MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

April 27, 1978

DRUG METABOLISM IN LIVER DISEASE

Raymond F. Burk, M.D.

The principal organs of drug elimination are the kidney and the liver. Alterations in the function of these organs are often associated with marked changes in unbound plasma drug concentrations with a given drug regimen. Such changes may result in adverse effects of the drugs when levels are elevated or in failure to achieve therapeutic goals when levels are depressed.

The role of the kidney in drug elimination is reasonably well understood. For the most part it eliminates drugs by excreting them unchanged in the urine. Most clinicians are familiar with the use of the creatinine clearance to alter dosages of drugs eliminated primarily by renal excretion. Under some conditions changes in protein binding of drugs and consequently their tissue distribution occur in renal disease. These may also affect drug elimination.

Less well understood is the role of the liver in drug elimination. Although it may excrete certain substances unchanged in the bile, e.g., indocyanine green, its greatest contribution by far to drug elimination is through its capacity to metabolize drugs to inactive forms or to forms which can be readily excreted. This drug metabolism or biotransformation, as it is sometimes called, is carried out by a number of enzyme systems with broad substrate specificities (Table 1). The activities of these enzyme systems are influenced by genetic, pharmacologic, hormonal, and nutritional factors.

No predictor of hepatic drug elimination analogous to the creatinine clearance is known. Consequently in recent years a great deal of research has been carried out to determine the factors which influence hepatic drug elimination in the hope that a rational approach to drug therapy in liver disease could be developed. Although the final goal has not been reached, many of these factors are better understood now and there is hope for the development of guidelines in the near future.

Possible Benefits From Better Understanding of Hepatic Drug Metabolism

1. Ability to predict altered dose requirements of drug based on some measure of hepatic function,
2. Use of drug metabolism measurements as tests of liver function,
3. Better understanding of conditions under which some drugs which are metabolized by the liver become hepatotoxic (2).

Table 1. General pathways of drug metabolism by nonspecific enzymes in liver.

Phase I Reactions	Localization of Enzymes
Oxidations	
hydroxylations	microsomes
dealkylations	microsomes
oxide formation	microsomes
desulfuration	microsomes
dehalogenation	microsomes
alcohol oxidation	soluble, microsomes (minor)
aldehyde oxidation	soluble
Reductions	
aldehyde reduction	soluble
azoreduction	microsomes
nitroreduction	microsomes, soluble
Hydrolyses	
de-esterification	microsomes, soluble
deamidation	microsomes, soluble
Phase II Reactions	**Localization of Enzymes**
glucuronide conjugation	microsomes
acylation	mitochondria, soluble
methylation	soluble
mercapturic acid formation	soluble
sulfate conjugation	soluble

(from ref. 1)

Hepatic and Intestinal Drug Elimination in Perspective

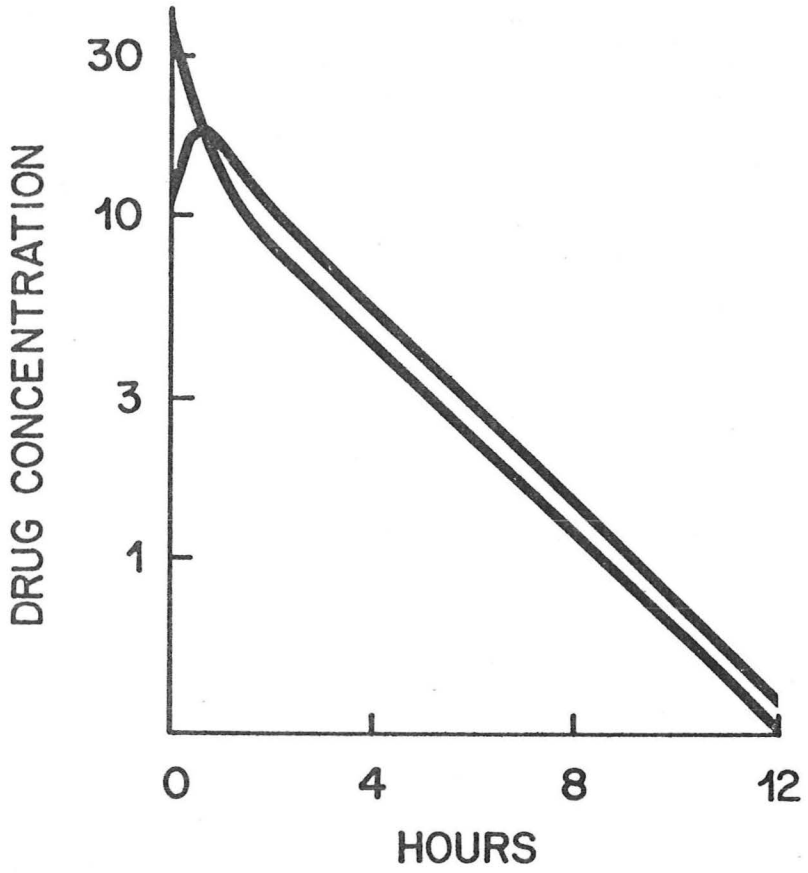

Fig. 1. Simulated time course of drug concentration in blood after intravenous and oral administration. The concentration scale is logarithmic.

Definitions (for more details see 3):

1. Elimination refers to irreversible removal of drug per se from the body. This results from excretion or metabolism. Metabolites may or may not accumulate.

2. Systemic availability refers to the fraction of drug which reaches the systemic circulation. When a drug is given intravenously, its systemic availability is 1. When a drug is given orally, its systemic availability may be reduced by: a) incomplete absorption (low bioavailability), b) elimination by the intestinal mucosa during absorption, and c) elimination during its first pass through the liver. In Fig. 1 the areas under the curves after oral and intravenous administration are the same indicating an oral systemic availability of 1.

