacologic effect. The pharmacokinetic or pharmacodynamic consequences of a specific hepatic disease may differ between individuals or even within a single individual over time. Each of the major determinants of hepatic clearance, $CL_{int}$, $f_u$, $Q$, and vascular architecture may be independently altered.

Although there are numerous causes of hepatic injury, it appears that the hepatic response to injury is a limited one and that the functional consequences are determined more by the extent of the injury than by the cause. At this time there is no generally
available test that can be used to correlate changes in drug absorption and disposition with the degree of hepatic impairment.

**Acute Hepatitis:**

Acute hepatitis is an inflammatory condition of the liver that is caused by viruses or hepatotoxins. In acute viral hepatitis, inflammatory changes in the hepatocyte are generally mild and transient, although they can be chronic (chronic active hepatitis) and severe, resulting in cirrhosis or death. Blaschke and Williams and their colleagues (10-13) have conducted informative studies of the effects of acute viral hepatitis on drug disposition. These investigators used a longitudinal study design in which each of a small number of patients was studied initially during the time that they had acute viral hepatitis and subsequently after recovery (Table 1).

**Table 1. Pharmacokinetics of some drugs during and after acute viral hepatitis**

<table>
<thead>
<tr>
<th></th>
<th>$f_u$</th>
<th>$V_d$</th>
<th>$CL_H$</th>
<th>$CL_{int}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DURING</td>
<td>AFTER</td>
<td>DURING</td>
<td>AFTER</td>
</tr>
<tr>
<td></td>
<td>L/kg</td>
<td>mL/hr/kg</td>
<td>mL/hr/kg</td>
<td>mL/hr/kg</td>
</tr>
<tr>
<td>PHENYTOIN*</td>
<td>0.126†</td>
<td>0.099</td>
<td>0.68†</td>
<td>0.63</td>
</tr>
<tr>
<td>TOLBUTAMIDE</td>
<td>0.087†</td>
<td>0.068</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>WARFARIN</td>
<td>0.012</td>
<td>0.012</td>
<td>0.09</td>
<td>0.21</td>
</tr>
<tr>
<td>LIDOCAINE</td>
<td>0.56</td>
<td>0.49</td>
<td>3.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

* A low dose of phenytoin was administered so that first-order kinetics would be approximated.
† Difference in studies during and after recovery from acute viral hepatitis was significant at $P < .05$ by paired t-test
†† Protein binding results for individual patients were not given so $CL_{int}$ was estimated from average values.

The drugs that were administered included phenytoin (10), tolbutamide (11), warfarin (12) and lidocaine (13). The most consistent significant finding was that the plasma protein binding of both phenytoin and tolbutamide was reduced during acute hepatitis. For both drugs, this was partly attributed to drug displacement from protein binding sites by elevated bilirubin levels. As a result of these changes, the distribution volume of phenytoin increased slightly during hepatitis (see Lecture 3). Although no significant change was noted in the average values of either phenytoin $CL_H$ or $CL_{int}$, $CL_{int}$ was reduced by approximately 50% in the two patients with the greatest evidence of hepatocellular damage. On the other hand, the reduction in tolbutamide binding to plasma proteins had no observable effect on distribution volume or $CL_{int}$ but did result in an increase in $CL_H$. No consistent changes were observed in warfarin kinetics during acute viral hepatitis. However, prothrombin time was prolonged to a greater extent than expected in 2 of the 5 patients, reflecting impaired synthesis of Factor VII. Lidocaine kinetics also were not altered consistently during acute viral hepatitis, although clearance decreased in 4 of the 6 patients that were studied.
In general, drug elimination during acute viral hepatitis is either normal or only moderately impaired. Observed changes tend to be variable and related to the extent of hepatocellular damage incurred. If the acute hepatitis resolves, drug disposition returns to normal. Drug elimination is likely to be impaired most significantly in patients who develop chronic hepatitis B virus-related liver disease, but even then only late in the evolution of this disease (14). This stands in marked contrast to the severity of acute hepatitis that can be caused by hepatotoxins. For example, Prescott and Wright (15) found that liver damage can occur within 2 to 3 hours after ingestion of an acetaminophen overdose. The elimination-phase half-life of acetaminophen averaged only 2.7 hours in patients without liver damage, but ranged from 4.3 to 7.7 hours (mean = 5.8 hr) in 4 patients with liver damage and from 4.3 to 13.9 hours (mean = 7.7 hr) in 3 patients with both liver and kidney damage resulting from acetaminophen toxicity. These authors observed that a fatal outcome was likely in patients whose acetaminophen elimination half-life exceeded 10 to 12 hours.

**Chronic Liver Disease and Cirrhosis:**

Chronic liver disease is usually secondary to chronic alcohol abuse or chronic viral hepatitis. Alcoholic liver disease is most common and begins with the accumulation of fat vacuoles within hepatocytes and hepatic enlargement. There is a decrease in cytochrome P450 content per weight of tissue but this is compensated for by the increase in liver size so that drug metabolism is not impaired (16). Alcoholic fatty liver may be accompanied or followed by alcoholic hepatitis, in which hepatocyte degeneration and necrosis become evident. In neither of these conditions is there significant diversion of blood flow past functioning hepatocytes by functional or anatomic shunts.

Cirrhosis occurs most frequently in the setting of alcoholic liver disease but represents the final common pathway of a number of chronic liver diseases. The development of cirrhosis is characterized by the appearance of fibroblasts and collagen deposition. This is accompanied by a reduction in liver size and the formation of nodules of regenerated hepatocytes. As a result, total liver content of cytochrome P450 is reduced in these patients. Initially, fibroblasts deposit collagen fibrils in the sinusoidal space, including the space of Disse (16). Collagen deposition not only produces characteristic bands of connective scar tissue but forms a basement membrane devoid of microvilli along the sinusoidal surface of the hepatocyte. The collagen barrier between the hepatocyte and sinusoid, in conjunction with alterations in the sinusoidal membrane of the hepatocyte, results in functional shunting of blood past the remaining hepatocyte mass. This can interfere significantly with the hepatic uptake of oxygen, nutrients, and plasma constituents, including drugs and metabolites.

The deposition of fibrous bands also disrupts the normal hepatic vascular architecture and increases vascular resistance and portal venous pressure. This reduces portal venous flow which normally accounts for 70% of total liver blood flow (17). However, the decrease in portal venous flow is compensated for by an increase in hepatic artery flow so that total blood flow reaching the liver is maintained at the normal value of 18 mL/min·kg
in patients with either chronic viral hepatitis or cirrhosis (18). The increase in portal venous pressure also leads to the formation of extrahepatic and intrahepatic shunts. Extrahepatic shunting occurs through the extensive collateral network that connects the portal and systemic circulations (17). Important examples include collaterals at the gastroesophageal junction, which can dilate to form varices, and the umbilical vein. In a study of cirrhotic patients with bleeding esophageal varices, an average of 70% of mesenteric and 95% of splenic blood flow was found to be diverted through extrahepatic shunts (19). Intrahepatic shunting results both from intrahepatic vascular anastomoses which bypass hepatic sinusoids and from the functional sinusoidal barrier caused by collagen deposition. In one study, the combination of anatomic and functional intrahepatic shunting averaged 25% of total liver blood flow in normal subjects but was increased to 33% in patients with chronic viral hepatitis and to 52% in cirrhotic patients (18).

**Pharmacokinetic Consequences of Liver Cirrhosis:**

The net result of chronic hepatic disease that leads to cirrhosis is that pathophysiologic alterations may result in both decreased hepatocyte function, with as much as a 50% decrease in cytochrome P450 content, and/or shunting of blood away from optimally functioning hepatocytes. Accordingly, cirrhosis affects drug elimination and the absorption of nonrestrictively eliminated drugs more than any other form of liver disease. An important consequence of these changes is that the clearance of drugs that are nonrestrictively eliminated in subjects with normal liver function no longer approximates hepatic blood flow but is influenced to a greater extent by hepatic intrinsic clearance (20).