3. Elimination kinetics. In most instances drug elimination is first order, i.e., a fixed fraction of the drug present is eliminated per time unit. This results in a linear plot on a logarithmic scale as

seen in Fig. 1. The finding of first order elimination implies that the elimination mechanisms are functioning far below their maximal capacity or saturation. In a few instances, e.g., ethanol and diphenylhydantoin, elimination mechanisms may become saturated and elimination may be zero order. This means that a fixed amount of drug is eliminated per time unit. Under these conditions blood levels of the drug will rise much more for a given dosage increment than when first order kinetics pertains.

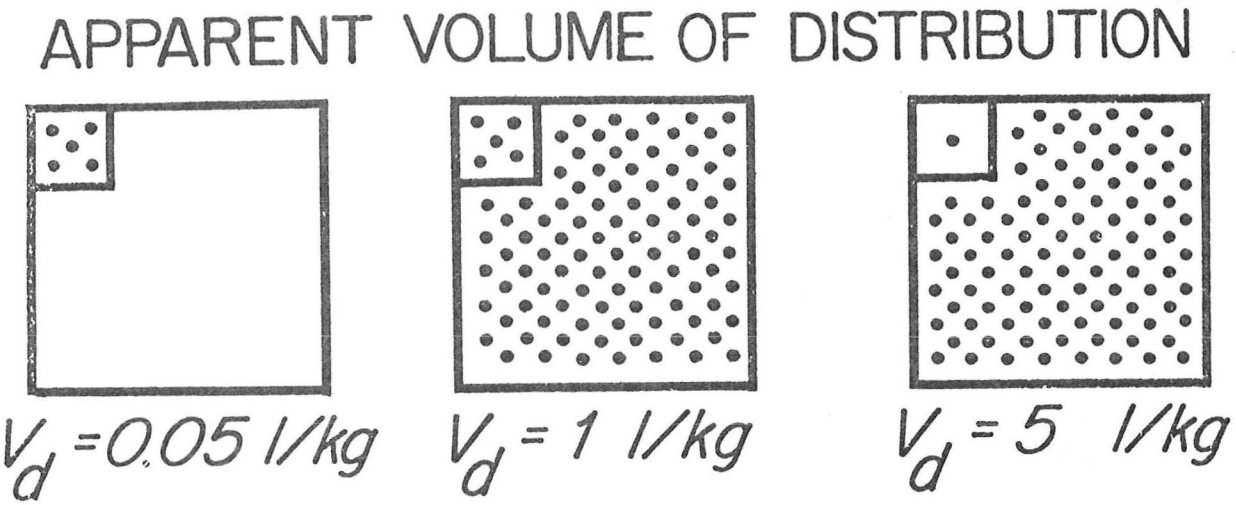

Fig. 2. Examples of low, intermediate, and high V_d's. The small square represents the plasma and is intended to be 5% of the total tissue volume represented by the larger square. The dots represent drug molecules.

4. Apparent volume of distribution (V_d) of a drug is the relationship between the amount of drug in the body and the plasma drug concentration after absorption and distribution. With the aid of this value, expressed in liters/kg or liters, plasma drug concentration can be used to calculate total body burden of the drug. If all the drug is present in the plasma the V_d would be the same as plasma volume (about .05 liter/kg) but if the drug distributes extensively in the tissues, this value may be many liters/kg.

5. Half-life of a drug is the time required for elimination processes to effect a halving of plasma drug concentration. This is applicable when elimination kinetics are first order. Since plasma drug is in equilibrium with total body drug, this implies that the total body burden of drug is halved also.

6. Clearance is most often used in connection with urinary excretion but it is possible to define total body clearance of a drug if elimination is first order. It is the rate of elimination of the drug by the body (sum of all elimination pathways) divided by the average plasma concentration of the drug. Intuitively clearance must be related to half-life and also to V_d. It can be expressed:

$$Cl_T = 0.693 \cdot \frac{V_d}{T_{1/2}}$$

Thus, half-life alone does not define clearance and the use of half-life alone as an indication of drug elimination or clearance is inadequate. V_d must also be considered. Clearance determines the plasma drug level achieved with a given dose rate.

Now that we have defined our terms and the total-body clearance (Cl_T) concept has been introduced it can be readily appreciated that

$$Cl_T = Cl_H + Cl_R + \ldots$$

where Cl_H is hepatic clearance and Cl_R is renal clearance. Pulmonary and skin clearances may be important in some cases. When drug elimination is virtually all due to urinary excretion this term reduces to

$$Cl_T = Cl_R$$

In that case the creatinine clearance can often serve as a guide in designing a drug regimen. If both kidneys and liver contribute significantly to drug elimination, decreased clearance by one pathway may be offset by the other with only a minimal rise in plasma concentration since first order kinetics usually are operating. In recent years it has been appreciated that many drugs are cleared almost exclusively by the liver, i.e.,

$$Cl_T = Cl_H$$

This has led to numerous studies of factors influencing Cl_H of these drugs and has resulted in proposal of a model describing Cl_H.

Hepatic Clearance

Hepatic clearance can be expressed:

$$Cl_H = QE = Q\ (\frac{Ca-Cv}{Ca})$$

where Q is hepatic blood flow and E is the extraction ratio defined as the fraction of the drug present in the blood entering the liver which is removed by that organ. Ca and Cv are the drug concentrations in blood entering and leaving the liver, respectively.