**Influence of portosystemic shunting:** When portosystemic shunting is present, total hepatic blood flow \( Q \) equals the sum of perfusion flow \( Q_p \) and shunt flow \( Q_s \). Portocaval shunting will impair the efficiency of hepatic extraction and reduce the extraction ratio, as indicated by the following modification of Equation 5 (21).

\[
ER = \frac{f_u \cdot CL_{int}}{Q} \cdot \frac{Q_p}{Q} + \frac{Q_p}{Q} \cdot \frac{f_u \cdot CL_{int}}{Q} = \frac{Q_p}{Q} \cdot \frac{f_u \cdot CL_{int}}{Q + f_u \cdot CL_{int}} \quad \text{Equation 11}
\]

The corresponding impact on hepatic clearance is given by the following equation:

\[
CL_H = Q_p \left[ \frac{f_u \cdot CL_{int}}{Q + f_u \cdot CL_{int}} \right] \quad \text{Equation 12}
\]

As a result, portocaval shunting will reduce hepatic clearance of nonrestrictively metabolized drugs but will have little impact on the clearance of restrictively eliminated drugs.

Similarly, restrictively metabolized drugs exhibit little first-pass metabolism even in subjects with normal liver function and portocaval shunting will have little impact on their
bioavailability. On the other hand, portocaval shunting will decrease the extraction ratio and increase the bioavailability of nonrestrictively metabolized drugs as follows:

\[
F = 1 - \frac{f_u \cdot CL_{int}}{Q} \cdot \frac{Q_p}{Q} \quad \text{Equation 13}
\]

For example, if the extraction ratio of a completely-absorbed but nonrestrictively metabolized drug falls from 0.95 to 0.90, the bioavailability will double from 0.05 to 0.10. Because this increase in absorption is accompanied by a decrease in elimination clearance, total exposure following oral administration of nonrestrictively eliminated drugs will increase to an even greater extent than the increase in bioavailability, as shown in Table 2 for meperidine (22), pentazocine (22) and propranolol (23). Cirrhosis also is associated with a reduction in propranolol binding to plasma proteins, so this also contributes to the increased exposure following either intravenous or oral doses of this drug (see below). Accordingly, the relative exposure estimates for propranolol in Table 2 are based on comparisons of area under the plasma-level-vs.-time curve of nonprotein bound plasma concentrations. The increase in drug exposure resulting from these changes may result in unexpected increases in intensity of pharmacologic response or in toxicity.

Table 2. Impact of cirrhosis on bioavailability and relative exposure to doses of nonrestrictively eliminated drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absolute Bioavailability (%)</th>
<th>Relative Exposure Cirrhotics/Control</th>
<th>IV (%)</th>
<th>Oral (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEPERIDINE</td>
<td>48</td>
<td>87</td>
<td>1.6</td>
<td>3.1</td>
</tr>
<tr>
<td>PENTAZOCINE</td>
<td>18</td>
<td>68</td>
<td>2.0</td>
<td>8.3</td>
</tr>
<tr>
<td>PROPRANOLOL</td>
<td>38</td>
<td>54</td>
<td>1.5*</td>
<td>2.0*</td>
</tr>
</tbody>
</table>

* These estimates also incorporate the 55% increase in propranolol free fraction that was observed in cirrhotic patients.

**Consequences of decreased protein binding:** Hypoalbuminemia frequently accompanies chronic liver disease and may reduce drug binding to plasma proteins (24). In addition, endogenous substances such as bilirubin and bile acids accumulate and may displace drugs from protein binding sites. Reductions in protein binding will tend to increase the hepatic clearance of restrictively metabolized drugs. For drugs that have low intrinsic clearance and tight binding to plasma proteins it is possible that liver disease results in a decrease in \( CL_{int} \) but also an increase in \( f_u \). The resultant change in hepatic clearance will depend on changes in both these parameters. Thus hepatic disease generally produces no change in warfarin clearance, a decrease in diazepam clearance, and an increase in tolbutamide clearance. However, as discussed in Lecture 5, unbound drug
concentrations will not be affected by decreases in the protein binding of restrictively metabolized drugs. Therefore, no dosage alterations are required for these drugs when protein binding is the only parameter that is changed.

Although reduced protein binding will not affect the clearance or total (bound plus free) plasma concentration of nonrestrictively eliminated drugs, this will increase the plasma concentration of free drug. This may increase the intensity of pharmacological effect that is observed at a given total drug concentration (24). Therefore, even in the absence of changes in other pharmacokinetic parameters, a reduction in the plasma protein binding of nonrestrictively eliminated drugs will necessitate a corresponding reduction in drug dosage.