Experimentally, it has been shown that some drugs have a high extraction ratio and thus one pass through the liver almost results in their complete removal. Other drugs have a very low extraction ratio and their elimination characteristics are quite different.

A model has been proposed to account for these characteristics and to quantitate them (4,5). At the heart of this model is the intrinsic clearance (Cl_{int}). This is defined as the maximum rate

of drug elimination by the liver in the absence of blood flow limitations. It is characteristic for a given drug and a given set of physiological conditions. Cl_{int} is an attempt to dissociate the factors responsible for Cl_H. Logically these factors are: 1) the rate at which drug is brought to the liver (Q) and 2) the ability of the liver to eliminate drug presented to it (Cl_{int}). Using these new terms the model redefines extraction:

$$E = \frac{Cl_{int}}{Q + Cl_{int}}$$

Thus, if Cl_{int} is very high relative to Q, E will be nearly 1 and will be changed very little by alterations in Q. In this case Cl_H is said to be flow dependent since $Cl_H = QE$ and E is nearly 1. Changes in Q will result in equivalent changes in Cl_H. Drugs with very high hepatic extraction ratios are said to be flow-dependent.

When Cl_{int} is very small relative to Q, then E will vary inversely with Q and this tends to counteract the effects of blood flow alterations. Under these conditions (low Cl_{int}) then Cl_H tends to be independent of Q and drugs with low Cl_{int} are termed flow-independent. These hypotheses have been supported by animal experiments (6,7).

Since flow-dependent drugs are almost totally extracted in one pass, the extent of binding in the blood (f_B) plays a minimal role in their clearance under most circumstances. The implication is that as unbound drug is eliminated, bound drug dissociates rapidly enough to be cleared. The situation is different with flow-independent drugs. Some are called binding-sensitive in which case high binding may restrict elimination. Some are binding-insensitive, the fraction of drug bound not affecting elimination. Obviously, the extent of drug binding in the blood may affect the V_d and lead to alterations in clearance in that way also.

First Pass Effect

The first pass effect is an important determinant of the systemic availability of a drug. Before it reaches the systemic circulation an orally-administered drug must negotiate two potential sites of elimination: the intestinal mucosal cell and the liver.

Table 2. Pharmacokinetic classification of some drugs eliminated primarily by hepatic metabolism (from 8).

	Drug	Approximate Extraction Ratio	f_B (%)
Flow-dependent	Lidocaine	.83	45-80
	Propranolol	.6-.8	93
	Meperidine	.6-.95	60
	Propoxyphene	.95	--
	Morphine	.5-.75	35
Flow-independent, binding-sensitive	Diazepam	.03	98
	Tolbutamide	.02	98
	Warfarin	.003	99
	Digitoxin	.005	97
Flow-independent, binding-insensitive	Theophylline	.09	59
	Amobarbital	.03	61
	Antipyrine	.07	10
	Acetaminophen	.43	<5

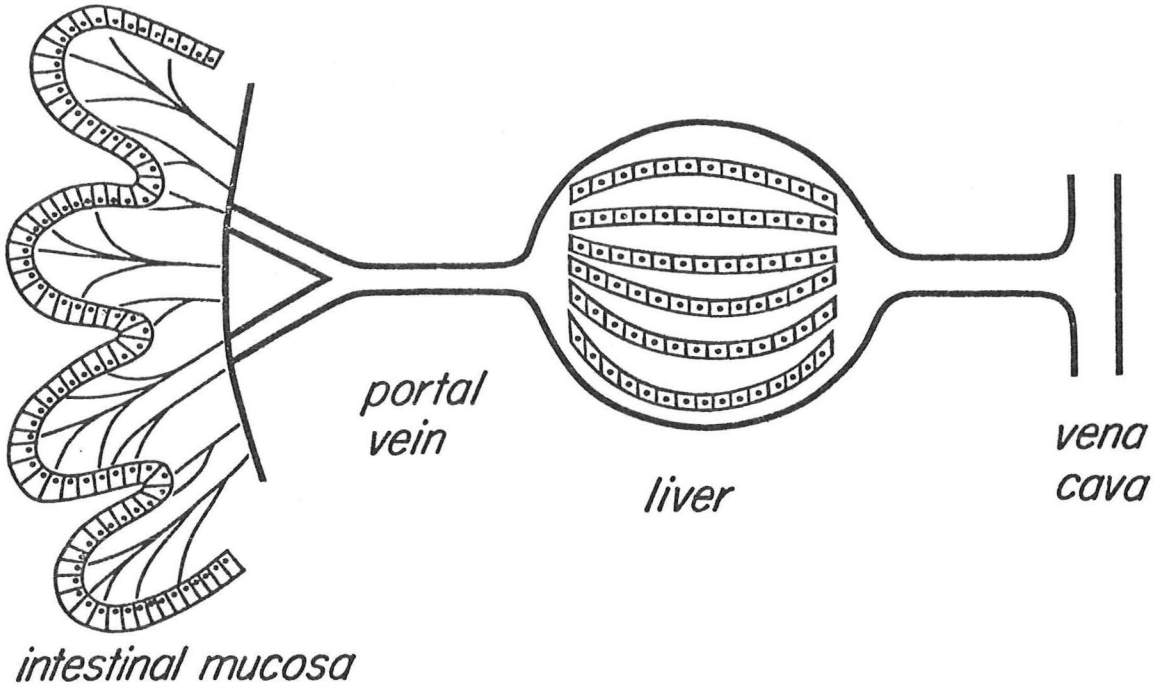

Fig. 3. Schematic view of route orally administered drug must take to reach systemic circulation. The intestinal mucosa and the liver are potential sites of elimination.