As previously discussed in the context of renal disease (Lecture 5), reduced protein binding will increase the distribution volume referenced to total drug concentrations and this will tend to increase elimination-phase half life (24).

**Consequences of hepatocellular changes:** The liver content of cytochrome P450 enzymes is decreased in patients with cirrhosis. In these patients, intrinsic clearance is the main determinant of the systemic clearance of lidocaine and indocyanine green, two drugs that have nonrestrictive metabolism in subjects with normal liver function. However, cirrhosis does not reduce the function of different drug metabolizing enzymes uniformly. As can be seen from the results of the two *in vitro* studies summarized in Table 3, CYP1A2 content is consistently reduced in cirrhosis (25, 26).

**Table 3. Differential alterations of cytochrome P-450 enzyme content in cirrhosis**

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>REPRESENTATIVE SUBSTRATE</th>
<th>% CHANGE IN CIRRHOSIS</th>
<th>GUENGERICH AND TURVY (25)</th>
<th>GEORGE et al. (26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 1A2</td>
<td>Theophylline</td>
<td>? 53%*</td>
<td>? 71%†</td>
<td></td>
</tr>
<tr>
<td>CYP 2C19</td>
<td>Omeprazole</td>
<td>? 95%</td>
<td>? 43%</td>
<td></td>
</tr>
<tr>
<td>CYP 2E1</td>
<td>Acetaminophen</td>
<td>? 59%*</td>
<td>? 19%</td>
<td></td>
</tr>
<tr>
<td>CYP 3A</td>
<td>Midazolam</td>
<td>? 47%</td>
<td>? 75%†</td>
<td></td>
</tr>
</tbody>
</table>

* * P < .05, † P < .005, ‡ P < .0005

Significant reductions in CYP2E1 and CYP3A also have been found by some investigators. Although CYP2C19 appears to be somewhat more resilient in these *in vitro* studies, content of this enzyme was markedly reduced in patients with cholestatic types of cirrhosis (26). More recent studies in patients with liver disease, in whom the presence or absence of cholestasis was not noted, have indicated that clearance of S-mephenytoin, a CYP2C19 probe, was decreased by 63% in cirrhotic patients with mild cirrhosis and by 96% in patients with moderate cirrhosis (27). On the other hand, administration of debrisoquine to these patients indicated normal function of CYP2D6. Glucuronide
conjugation of morphine, and presumably of other drugs, is relatively well preserved in patients with mild and moderate cirrhosis but morphine clearance was 59% reduced in patients whose cirrhosis was severe enough to have caused previous hepatic encephalopathy (28).

**USE OF THERAPEUTIC DRUGS IN PATIENTS WITH LIVER DISEASE:**

A number of clinical classification schemes and laboratory measures have been proposed as a means of guiding dose adjustments in patients with liver disease, much as creatinine clearance has been used to guide dose adjustments in patients with impaired renal function. The Pugh modification of Child’s classification of liver disease severity (Table 4) is the classification scheme that is used most commonly in studies designed to formulate drug dosing recommendations for patients with liver disease (29, 30).

**Table 4. Pugh modification of Child’s classification of liver disease severity***

<table>
<thead>
<tr>
<th>ASSESSMENT PARAMETERS</th>
<th>1 POINT</th>
<th>ASSIGNED SCORE 2 POINTS</th>
<th>3 POINTS</th>
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<tbody>
<tr>
<td>Encephalopathy Grade*</td>
<td>0</td>
<td>1 or 2</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1 – 2</td>
<td>2 – 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
<td>&gt; 3.5</td>
<td>2.8 – 3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>1 – 4</td>
<td>4 – 10</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

**CLASSIFICATION OF CLINICAL SEVERITY**

<table>
<thead>
<tr>
<th>CLINICAL SEVERITY</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL POINTS</td>
<td>5 – 6</td>
<td>7 – 9</td>
<td>&gt; 9</td>
</tr>
</tbody>
</table>

* **ENCEPHALOPATHY GRADE**

| Grade 0 | Normal consciousness, personality, neurological examination, EEG |
| Grade 1 | Restless, sleep disturbed, irritable/agitated, tremor, impaired hand writing, 5 cps waves on EEG |
| Grade 2 | Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves on EEG |
| Grade 3 | Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves on EEG |
| Grade 4 | Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta waves on EEG |

* Adapted from Pugh et al. Br J Surg 1973;60:646-9 (29), and CDER, CBER. Draft Guidance for Industry, "Drug Metabolism and Pharmacokinetic Changes and Altered Pharmacologic Response Are Expected to be..."
most pronounced. The administration of narcotic, sedative and psychoactive drugs to patients with severe liver disease is particularly hazardous because these drugs have the potential to precipitate life-threatening hepatic encephalopathy.

**Effects of Liver Disease on the Hepatic Elimination of Drugs:**

A number of probe drugs have been administered to normal subjects and to patients to evaluate hepatic clearance. In one such test, a 1 mg/kg dose of lidocaine is administered intravenously and plasma concentrations of its N-dealkylated metabolite, monoethylglycinexylidide (MEGX) are measured either 15 or 30 minutes later. Testa et al. (31) found that a 30-minute post dose MEGX concentration of 50 ng/ml provided the best discrimination between chronic hepatitis and cirrhosis (sensitivity: 93.5%, specificity: 76.9%). These authors concluded that both hepatic blood flow and the CYP3A4 pathway responsible for metabolizing lidocaine to MEGX were well preserved in patients with mild and moderate chronic hepatitis. However, MEGX levels fell significantly in patients with cirrhosis and were well correlated with the clinical stage of cirrhosis. Because no single probe drug estimates the activity of all drug metabolizing enzymes, the strategy has been developed of simultaneously administering a combination of probes (32). As many as five probe drugs have been administered in this fashion to provide a profile of CYP1A2, CYP2E1, CYP3A, CYP2D6, CYP2C19 and N-acetyltransferase activity (33). The method was evaluated to exclude the possibility of a significant metabolic interaction between the individual probes. Unfortunately, tests with probe drugs are too cumbersome for routine clinical use. Nevertheless, clinical studies in which the clearance of probe drugs has been examined in patients with different gradations of liver disease suggest the approximate relationships shown in Figure 3.

**Figure 3:** Schematic diagram showing the effects of various stages of liver disease severity on the intrinsic clearance of drugs mediated by representative metabolic pathways. Estimates for glucuronidation (28), CYP2D6 (27), CYP3A4 (31) and CYP2C19 (27) pathways are based on the literature sources indicated in parentheses.
Bergquist et al. (34) have presented examples in which several laboratory tests that are commonly used to assess liver function provide a more reliable indication of impaired drug metabolic clearance than this clinical classification scheme (Table 5).

Table 5. Correlation of laboratory test results with impaired hepatic clearance *

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ENZYME(S)</th>
<th>LABORATORY TEST</th>
<th>ALBUMIN</th>
<th>BILIRUBIN</th>
<th>PT†</th>
</tr>
</thead>
<tbody>
<tr>
<td>“A”</td>
<td>CYP2C9</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“B”</td>
<td>Not given</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atorvastatin</td>
<td>CYP3A4</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>lansoprazole</td>
<td>CYP3A4 + CYP 2C19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Serum albumin concentrations were of greatest predictive value for two of the drugs shown in the table. However, this marker was not correlated with the hepatic clearance of lasoprazole, and a combination of all three laboratory tests was better correlated with hepatic clearance of atorvastatin than serum albumin alone. Serum concentrations of AST or ALT were not correlated with hepatic drug clearance, as might be expected from the fact that these enzymes reflect hepatocellular damage rather than hepatocellular function.