Enzyme systems for drug metabolism are present in the intestinal mucosal cell (9). These systems can be induced by cigarette smoking, eating charcoal-broiled meat, and eating cabbage or brussels sprouts (10,11). Under some of these conditions the systemic availability of phenacetin has been shown to be lowered markedly. Virtually nothing is known about how intestinal disease affects mucosal cell drug metabolism. Potentially this is very important.

Drugs with a high hepatic extraction ratio may be almost completely eliminated before reaching the systemic circulation. This requires that oral doses of such drugs be much higher than parenteral doses. If $E = .90$ and $Q = 1.5$ l/min then $Cl_{int} = 13.5$ l/min by

$$E = \frac{Cl_{int}}{Q + Cl_{int}}$$

Doubling Cl_{int} (by enzyme induction, for example) to 27 l/min increases E to .947 which is a small increase and has little effect on terminal half-life. But when $E = .90$, 10% of the absorbed drug would be systemically available; and when $E = .947$, only 5.3% would be available. Thus

raising intrinsic clearance of flow-dependent drugs markedly diminishes their systemic availability but has little effect on systemic clearance (which is more affected by blood flow changes).

Drugs with a low extraction ratio (E = .10) have a small hepatic first-pass effect (90% available). Doubling Cl_{int} from .17 to .34 l/min raises the E to .185 and lowers systemic availability only trivially (from 90% to 81.5%). However, since Cl_H is flow-independent and directly dependent on Cl_{int}, systemic clearance will be markedly increased and half-life will be shortened markedly.

General Physiological and Pathophysiological Considerations

Drug metabolizing enzymes. Cl_{int} is often dependent on the activity of enzymes for which the drug is substrate. Thus changes in the activity of those enzymes can result in Cl_{int} changes. Aside from the effects of disease many other factors may influence these activities. Genetic (12), nutritional (13), and environmental (14) effects have been documented. Especially important are pharmacological interactions. Several commonly-used drugs-barbiturates, diphenylhydantoin, rifampicin (15,16) - are known inducers of drug metabolizing enzymes. Patients receiving these agents may have increased Cl_{int} for some drugs.

Inhibition of drug metabolizing enzyme systems by therapeutic agents has also been documented. Chloramphenicol inhibits the elimination of tolbutamide (17) presumably through its effect on the hepatic cytochrome P-450 system (18). Probenecid inhibits the metabolism of azathioprine to 6-mercaptopurine, a drug activation, by blocking glutathione S-transferase activity in liver (19). Ethanol may either inhibit or stimulate drug metabolism (20,21).

Hepatic blood flow. Changes in total hepatic blood flow could lead to marked changes in clearance of endogenous substances and drugs which have a high Cl_{int}, i.e., they are flow-dependent. About two-thirds of hepatic blood flow is supplied by the portal vein with the rest coming from the hepatic artery. It has been recently hypothesized that a major function of the hepatic artery is to maintain hepatic blood flow - and thus metabolic clearances - constant in the face of changes in portal blood flow (22). In spite of this, published values of hepatic blood flow in normal subjects vary widely (23). At the present time then, the factors which determine hepatic blood flow are not known with certainty.

Portal-systemic shunts result in elimination of the hepatic contribution to the first-pass effect. Marked increases in systemic availability of highly extracted drugs have been demonstrated in dogs after end-to-side portacaval shunts (24). For this reason oral doses of drugs with a large first-pass effect should be decreased in patients with portal-systemic shunts.

Liver disease. Liver disease may alter all the factors determining Cl_H. Hepatic blood flow may be decreased and portal-systemic shunting may be present. Hepatic mass may be diminished with consequent decrease

in Cl_{int}. Binding of the drug in the blood may be altered because of changes in plasma protein concentrations or by accumulation of substances, e.g., bilirubin, which can displace drugs from binding sites. Cholestasis has been associated with decreases in hepatic drug metabolizing enzymes in animals (25), but studies in patients with cholestasis have not shown consistent decreases in drug metabolism (26).

Specific Drugs

Antipyrine. Antipyrine and the related aminopyrine (27,28) are the most commonly used drugs for assessing the hepatic cytochrome P-450 system in man. They are well suited for this because 1) systemic availability is almost 1, 2) distribution is rapid and protein binding is minimal, 3) less than 5% is excreted unchanged, and 4) virtually all metabolism takes place in the liver.

Antipyrine has a low Cl_{int} and is considered to be flow-independent. $Cl_H \pm SD = 48 \pm 9.0$ ml/min ($n = 29$) in one study of normal persons (29). Therefore changes in its clearance might be expected to reflect the activity of its metabolizing enzymes (cytochrome P-450 system). Genetic studies indicate a wide range of clearances which, however, change little for an individual at different times if conditions are similar (29) and identical twins have similar clearances (12). Exposure of patients to cytochrome P-450-inducing drugs causes an increase in clearance (15). Because of the wide individual variation and the susceptibility to alteration by other agents, the clearance of antipyrine may not correlate with other measures of liver function (27). For this reason it and other drugs like it are not very useful for assessing hepatic mass or function in an individual, although significant differences are seen between groups with and without liver disease.

Lidocaine. Lidocaine is highly extracted ($E = 0.7$) and is therefore flow-dependent under most circumstances (30). For this reason patients with low-flow states, such as heart failure, may have impaired clearance (31). The high extraction also explains the need to give lidocaine parenterally.

Lidocaine clearance has been studied in patients with acute viral hepatitis and with cirrhosis and found to be decreased in most patients (32). However, some with viral hepatitis showed no change or an increased clearance. Attempts to correlate lidocaine and indocyanine green clearances in these patients failed. Thus no concrete rules for lidocaine administration can be given but special caution should be exercised in patients with low-flow states and in patients with liver disease.

Theophylline. Theophylline is metabolized extensively by the hepatic cytochrome P-450 system and has a low Cl_{int} (8). Thus it should be flow-independent. A high incidence of adverse reactions has been noted in patients with hepatic dysfunction who received theophylline (33).

A recent study of cirrhotics (34) has demonstrated impaired clearance of the drug, which was marked in some patients, but no change in V_d was found. This means that dosage schedules of theophylline should be revised in patients with liver dysfunction. The only predictive factor found was that a serum albumin of less than 3 g/dl was associated with markedly diminished clearance. Those authors suggest use of theophylline levels as a therapeutic guide.

Diazepam (Valium®) and Oxazepam (Serax®). Diazepam is one of the most widely-used drugs in medical practice. Its tranquilizing effects are often needed in patients with liver disease but these patients may suffer hepatic encephalopathy due to its inappropriate use. It is important then to understand the effects of liver disease on its metabolism.

Insignificant amounts of unchanged diazepam are excreted in the urine and the bile (35). The drug is metabolized almost exclusively in the liver (Fig. 4). The major metabolite is demethyldiazepam which is hydroxylated in the liver to form oxazepam. Oxazepam is conjugated with glucuronic acid and excreted in the urine. Diazepam, demethyldiazepam, and oxazepam are all pharmacologically active.

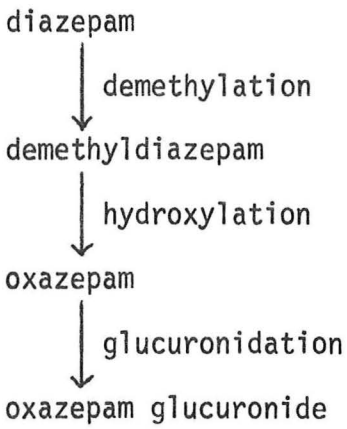

Fig. 4. Metabolism of diazepam in the liver.

Systemic availability of diazepam is around 75%, likely due to incomplete absorption (35). Its V_d is increased in older persons but Cl_T is unaffected by age (35). Cl_{int} and therefore E are low so Cl_T should be flow-independent but sensitive to changes in Cl_{int}.

Indeed, studies of patients with cirrhosis and with acute viral hepatitis have demonstrated marked decreases in diazepam clearance (35). No correlation could be established, however, between Cl_T and any standard tests of liver function.

Demethyldiazepam accumulates in patients treated with diazepam. Its subsequent hydroxylation to oxazepam is considerably slower than its formation rate (35,36). The Cl_T of demethyldiazepam has also been shown to be decreased in patients with cirrhosis (36).

Oxazepam does not accumulate in patients treated with diazepam because of its rapid glucuronidation and excretion (36). Since it is an effective tranquilizer, its disposition has been studied in patients with cirrhosis and with viral hepatitis (37). No parenteral preparation is available so complete study of pharmacokinetic parameters was not possible. However, apparent oral clearance, V_d, and $T_{\frac{1}{2}}$ were unaffected by either type of liver disease. Furthermore, chronic administration of the drug resulted in similar plasma levels in subjects with and without liver disease. Based on these findings, it has been recommended that oxazepam be used as the tranquilizer-sedative of choice in patients with liver disease (37).

Meperidine. Meperidine (Demerol) is a widely used analgesic which has been implicated in precipitating hepatic encephalopathy. It is a highly extracted drug but its V_d is large. Its disposition and elimination have been studied in patients with cirrhosis and with viral hepatitis (38,39).

Both these groups had diminished plasma clearance of meperidine without significant alterations in V_d. pH of urine was maintained above 7.0, eliminating renal meperidine excretion. Thus Cl_H of meperidine is low in these patients with liver disease. Since the drug has a high E, its oral systemic availability might be raised dramatically by portal-systemic shunting. These findings indicate that caution should be exercised 1) when prolonged administration of meperidine is required in liver disease and 2) when meperidine is administered orally to patients with portal-systemic shunting.

Propranolol. Propranolol (Inderal) is widely used in the treatment of angina, cardiac arrhythmias, and hypertension. It can be given by mouth or parenterally but the oral dose is 6-10 times higher than the parenteral dose (40). This is due to the first pass effect. E has been shown to be in the range 0.64 to 0.73 (23,40,41). This extraction ratio indicates that Cl_H should be dependent both on flow and on Cl_{int}.

A recent study of d-propranolol pharmacokinetics in patients with cirrhosis demonstrates impaired Cl_H of the drug (41). E was reduced from 0.73 in controls to 0.41 in cirrhotics. Hepatic blood flow was also decreased in cirrhosis. Cl_T was 21 ml/min/kg in normals and only 8 ml/min/kg in cirrhotics. These authors calculated that the decrease in Cl_T was due mainly to impaired ability of the liver to remove drug from the blood (Cl_{int}).

Tolbutamide. Clearance of tolbutamide is accelerated in some forms of liver disease. It has a moderately low Cl_{int}, and Cl_H is binding-sensitive. Thus the accelerated clearance in acute viral hepatitis can be explained by diminished plasma binding which overcomes the decrease in Cl_{int} (42). Substances are thought to accumulate which decrease plasma binding and also tissue binding so no change in V_d occurs. Similar observations have been made in patients with bile duct obstruction (26). The authors point out that while clearance is accelerated in these cases, the unbound drug concentration in the plasma may be unaffected and it is thought that this is the critical determinant of drug action.

Inhibition of tolbutamide metabolism by chloramphenicol has been described (17). This is probably due to the inhibition of a cytochrome P-450 dependent system (18).

Prednisone. Since prednisone is frequently employed in the treatment of chronic active hepatitis and active post-necrotic cirrhosis, the effect of liver disease on its metabolism is important. Like cortisone, prednisone presumably has no antiinflammatory activity and must be converted to prednisolone. In normal subjects this conversion is complete and occurs mainly in the liver (43).

A recent study of patients with chronic active liver disease of varying severity has shown only minimal effects of liver disease on prednisone pharmacokinetics (43). Furthermore it showed that conversion to prednisolone was not impaired under those circumstances.

Azathioprine. Another immunosuppressive drug used to treat liver disease is azathioprine. It is converted to 6-mercaptopurine in the liver by the glutathione S-transferases (19). No recent studies are available but immunosuppressive activity of serum from patients receiving the drug is lower in those with severe liver disease than in normals (44). This raises the possibility that azathioprine clearance may be lowered by liver disease.

Drug Metabolism as a Liver Function Test

Since drug metabolism is a liver function, it seems that one should be able to use it as a liver function test if the proper conditions and drug are chosen. Cl_{int} would seem to best reflect the hepatic mass. Cl_{int} is measured most easily with flow-independent drugs. Most investigators have used antipyrine for this since its distribution is little affected by protein binding. However, as mentioned above there is wide individual variation in clearance of antipyrine. In addition the enzymes which metabolize antipyrine are induced by a number of drugs, environmental agents, and dietary factors. Because of these additional factors affecting Cl_{int}, its measurement may not be a good estimation of functioning hepatic mass. It may be especially misleading in an individual as opposed to group studies.

Recently a method has been developed for estimating hepatic blood flow by determining simultaneously the clearance of orally and intravenously administered propranolol (23). The method can only be used in subjects with normal hepatic vasculature (no portal-systemic shunting) so it cannot be used in patients with liver disease. This limits its value.

Prediction of Drug Dosage Requirements in Liver Disease

Many investigators have tried to correlate drug $T_{\frac{1}{2}}$ or Cl_T with commonly available clinical markers of liver disease. In general these attempts have failed. Patients with markers of severe hepatocellular dysfunction such as low serum albumin and prolonged prothrombin time

Table 3. Pharmacokinetic data: the effect of liver disease on disposition of some commonly used drugs. (For data on more drugs see 47).

Drug	Liver Disease	Cl_T (ml/min)*	$T_{½}$ (h)	V_d (l/kg)	f_B (%)	Ref.
Diazepam	None	44.8 ± 9.1	46.6 ± 14.2	1.13 ± 0.28	97.8 ± 1.0	35
	Cirrhosis	24.8 ± 12.7	105.6 ± 15.2	1.74 ± 0.21	95.3 ± 1.8	
	Acute hepatitis	--	74.5 ± 27.5	--	--	
Oxazepam	None	136.0 ± 17.5	5.6 ± 0.3	--	89.3 ± 1.6	37
	Cirrhosis	155.5 ± 31.5	5.8 ± 0.5	--	87.6 ± 1.4	
	Acute hepatitis	137.4 ± 21.0	5.3 ± 0.3	--	86.0 ± 1.4	
Tolbutamide	Acute hepatitis	30 ± 6.3	4.0 ± 0.9	0.15 ± .03	91.3 ± .8	42
	After recovery	21 ± 3.3	5.9 ± 1.4	0.15 ± .03	93.2 ± .6	
Meperidine	None	1316 ± 383	3.2 ± .8	4.2 ± 1.3	64.3 ± 13.5	38,39
	Cirrhosis	664 ± 293	7.0 ± .9	5.8 ± 2.6	64.9 ± 5.8	
	Acute hepatitis	649 ± 228	7.0 ± 2.7	5.6 ± 1.8	56.0 ± 11.8	
Lidocaine	Acute hepatitis	910 ± 273	2.7	3.1 ± 1.8	44.0 ± 8.0	32
	After recovery	1400 ± 273	1.9	2.0 ± .5	51.0 ± 12.0	
	None	703	1.8	1.3	--	31
	Heart failure	443	1.9	0.9	--	
	Cirrhosis	419	4.9	2.3	--	
Propranolol	None	1470 ± 490	4.2	5 ± 2	--	41
	Fibrosis	1260 ± 560	4.2	5 ± 2	--	
	Cirrhosis	560 ± 350	11.1	5 ± 3	--	

*Some Cl_T are in terms of blood and some are in terms of plasma.

have usually had impaired drug clearance, but the degree of impairment could not be accurately predicted from the albumin level or prothrombin time (27,45).

More success has been achieved in correlating impairment of metabolism of one drug with that of another. While correlations of metabolism of different drugs are notoriously poor in normal subjects (Table 4), they are better in patients with hepatic disease. Indeed, clearance of flow-dependent and flow-independent drugs have been correlated in subjects with liver disease (46). This has caused some investigators to question whether the Cl_{int} is a valid concept in the presence of liver disease (8,41).

One group has observed correlations between clearance of diazepam (flow-independent) and meperidine (flow-dependent) in patients with liver disease (45). On the other hand another group found a poor correlation between clearances of 2 flow-dependent drugs, indocyanine green and lidocaine, in patients with acute viral hepatitis (32).

The information presently available on drug metabolism in patients with liver disease does not allow use of any clinical or drug metabolism parameter to adjust drug dosage in the manner in which creatinine clearance can be used in renal disease. However, the clearances of several drugs have been studied in patients with liver disease and those results can serve as a rough guide in their use. Until further advances are made in this field, clinicians will have to continue to rely on cautious drug administration and use of plasma drug levels when available to compensate for alterations of drug metabolism and disposition caused by liver disease.

Table 4. Comparative drug elimination in man. (from 12)

Drugs Compared	No. of Subjects	Correlation Coefficient, r	Significance $p <$
Antipyrine(a)-PBZ(a)	14	0.58(f)	0.05
Antipyrine(a)-PBZ(a)	16	0.58	0.05
Antipyrine(a)-PBZ(b)	11	0.91	0.001
Antipyrine(a)-PBZ(a)	12	0.35	ns
Antipyrine(c)-PBZ(c)	16	0.33	ns
Antipyrine(a)-OBZ(b)	8	0.89	0.01
Antipyrine(a)-OBZ(a)	9	0.66	ns
Antipyrine(a)-DPH(a)	7	0.04	ns
Antipyrine(a)-DPH(a)	11	0.07	ns
Antipyrine(c)-DPH(c)	11	0.66	0.05
Antipyrine(a)-dicumarol(a)	14	0.05(f)	ns
Antipyrine(a)-warfarin(a)	16	0.38	ns
Antipyrine(c)-warfarin(c)	16	0.50	ns
Antipyrine(a)-amobarbital(a)	10	0.10	ns
Antipyrine(a)-pentobarbital(a)	6	0.12	ns
Antipyrine(a)-glutethimide(a)	10	0.02	ns
Antipyrine(a)-SPZ(e)	10	0.44	ns

References

1. J.R. Gillette. Factors affecting drug metabolism. Ann. N.Y. Acad. Sci. 179:43-66, 1971.

2. R.F. Burk. Some Aspects of Toxic Hepatitis. Grand Rounds, August 5, 1976.

3. M. Gibaldi and G. Levy. Pharmacokinetics in clinical practice. 1. concepts, 2. applications. JAMA 235:1864-1867 and 1987-1992, 1976.

4. M. Rowland, L.Z. Benet, and G.G. Graham. Clearance concepts in pharmacokinetics. J. Pharmacokinet. Biopharmaceut. 1:123-136, 1973.

5. G.R. Wilkinson and D.G. Shand. A physiologic approach to hepatic drug clearance. Clin. Pharmacol. Ther. 18:377-390, 1975.

6. D.G. Shand, D.M. Kornhauser, and G.R. Wilkinson. Effects of route of administration and blood flow on hepatic drug elimination. J. Pharmacol. Exp. Ther. 195:424-432, 1975.

7. A. Rane, G.R. Wilkinson, and D.G. Shand. Prediction of hepatic extraction ratio from in vitro measurement of intrinsic clearance. J. Pharmacol. Exp. Ther. 200:420-424, 1977.

8. T.F. Blaschke. Protein binding and kinetics of drugs in liver diseases. Clin. Pharmacokinet. 2:32-44, 1977.

9. H. Hoensch, C.H. Woo, S.B. Raffin, and R. Schmid. Oxidative metabolism of foreign compounds in rat small intestine: cellular localization and dependence on dietary iron. Gastroenterology 70:1063-1070, 1976.

10. A.H. Conney, E.J. Pantuck, K.-C. Hsiao, W.A. Garland, K.E. Anderson, A.P. Alvares, and A. Kappas. Enhanced phenacetin metabolism in human subjects fed charcoal-broiled beef. Clin. Pharmacol. Ther. 20:633-642, 1976.

11. E.J. Pantuck, K.-C. Hsiao, W.D. Loub, L.W. Wattenberg, R. Kuntzman, A.H. Conney. Stimulatory effect of vegetables on intestinal drug metabolism in the rat. J. Pharmacol. Exp. Ther. 198: 278-283, 1976.

12. W. Kalow and T. Inaba. Genetic factors in hepatic drug oxidations. Progress in Liver Dis. V, (H. Popper and F. Schaffner, eds.), pp. 246-258, 1976.

13. T.C. Campbell and J.R. Hayes. Role of nutrition in the drug-metabolizing enzyme system. Pharmacol. Rev. 26:171-197, 1974.

14. A.H. Conney and J.J. Burns. Metabolic interactions among environmental chemicals and drugs. Science 178:576-586, 1972.

15. I.H. Stevenson, M. Browning, J. Crooks, and K. O'Malley. Changes in human drug metabolism after long-term exposure to hypnotics. Brit. Med. J. 4:322-324, 1972.

16. J.P. Miguet, P. Mavier, C.J. Soussy, and D. Dhumeaux. Induction of hepatic microsomal enzymes after brief administration of rifampicin in man. Gastroenterology 72:924-926, 1977.

17. L.K. Christensen and L. Skovsted. Inhibition of drug metabolism by chloramphenicol. Lancet 2:1397-1399, 1969.

18. H.R. Adams, E. Isaacson, and B.S.S. Masters. Inhibition of hepatic microsomal enzymes by chloramphenicol. J. Pharmacol. Exp. Ther. 203:388-396, 1977.

19. N. Kaplowitz and J. Kuhlenkamp. Inhibition of hepatic metabolism of azathioprine in vivo. Gastroenterology 74:90-92, 1978.

20. J.G. Joly, J.P. Villeneuve, P. Mavier, and C. Hetu. Mechanism of induction by ethanol of hepatic microsomal drug metabolizing enzymes. In Alcohol and the Liver (M.M. Fisher and J.G. Rankin, eds.) Plenum Press (1977) pp. 101-117.

21. P.S. Misra, A. Lefevre, H. Ishii, E. Rubin, and C.S. Lieber. Increase of ethanol, meprobamate, and pentobarbital metabolism after chronic ethanol administration in man and in rat. Am. J. Med. 51:346-351, 1971.

22. W.W. Lautt. The hepatic artery: subservient to hepatic metabolism or guardian of normal hepatic clearance rates of humoral substances. Gen. Pharmacol. 8:73-78, 1977.

23. D.M. Kornhauser, A.J.J. Wood, R.E. Vestal, G.R. Wilkinson, R.A. Branch, and D.G. Shand. Biological determinants of propranolol disposition in man. Clin. Pharmacol. Ther. 23:165-174, 1978.

24. R. Gugler, P. Lain, and D.L. Azarnoff. Effect of portacaval shunt on the disposition of drugs with and without first-pass effect. J. Pharmacol. Exp. Ther. 195:416-423, 1975.

25. A.M. Mackinnon. Hepatic microsomal mixed function oxidase system response to selective biliary obstruction. Biochim. Biophys. Acta 444:613-617, 1976.

26. N. Carulli, F. Manenti, M. Ponce de Leon, A. Ferrari, G. Salvioli, and M. Gallo. Alteration of drug metabolism during cholestasis in man. Europ. J. Clin. Invest. 5:455-462, 1975.

27. P.B. Andreasen, L. Ranek, B.E. Statland, and N. Tygstrup. Clearance of antipyrine-dependence of quantitative liver function. Europ. J. Clin. Invest. 4:129-134, 1974.

28. G.W. Hepner and E.S. Vesell. Assessment of aminopyrine metabolism in man by breath analysis after oral administration of ^{14}C-aminopyrine. New Engl. J. Med. 291:1384-1388, 1974.

29. E.S. Vesell, C.A. Shively, and G.T. Passananti. Temporal variations of antipyrine half-life in man. Clin. Pharmacol. Ther. 22:843-852, 1977.

30. R.E. Stenson, R.T. Constantino, and D.C. Harrison. Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. Circulation 43:205-211, 1971.

31. P.D. Thomson, K.L. Melmon, J.A. Richardson, K. Cohn, W. Steinbrunn, R. Cudihee, and M. Rowland. Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. Ann. Int. Med. 78:499-508, 1973.

32. R.L. Williams, T.F. Blaschke, P.J. Meffin, K.L. Melmon, and M. Rowland. Influence of viral hepatitis on the disposition of two compounds with high hepatic clearance: lidocaine and indocyanine green. Clin. Pharmacol. Ther. 20:290-299, 1976.

33. C.W. Zwillich, F.D. Sutton, T.A. Neff, W.M. Cohn, R.A. Matthay, and M.M. Weinberger. Theophylline-induced seizures in adults. Ann. Int. Med. 82:784-787, 1975.

34. K.M. Piafsky, D.S. Sitar, R.E. Rangno, and R.I. Ogilvie. Theophylline disposition in patients with hepatic cirrhosis. New Engl. J. Med. 296:1495-1497, 1977.

35. U. Klotz, G.R. Avant, A. Hoyumpa, S. Schenker, and G.R. Wilkinson. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J. Clin. Invest. 55: 347-359, 1977.

36. U. Klotz, K.H. Antonin, H. Brugel, and P.R. Bieck. Disposition of diazepam and its major metabolite desmethyldiazepam in patients with liver disease. Clin. Pharmacol. Ther. 21:430-436, 1977.

37. H.J. Shull, G.R. Wilkinson, R. Johnson, and S. Schenker. Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. Ann. Int. Med. 84:420-425, 1976.

38. U. Klotz, T.S. McHorse, G.R. Wilkinson, and S. Schenker. The effect of cirrhosis on the disposition and elimination of meperidine in man. Clin. Pharmacol. Ther. 16:667-675, 1974.

39. T.S. McHorse, G.R. Wilkinson, R.F. Johnson, and S. Schenker. Effect of acute viral hepatitis in man on the disposition and elimination of meperidine. Gastroenterology 68:775-780, 1975.

40. A.S. Nies and D.G. Shand. Clinical pharmacology of propranolol. Circulation 52:6-15, 1975.

41. D. Pessayre, D. Lebrec, V. Descatoire, M. Peignoux, and J.P. Benhamou. Mechanism for reduced drug clearance in patients with cirrhosis. Gastroenterology 74:566-571, 1978.

42. R.L. Williams, T.F. Blaschke, P.J. Meffin, K.L. Melmon, and M. Rowland. Influence of acute viral hepatitis on disposition and plasma binding of tolbutamide. Clin. Pharmacol. Ther. 21:301-309, 1977.

43. S.W. Schalm, W.H.J. Summerskill, and V.L.W. Go. Prednisone for chronic active liver disease: pharmacokinetics, including conversion to prednisolone. Gastroenterology 72:910-913, 1977.

44. G. Whelan and S. Sherlock. Immunosuppressive activity in patients with active chronic hepatitis and primary biliary cirrhosis treated with azathioprine. Gut 13:907-914, 1972.

45. G.R. Wilkinson and S. Schenker. Drug disposition and liver disease. Drug Metab. Rev. 4:139-175, 1975.

46. R.A. Branch, J.A. James, and A.E. Read. The clearance of antipyrine and indocyanine green in normal subjects and in patients with chronic liver disease. Clin. Pharmacol. Ther. 20:81-86, 1976.

47. L.A. Pagliaro and L.Z. Benet. Pharmacokinetic data. Critical compilation of terminal half-lives, percent excreted unchanged, and changes of half-life in renal and hepatic dysfunction for studies in humans with references. J. Pharmacokinet. and Biopharmaceut. 3:333-383, 1975.