Equation 12 emphasizes the central point that changes in perfusion and protein binding, as well as intrinsic clearance, will affect the hepatic clearance of a number of drugs. The intact hepatocyte theory has been proposed as a means of simplifying this complexity (35). This theory is analogous to the intact nephron theory (see Lecture 5) in that it assumes that the increase in portocaval shunting parallels the loss of functional cell mass, and that the reduced mass of normally functioning liver cells is perfused normally. Other theories have been proposed to account for the effects of chronic liver disease on hepatic drug clearance and it currently is not clear which, if any, of these theories is most appropriate (36). However, what is apparent from studies in patients with significantly impaired liver function, is that the intrinsic clearance of some drugs that normally are nonrestrictively metabolized is reduced to the extent that \( f_uCL_{int} \) now becomes rate limiting and clearance is no longer approximated by hepatic perfusion rate (20). It also is apparent from Equation 13 that the presence of portosystemic shunting and hepatocellular damage will significantly increase the bioavailability of drugs that normally have extensive first pass hepatic metabolism.
**Effects of Liver Disease on the Renal Elimination of Drugs:**

Drug therapy in patients with advanced cirrhosis is further complicated by the fact that renal blood flow and glomerular filtration rate are frequently depressed in these patients in the absence of other known causes of renal failure. This condition, termed the *hepatorenal syndrome*, occurs in a setting of marked hemodynamic change and is a functional abnormality that reverses following successful liver transplantation. Ginès et al. (37) monitored 234 patients with cirrhosis, ascites and a glomerular filtration rate (GFR) of more than 50 mL/min. These authors found that this syndrome developed within one year in 18%, and within five years in 39%, of these patients. Although Pugh score was of no predictive value, high plasma renin activity, low serum sodium concentrations and small liver size were independent predictors of the onset of the hepatorenal syndrome. Baseline GFR also was of predictive value but serum creatinine and creatinine clearance, either measured or calculated from the Cockcroft and Gault equation (Lecture 5), overestimated renal function in this group of patients (38). This overestimation reflects the fact that the rate of creatinine synthesis is depressed in these patients, so serum creatinine concentrations may remain within the normal range even when inulin clearance falls as low as 10 mL/min. As a result, many patients with cirrhosis and ascites have a normal serum creatinine concentration but a GFR of less than 60 mL/min.

The need for caution in estimating drug dosage for patients with the hepatorenal syndrome is exemplified by carbenicillin, an antipseudomonal, semisynthetic penicillin that is excreted primarily by the kidneys with biliary excretion normally accounting for less than 20% of total elimination. The decline in renal function that is associated with severe liver disease prolongs the elimination half-life of this drug from 1 hour in subjects with normal renal and liver function to approximately 24 hours (39). Although studies in patients with hepatorenal syndrome were not reported, similar half-life prolongations have been described in patients with combined renal and hepatic functional impairment who were treated with the newer but pharmacokinetically similar antipseudomonal penicillins piperacillin (40) and mezlocillin (41). Consequently, it is advisable to consider reducing doses even for drugs that are eliminated to a significant extent by renal excretion when treating patients with cirrhosis that is severe enough to be accompanied by ascites.

**Effects of Liver Disease on Patient Response:**

The relationship between drug concentration and response also can be altered in patients with advanced liver disease. Of greatest concern is the fact that customary doses of sedatives may precipitate the disorientation and coma that are characteristic of portal-systemic or hepatic encephalopathy. Experimental hepatic encephalopathy is associated with increased γ-aminobutyric acid-mediated inhibitory neurotransmission, and there has been some success in using the benzodiazepine antagonist flumazenil to reverse this syndrome (42). This provides a theoretical basis for the finding that brain hypersensitivity, as well as impaired drug elimination, is responsible for the exaggerated sedative response to diazepam that is exhibited by some patients with chronic liver disease (43). Bakti et al. (44) conducted a particularly well-controlled demonstration of benzodiazepine
hypersensitivity by showing that CNS performance in cirrhotic patients was impaired when compared to subjects with normal liver function at a time when plasma concentrations of unbound triazolam were the same in both groups. Changes in the CSF/serum concentration ratio of cimetidine have been reported in patients with liver disease, suggesting an increase in blood-brain barrier permeability that also could make these patients more sensitive to the adverse CNS effects of a number of other drugs (45).

Although cirrhotic patients frequently are treated with diuretic drugs to reduce ascites, they exhibit a reduced responsiveness to loop diuretics that cannot be overcome by administering larger doses and is presumably related to the pathophysiology of increased sodium retention that contributes to the development of ascites (46). In addition, decreases in renal function, which are often unrecognized in these patients (38), may lead to decreased delivery of loop diuretics to their renal tubular site of action. Because hyperaldosteronism is prevalent in these patients and spironolactone is not dependent on glomerular filtration for efficacy, it should be the mainstay of diuretic therapy in this clinical setting (47).

When diuretic therapy does result in effective fluid removal in cirrhotic patients, it is associated with a very high incidence of adverse reactions. In one study of diuretic therapy in cirrhosis, furosemide therapy precipitated the hepatorenal syndrome in 12.8% and hepatic coma in 11.6% of the patients (48). Although daily doses of this drug did not differ, patients who had adverse drug reactions received total furosemide doses that averaged 1384 mg, whereas patients without adverse reactions received lower total doses that averaged 743 mg. Accordingly, when spironolactone therapy does not provide an adequate diuresis, only small frequent doses of loop diuretics should be added to the spironolactone regimen (47). Cirrhotic patients also appear to be at an increased risk of developing acute renal failure after being treated with angiotensin converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs (49).

**Modification of Drug Therapy in Patients with Liver Disease:**

It is advisable to avoid using certain drugs in patients with advanced liver disease. For example, angiotensin converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs should be avoided because of their potential to cause acute renal failure. Paradoxically, administration of captopril to cirrhotic patients with ascites actually impairs rather than promotes sodium excretion (50). Since coagulation disorders are common in patients with advanced cirrhosis, alternatives should be sought for therapy with ß-lactam antibiotics that contain the N-methylthiotetrazole side chain (e.g. cefotetan) that inhibits ß-carboxylation of vitamin K-dependent clotting factors (49).

It also is prudent to reduce the dosage of a number of other drugs that frequently are used to treat patients with liver disease (51). Particular attention has been focused on drugs whose clearance is significantly impaired in patients with moderate hepatic impairment, as assessed in Table 4 (30). Even greater caution should be exercised in using these drugs to treat patients with severely impaired liver function. Table 6 lists several
drugs whose dose should be reduced by 50% in treating patients with moderate hepatic impairment.

Table 6. Some drugs requiring at least a 50% dose reduction in patients with moderate cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>$F$ (%)</th>
<th>$F$ (%)</th>
<th>CLEARANCE</th>
<th>$f_u$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANALGESIC DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>47</td>
<td>100</td>
<td>? 59%</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>47</td>
<td>91</td>
<td>? 46%</td>
<td></td>
</tr>
<tr>
<td>Pentazocine</td>
<td>17</td>
<td>71</td>
<td>? 50%</td>
<td></td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>21</td>
<td>75</td>
<td>? 24%</td>
<td>? 213%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>22</td>
<td>52</td>
<td>? 51%</td>
<td>No Change</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>51</td>
<td>91</td>
<td>? 60%</td>
<td>? 93%</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>40</td>
<td>54</td>
<td>? 34%</td>
<td>? 43%</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>4</td>
<td>15</td>
<td>? 42%</td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>33</td>
<td>66</td>
<td>? 50%</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>56</td>
<td>98</td>
<td>? 89%</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>27</td>
<td>36</td>
<td>? 72%</td>
<td></td>
</tr>
</tbody>
</table>

Most of the drugs in this table have first-pass metabolism that is greater than 50% in normal subjects but is substantially reduced when liver function is impaired. Drug exposure to standard doses is further increased by what is generally a substantial decrease in elimination clearance. Although not routinely evaluated in most studies of patients with liver disease, drug binding to plasma proteins also may be reduced in these patients and may contribute to exaggerated responses. Formation of pharmacologically active metabolites is another complicating factor that deserves consideration. For example, losartan has an active metabolite, EXP3174, that is primarily responsible for the extent and duration of pharmacological effect in patients treated with this drug (57). Although standard doses produce plasma concentrations of losartan that are four to five times higher in patients with cirrhosis than those observed in normal subjects, plasma levels of EXP3174 are only increased by a factor of 1.5 to 2.0 (59). This provided the rationale for reducing the usual losartan dose by only half in a trial in which this drug was used to reduce portal pressure in patients with cirrhosis and esophageal varices (62).
REFERENCES:


