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# Clinical Pharmacokinetic and Pharmacodynamic Considerations in Patients with Liver Disease

## An Update

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## Summary

The effects of liver disease on pharmacokinetics and pharmacodynamics are highly variable, and difficult to predict as the mechanisms of these effects are not well understood. Since the majority of the published literature is concerned with cirrhotic liver disease, this review also focuses mainly on this area.

Four different theories have been proposed to account for the effects of chronic liver disease with cirrhosis on hepatic drug elimination: the sick cell theory; the intact hepatocyte theory; the impaired drug uptake theory; and the oxygen limitation theory. While some data in support of each of the first 2 theories have been published recently, a large amount of clinical data would appear to refute both of these theories. These clinical data are substantially consistent with the latter 2

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theories, which regard the decreased permeability of the capillarised sinusoid as the critical feature in cirrhosis. Further work is required to determine the applicability of each of these theories.

In cirrhosis, drug glucuronidation is spared relative to oxidative drug metabolism; however, in advanced cirrhosis this pathway may also be impaired substantially. There is evidence that in cirrhosis other conjugation pathways may also be impaired to variable degrees. Growing evidence suggests that biliary drug excretion is impaired in cirrhosis. Recent studies with several racemic drugs indicate that the disease can have different effects on the hepatic elimination of individual enantiomers, which may lead to a change in the concentration-response relationships of racemic drugs in cirrhosis.

A major finding which has emerged in recent years is that, even with moderate degrees of hepatic impairment, there is a decrease in clearance of drugs or active metabolites normally cleared by the kidney. The effect on renal clearance of unbound drug may be masked if there is a concomitant decrease in plasma protein binding of the drug. Neither serum creatinine levels nor creatinine clearance are useful markers of the renal dysfunction associated with cirrhosis. Both may greatly overestimate renal function in patients with cirrhosis due to increased fractional renal tubular secretion of creatinine.

Altered receptor sensitivity has been observed with some drugs in cirrhosis, while for other drugs there is no change in pharmacodynamics. Precise determination of drug dosage in cirrhosis requires information on changes in pharmacodynamics and plasma protein binding in addition to changes in drug elimination.

Pharmacokinetic investigations in a variety of chronic liver diseases without cirrhosis (e.g. carcinoma, schistosomiasis and viral hepatitis) suggest that in the absence of cirrhosis, impairment of drug elimination is not sufficient to warrant reduction of drug dosage. However, if cirrhosis is present, 'safe' drug use requires an awareness of the possibility of multiple interactions between changes in hepatic and renal disposition and pharmacodynamics.

In chronic liver disease with cirrhosis, dosage reduction is the general rule regardless of the route of elimination of drug or metabolite.

Liver disease comprises a variety of disease syndromes associated with hepatic parenchymal injury, cell death and pathological repair processes, changes in the hepatic microcirculation and changes in the endothelial lining of the sinusoids.[1] The elimination of drugs which are metabolised or excreted by the liver may be substantially impaired in liver disease as a result of these changes.

In 1991, we reviewed this topic and concluded that the effect of liver disease on pharmacokinetics and pharmacodynamics is highly variable and difficult to predict.[2] We paid particular attention to the pathological changes which occur in chronic liver disease (with cirrhosis), and examined the various mechanisms that had been proposed to account for altered drug disposition. As none of the current findings could account for all the experimental findings, we introduced the oxygen limitation theory as a possible alternative, based on laboratory and clinical data.[2]

We raised a number of other issues, such as the scarcity of specific dosage requirements in chronic liver disease without cirrhosis, changes in biliary and renal excretion and in metabolic conjugation in cirrhosis, and the use of biochemical and pharmacological markers of liver function in liver disease. We concluded that more information was needed on these issues.[2]

The simplest assessment of liver function involves a combination of clinical features (e.g. pre-

sence of ascites) and biochemical tests (e.g. for serum albumin), which are expressed as indices such as the Child score[3] or Child-Turcotte score.[4] However, a large body of data shows that such tests do not have sufficient sensitivity or selectivity for prediction of hepatic clearance of drugs.[5,6] Assessment of liver metabolic function has been reviewed in detail in *Clinical Pharmacokinetics* recently;[5,6] it was concluded that a battery of tests will probably be required to give accurate information about the different metabolic pathways and processes in liver disease. The authors pointed to the strategic advantage of simultaneously monitoring several metabolites of the same drug to assess different pathways, rather than the traditional practice of monitoring only the parent drug.[4] Reviews have also appeared recently on the pharmacokinetics in liver disease of cytotoxic agents[7] and newer antibacterials.[8]

We present here an update covering developments in the field since our previous review, with the emphasis on mechanisms of hepatic elimination, changes in renal elimination secondary to liver disease, and altered pharmacodynamics.

## 1. Mechanisms Of Impairment of Hepatic Drug Elimination in Chronic Liver Disease

Figure 1 depicts the structure of the sinusoid, extracellular space (space of Disse) and hepatocyte in the healthy liver. Traditional models of hepatic drug uptake make the following assumptions: (a) no limitation on supply of oxygen, drug or other substrates to all systems; (b) ready access (including bulk fluid exchange) and free diffusion of drug molecules and carrier macromolecules (if any) to the hepatocyte layer; (c) dissociation of bound drug at the cell surface with a dissociation rate well above other transfer rates; and (d) free diffusion of unbound drug into the cell with free access to enzyme-based translocation or biotransformation processes.[2]

As a result of the pathological changes which occur in cirrhosis, and observations in a wide variety of human and animal experiments, there are currently 4 main theories under consideration to explain the impairment of hepatic elimination in cirrhosis.

The *sick cell theory* envisages that there is a reduction in the content and activity of the hepatic drug metabolising enzymes while blood flow is maintained[9] (fig. 2A).

The *intact hepatocyte theory,* on the other hand, envisages a reduced mass of cells which function relatively normally and are normally perfused[9] (fig. 2B).

The third theory, which may be termed the *impaired drug uptake theory,* proposes that the most significant feature of cirrhosis is the process of sinusoidal capillarisation. This results from loss of fenestration of the sinusoidal endothelium, development of basal laminae and deposition of complex macromolecules in the space of Disse. This theory envisages that hepatic drug elimination is impaired primarily because of impaired uptake of drug across the capillarised endothelium[10-12] (fig. 2C).

Finally, there is the *oxygen limitation theory,* which envisages that it is impaired uptake of oxygen, rather than that of the drug itself, across the capillarised endothelium that is responsible for the impairment of hepatic drug metabolism in cirrhosis[2,13] (fig. 2C).

Superimposed on these postulated mechanisms will be the effect of the reduction in extent of drug plasma protein binding which usually accompanies cirrhosis.[2,14,15] Reduced plasma binding increases the availability of the total drug concentration in the blood for uptake and elimination by the liver.

Since our last review,[2] each of these theories has received some experimental support, although evidence against the sick cell and intact hepatocyte theories is mounting. At this point it is not clear which, if any, of these theories is most appropriate.

### 1.1 The Sick Cell Theory

A decrease in the hepatic extraction ratio of indocyanine green by functional hepatocytes, and a correlation between systemic and intrinsic hepatic clearances of pethidine and morphine in cirrhotic rats, has been used as evidence to support the sick

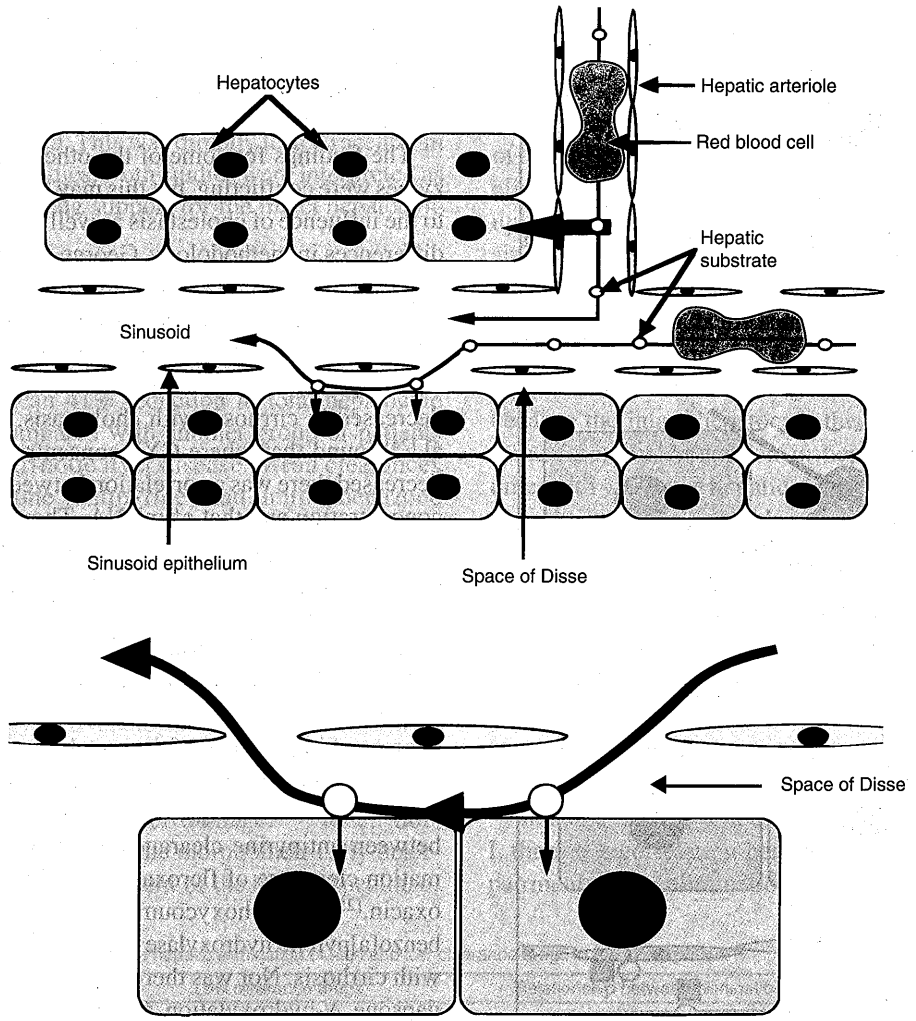


**Fig. 1.** Schematic representation of the relationships between the hepatic sinusoid, the space of Disse and hepatocytes in the healthy liver. **Top:** the anatomy of the junction between a hepatic arteriole and the sinusoid in addition to the macroscopic relationships. **Bottom:** the free exchange of fluid and substrate(s) between the sinusoidal lumen and the space of Disse.

cell theory rather than the intact hepatocyte theory.[16,17] Further support for the sick cell theory has been provided by the finding, in patients with chronic liver disease, of a good correlation between the *in vitro* metabolism of 7-ethoxycoumarin by liver biopsy samples and the *in vivo* elimination of dipyrone (metamizole).[18] Further insight into the mechanism of the loss of hepatocellular function comes from Buters et al.,[19] who found that increased microsomal membrane rigidity also contributed to reduced hepatocellular function, in addition to altered enzyme content or activity.

With the realisation that there are at least 12 distinct isoenzymes of cytochrome P450 (CYP) that participate in oxidative drug metabolism, there has been much interest in studying the effect of liver disease on the regulation and expression of each of the individual enzymes.[20] Three studies have measured the microsomal content of individual CYP isoenzymes in biopsy samples from pa-

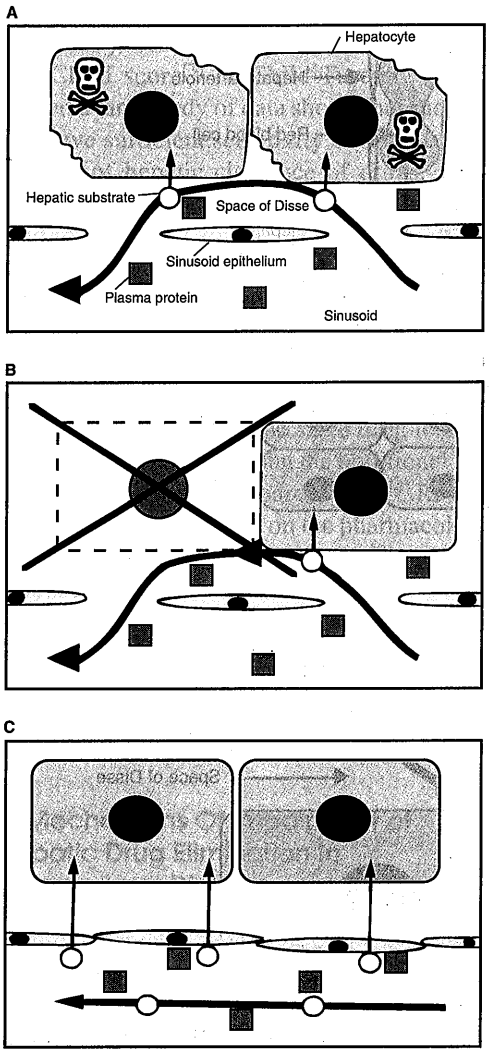


**Fig. 2.** Schematic representation of the major theories of impairment of hepatic drug elimination in chronic cirrhotic liver disease (with reference to fig. 1, bottom). Panel **A** illustrates the disposition of substrate and plasma protein according to the sick cell theory, in which hepatocellular function is impaired. Panel **B** illustrates the intact hepatocyte theory, in which a reduced number of hepatocytes function normally and are normally perfused. Panel **C** illustrates the influence of sinusoidal capillarisation (consisting of endothelial defenestration, basal lamina deposition and collagenisation of the space of Disse) on access to the hepatocytes of substrate and plasma protein. The impaired drug uptake theory assumes that drug uptake (delivery) is rate limiting, whereas the oxygen limitation theory assumes that uptake of oxygen is rate limiting. For drugs with high degrees of plasma protein binding, any decrease in plasma binding due to cirrhosis will tend to offset the reduction in drug uptake due to capillarisation.

tients with cirrhosis.[21-23] These studies found that the concentrations of CYP1A2 and epoxide hydrolase are decreased while those of NADPH cytochrome c reductase are unchanged in cirrhosis.

The findings for some of the other CYP isoenzymes were conflicting, but this may have been due to the influence of cholestasis as well as to possible differences in methodology. George et al.[23] found that CYP3A concentrations were decreased in cirrhosis, but only if cholestasis was absent, whereas CYP2E1 and CYP2C concentrations were unchanged in cirrhosis without cholestasis but were decreased in cirrhosis with cholestasis. George et al.[24] found that where CYP concentrations were decreased there was a correlation between the CYP concentration and that of mRNA. They concluded that the regulation of CYP genes in cirrhosis was due, at least in part, to pre-translational mechanisms.

The finding of a variable effect of cirrhosis on individual CYP isoenzymes is consistent with clinical data showing, in the same patient, different degrees of impairment of the metabolism of different drugs and of different metabolic pathways of the same drug. For example, there was no correlation between antipyrine clearance and metabolite formation clearance of fleroxacin *N*-oxide from fleroxacin,[25] or 7-ethoxycoumarin *O*-deethylase and benzo[a]pyrene hydroxylase activities[26] in patients with cirrhosis. Nor was there a correlation between dapsone *N*-hydroxylation and *S*-mephenytoin hydroxylation,[27] nor between the formation clearances of fleroxacin *N*-oxide and *N*-demethyl-fleroxacin formed from fleroxacin.[25]

From its inception, a major problem with the sick cell theory was that it could not account for impaired hepatic elimination of high clearance, flow-limited drugs (such as propranolol) in cirrhosis.[9] Recent developments showing varying changes in hepatic enzyme content and activity,[21-23] and varying changes in the metabolism of different drugs and in different metabolic pathways of the same drug in the same individual,[25-27] indicate that this theory may not be appropriate even for low clearance drugs.

### 1.2 The Intact Hepatocyte Theory

The main tenet of this theory is that a reduced mass of hepatocytes functions normally and is normally perfused. This was directly tested recently in 2 separate studies. Both studies were interpreted as providing strong support for the intact hepatocyte theory.

Kawasaki et al.[28] measured the liver volume of 26 patients with cirrhosis, using computerised tomography. They then estimated hepatocyte number morphometrically in liver biopsy specimens, and found a mean 41% reduction in total hepatocyte number compared with another group of patients with noncirrhotic liver disease. Mean clearances of phenazone (antipyrine) and aminophenazone (aminopyrine) were reduced by 44% and 38%, respectively, compared with the noncirrhotic group. However, they found that there was no significant difference between patients with and without cirrhosis in the clearance of phenazone and aminophenazone per hepatocyte.

Similarly, in liver biopsies from 15 patients with cirrhosis, *in vitro* hydroxylation of bufuralol was reduced by 50% compared with another group of patients with mild liver damage.[29] When normalised in relation to the morphometrically determined hepatocyte content of the biopsy specimen, there was no significant difference between the 2 groups in hydroxylation rate.

These two studies, showing unchanged clearance per hepatocyte in cirrhosis,[28,29] are capable of an alternative interpretation: the reduced hepatic elimination could be more a result of impaired uptake of drug by healthy cells via the capillarised sinusoid than of the reduced number of viable cells. A fundamental feature of the intact hepatocyte theory is that it predicts the same fractional reduction in degree of impairment of hepatic clearances of high and low clearance drugs in cirrhosis. This is because the intact hepatocyte theory assumes the same fractional reduction in hepatocellular volume, with which the hepatic clearance of low clearance drugs is proportional, as the fractional reduction in functional hepatic blood flow rate (i.e. flow through remaining functional tissue), with which the hepatic clearance of high clearance drugs is proportional. There are many examples of clinical studies in which the degree of impairment of hepatic elimination in cirrhosis is *not* the same for a high clearance drug as it is for a low clearance drug in the same patient (see table I).

In some instances in the studies shown in table I, there is a correlation between the degree of impairment of the elimination of the drugs in ques-

**Table I.** Varying impairment of hepatic elimination of high and low clearance drugs in the same patient

| High clearance drugs | Low clearance drugs | Relationship between elimination rates | Reference |
|---|---|---|---|
| Indocyanine green | Caffeine | $r = 0.40$, $p < 0.05$ | 30 |
| Lignocaine | Aminophenazone (aminopyrine)[a] | $r = 0.39$, $p < 0.0001$ | 31 |
| Galactose | Aminophenazone | $r = 0.25$, $p > 0.05$ | 31 |
| Encainide | Phenazone (antipyrine)[a] | No significant correlation | 32 |
| Nicardipine[b] | Phenazone | $r = 0.37$, $p > 0.05$ | 33 |
| Indocyanine green[b] | Dapsone | No significant correlation | 27 |
| Lignocaine[a] | Coumarin | $r = 0.67$, $p > 0.01$ | 34 |
| Dextropropoxyphene | Aminophenazone | $r = 0.43$, $p < 0.05$ | 35 |
| Indocyanine green | Fluoxetine | $r = 0.27$, $p > 0.05$ | 36 |
| Indocyanine green[b] | Phenazone | Indocyanine green CL ↓ by 85%; phenazone CL ↓ by 61% | 37 |
| Galactose | Phenazone | Galactose CL ↓ by 30%; phenazone CL ↓ by 61% | 37 |
| Lignocaine[b] | Theophylline | $r = 0.47$, $p < 0.002$ | 38 |

a Greater impairment with the lesser plasma protein bound drug.

b Greater impairment with the more highly plasma protein bound drug.

*Abbreviations and symbols:* CL = systemic plasma clearance; ↓ denotes decrease.

tion. As has been pointed out previously,[37,39] the presence of a correlation between the degree of impairment of clearance of 2 drugs in cirrhosis does not necessarily mean that the fractional reduction in clearance is the same. It is also worth noting that the intact hepatocyte theory would predict the same fractional reduction in hepatic clearance of low clearance drugs in a single patient, and in different metabolic pathways of the same drug in a given patient. Data showing different fractional reductions in hepatic clearance of low clearance drugs and metabolic pathways clearly indicate that this is not the case.[25-27] This large body of clinical data would appear to refute the intact hepatocyte theory.

### 1.3 The Impaired Drug Uptake Theory

A recent electron microscopic study has shown clearly that, in cirrhosis, capillarisation involves the formation of continuous filtration and diffusion barriers which hinder bidirectional macromolecular exchange.[40] This study showed that the basement membrane is the major filtration barrier, as illustrated in figure 2C. Multiple indicator dilution techniques have shown that, in the cirrhotic liver, macromolecules (such as albumin) are confined to the sinusoids because free exchange with the extracellular space (space of Disse) is prevented.[10-12] Furthermore, small extracellular markers (such as sucrose) show altered kinetic behaviour consistent with capillary exchange at the newly formed diffusional barrier at the sinusoidal wall.[10-12]

A detailed *in vitro* study of the hepatic disposition of propranolol in the cirrhotic rat liver found that microsomal propranolol–metabolising activity was the same as in healthy livers, but that the impaired hepatic extraction of propranolol could be accounted for solely in terms of impaired hepatic uptake of the drug.[41,42] The authors concluded that capillarisation was unlikely to be a barrier for a lipophilic compound such as propranolol, and hypothesised that the limitation of propranolol cellular entry in cirrhosis could be due to restricted diffusion of protein-bound propranolol into the space of Disse, to the presence of small intrahepatic shunts, or to both.

The shunt alternative is unlikely because it would mean a similar fractional reduction in cirrhosis of the clearance of high clearance drugs, which is not seen in practice.[31,37] If impaired uptake is the primary cause of impaired drug elimination in cirrhosis,[10-12] and protein binding results in restricted diffusion of drug to the space of Disse, then lipid-soluble drugs with low degrees of protein binding (such as phenazone, caffeine and theophylline) would be expected to exhibit a much reduced impaired elimination than highly bound substrates such as propranolol and indocyanine green. Table I summarises the results of studies in which more than one drug was tested in the same patient. These data do not indicate a consistent pattern in cirrhosis of less-impaired hepatic elimination of poorly bound compared with highly bound drugs.

The impaired drug uptake theory would also predict that the hepatic elimination in cirrhosis of drugs which cross membranes easily would be less impaired than that of drugs of lower membrane permeability. Therefore, the elimination of highly diffusible, lipophilic drugs such as phenazone, caffeine and theophylline, which are metabolised primarily by oxidation, would be less impaired than less highly diffusible drugs such as paracetamol and morphine, many of which are metabolised primarily by conjugation with glucuronic acid or sulphate.[43] However, while this has not been tested directly, it would appear that the opposite is the case: i.e. elimination of drugs which undergo conjugation is spared relative to that of drugs which undergo oxidation (see section 2.1).

### 1.4 The Oxygen Limitation Theory

This theory envisages that sinusoidal capillarisation results in a significant limitation of access of free oxygen supply to the hepatocytes. This theory was prompted by the observations of a relative insensitivity of conjugative drug metabolism (compared with oxidative drug metabolism) to reduced oxygenation in the healthy liver tissues *in vitro*, the relative sparing of drug conjugation in cirrhosis, and biochemical evidence of a hepatic

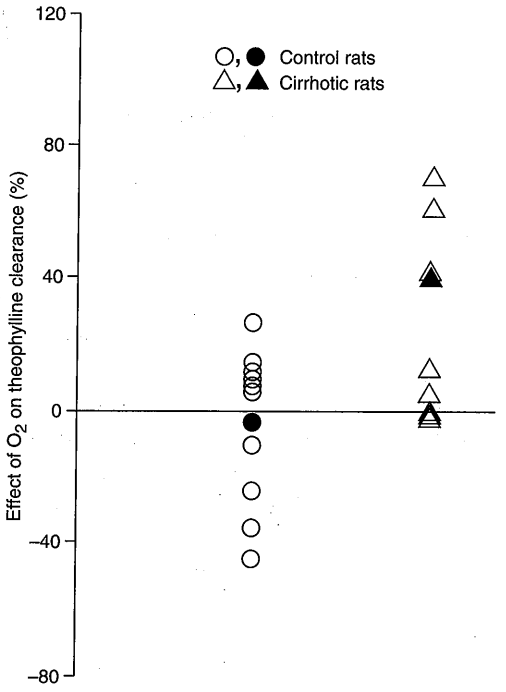


**Fig. 3.** Percentage change in theophylline clearance caused by inhaled oxygen supplementation in individual control and carbon tetrachloride–induced cirrhotic rats (from Hickey et al.,[44] with permission). The filled symbols indicate mean values.

intracellular hypoxia in cirrhosis.[2,13] In support of this theory, inhaled oxygen supplementation was found to increase theophylline clearance in cirrhotic but not in healthy rats (fig. 3).[44] Moreover, hepatic oxygen supply appeared to be rate limiting for propranolol elimination in the perfused cirrhotic rat liver but not in the healthy rat liver (unpublished observations).

The logical extension of the oxygen limitation theory is that it should be possible to use vasodilators to increase oxygen levels in the sinusoid through increase in the arterial inflow (see fig. 1). This is based on clear evidence in the perfused rat liver that the hepatic artery meets the sinusoid somewhat downstream from the portal entry-point,[45,46] and that a substrate administered via the artery has better access to the space of Disse than one administered portally.[47] Given that hydralazine has been shown to act selectively on the arterial flow,[48] it should be possible to improve liver function by oral administration of a lipophilic vasodilator at a dose well below that required for systemic vasodilator action (systemic hypotension) via $Ca^{++}$-channel blockade or other mechanisms of vascular action. Any increase in the partial pressure ($pO_2$) of sinusoidal oxygen should increase $O_2$ diffusion across the capillary barrier and space of Disse, resulting in increased delivery to the hepatocytes – as shown recently in $O_2$ supplementation studies.[44] Such an action would be optimised if the vasodilator only acted locally within the hepatic vascular bed with little or no systemic effect. This would then avoid the possibility of a reflex-mediated reduction in hepatic arterial flow.[49]

In cirrhotic rats, verapamil has been shown consistently to improve hepatic oxidative drug metabolism, as measured by aminophenazone, caffeine and phenazone elimination.[50,51] However, in humans with cirrhosis the situation is not clear. In one study, verapamil was found to decrease the systemic and intrinsic clearances of indocyanine green,[52] but no effect on indocyanine elimination has been observed with verapamil,[53] clonidine[54] and nifedipine.[52] On the other hand, nicardipine has been found to produce an increase in systemic and intrinsic clearances of indocyanine green.[55,56] These discrepancies could be due to differences in disease aetiologies, disease severity or doses given, and also to the use of indocyanine green as a marker of liver function. Indocyanine green undergoes biliary excretion, a process that does not use oxygen directly,[57] and therefore would not be expected to accurately reflect changes in oxidative drug metabolism resulting from increased hepatic oxygenation.

At present, there exist good animal data in support of the oxygen limitation hypothesis, but appropriately designed clinical studies are required to investigate the applicability of this theory to humans.

## 2. Recent Observations on Specific Hepatic Pathways

### 2.1 Metabolic Conjugation

Data in humans accumulated over many years indicate that, in cirrhosis, drug glucuronidation is relatively spared compared with drug oxidation. This issue was reviewed extensively in 1991[2,43] with attention drawn to the lack of appropriate data, especially of experimental comparisons of glucuronidation and oxidation in the same patients with cirrhosis. Possible reasons were also suggested for the apparent variation in the effect of cirrhosis on the glucuronidation of different drugs.

Few data have been forthcoming in the intervening period, but two recent studies do illustrate further the varying effect of cirrhosis on glucuronidation. In one study,[58] the systemic clearance of zidovudine and the plasma concentrations of the 5′-ether glucuronide (the major metabolite) were reduced 4-fold in HIV patients with cirrhosis.[58] In the other,[59] glucuronidation of rhein (the active metabolite of the prodrug diacerein) was not impaired, even in advanced cirrhosis.[59]

One hypothesis that had been gaining support was that acyl glucuronidation is more impaired in cirrhosis than is phenolic glucuronidation.[2,43] However, in a direct test of this hypothesis the unbound partial clearances of both the acyl and phenolic glucuronides of diflunisal were impaired to the same extent in patients with cirrhosis.[60] More recently, immunohistochemical staining techniques have shown that there is up-regulation of uridine 5′-diphosphate-glucuronosyl transferase, the enzyme responsible for drug glucuronidation, in remaining viable hepatocytes in human liver disease.[61]

There are few data available concerning other conjugation pathways in liver disease. There is some evidence of preservation of sulphation;[2] this is consistent with a recent study showing that sulphation of rhein is unchanged in cirrhosis.[59] However, the systemic clearance of metoclopramide is impaired in cirrhosis, which has been taken as evidence of impaired sulphation because the sulphate conjugate is a major metabolite of the metoclopramide.[62,63]

There are limited data suggesting that acetylation is impaired in liver disease.[2] Recently, the acetylation of dapsone was found to be only modestly impaired in cirrhosis;[27] however, a very high proportion of patients with cirrhosis (86%) tended to exhibit acetylation activity equivalent to the slow acetylator genetic phenotype – the proportion of slow acetylators in a healthy control group was 39%.[27] Similar observations have been made with the acetylation of isoniazid.[64,65] The authors[27] concluded that in patients with hepatic dysfunction, the acetylation of all drugs metabolised by this enzyme system will be equivalent to that of slow acetylators, and that this would be expected to have serious clinical consequences where there is a narrow therapeutic window and clinically important dosage differences between fast and slow acetylators.

### 2.2 Biliary Excretion

Earlier studies have shown that, in cirrhosis, intrahepatic shunting is the main determinant of the serum concentrations of bile acids, which in healthy people undergo flow-limited elimination.[2] However, another study[66] (which used indicator dilution techniques) found a strong correlation in patients with cirrhosis between the degree of capillarisation and hepatic extraction of the flow-limited compound indocyanine green, which is excreted unchanged in bile. The authors concluded that hepatic elimination of indocyanine green in cirrhosis is determined by the degree of sinusoidal capillarisation.[66] A recent study produced the essentially paradoxical finding that when patients with cirrhosis engage in short term (duration 3 minutes) physical exercise, the plasma disappearance rate and biliary excretion rate of indocyanine green increases.[67] If confirmed, this would suggest that functional hepatic blood flow rate rather than capillarisation is the main determinant of indocyanine green elimination in cirrhosis.

Data on biliary excretion of drugs in cirrhosis have been scanty, but several recent studies have

shown that biliary clearance of a number of drugs or metabolites known to be excreted largely unchanged in bile is reduced in cirrhosis.[68-71] Where the biliary elimination of unchanged drug was impaired, there was a concomitant increase in urinary excretion of unchanged drug.[69-71] Another study concluded that the biliary elimination of the diacid metabolite of temocapril was not altered in cirrhosis;[72] however, impaired formation of the diacid metabolite may have obscured a reduction in its biliary elimination. In patients with advanced cirrhosis, the clearance of rocuronium was found to be the same as in healthy individuals. The authors concluded that, as the drug is thought to be eliminated mainly by biliary excretion, biliary excretion of the drug is perhaps preserved in cirrhosis.[73] Nevertheless, a study of long term bismuth administration to cirrhotic rats found substantial plasma and tissue accumulation of bismuth over a 70-day period, due to reduced biliary and renal elimination.[74] The authors concluded that patients with cirrhosis may therefore be at risk of a similar accumulation of bismuth and of other metals sharing common mechanisms of disposition.

Growing evidence indicates that biliary drug elimination is impaired in cirrhosis. On the other hand, in chronic liver diseases where there is obvious impairment of biliary function (such as cholelithiasis and primary biliary cirrhosis), limited data suggest that there is minimal impairment of hepatic oxidative drug metabolism.[30,75]

### 2.3 Prodrug Metabolism

The successful use of a prodrug relies on its conversion to the active moiety, usually in the liver. Therefore, it is important to examine prodrug conversion in liver disease. The angiotensin converting enzyme (ACE) inhibitors are a particularly useful group of prodrugs requiring metabolic conversion to their active diacid metabolite.

Conversion of enalapril,[76,77] cilazapril,[78] perindopril,[79] spirapril,[68] and possibly temocapril[72] to their respective diacid metabolites is substantially reduced in cirrhosis, reflecting impaired ester hydrolysis. However, with the exception of cilazapril,[78] this seems to be of no clinical significance because ACE inhibition and the antihypertensive effect of these drugs are not altered in cirrhosis.[68,72,76,77,79] This is consistent with the absence of a change in the plasma concentrations of the diacid metabolites for all but cilazaprilat;[78] plasma concentrations of cilazaprilat were found to be increased due to impaired renal clearance, resulting in an increase in hypotensive and adverse effects.[78]

Studies of enalapril and spirapril showed a prolonged elimination half-life for the diacid, consistent with a reduction in clearance.[68,77] This would suggest that, with these drugs, inhibition of the conversion of prodrug to diacid may be compensated by reduced clearance of the diacid metabolite formed. Equally, without an alternative elimination pathway, it may be that only the rate and not the extent of formation of the diacid is reduced, and that its elimination is unchanged. Both scenarios would result in unchanged plasma diacid concentrations and pharmacological effect of these agents in cirrhosis. A direct measure of the clearance of diacid metabolites in cirrhosis will be required before the disposition of these ACE inhibitors in cirrhosis can be fully described.

In cirrhosis, the conversion to methylprednisolone of the prodrug methylprednisolone hemisuccinate is halved, but the clearance of the methylprednisolone formed is unchanged.[80] Here, it was concluded that, because of the less predictable conversion of prednisone to prednisolone and the modest impairment of prednisolone clearance in cirrhosis,[81,82] methylprednisolone hemisuccinate may offer a therapeutic advantage in this group of patients.

In contrast to the effect of cirrhosis on de-esterification of prodrugs, the de-acetylation of the prodrug diacerein to the active metabolite rhein is not impaired, even in advanced cirrhosis.[59]

### 2.4 Stereoselective Metabolism

Over 60% of drugs in clinical use are optically active, and a majority of the synthetic chiral compounds are administered as racemates.[83] Pharmaco-

kinetic and pharmacodynamic differences between enantiomers are commonplace;[83] pharmacokinetic changes in one enantiomer relative to the other could cause a change in the relationship between racemic drug concentration and response. Stereoselective hepatic drug metabolism is an important cause of differences in pharmacokinetics between enantiomers; accordingly, it is surprising that the effect of liver disease on stereoselective drug elimination has received scant attention.

The *R*(+)- and *S*(–)-enantiomers of carvedilol are equally potent $\alpha_1$-antagonists, but only the *S*(–) isomer is a β-antagonist. In healthy individuals, the systemic clearance of the *R*(+) isomer is about 20% less than that of the *S*(–) isomer and, after oral administration, the absolute bioavailability (F) of the *S*(–) isomer is approximately half (15%) that of the *R*(+) isomer (31%).[84] In cirrhosis, systemic clearance of both enantiomers is reduced but stereoselectivity is maintained. This results in a much smaller relative difference between isomers as regards absolute bioavailability in cirrhosis, as F for *S*(–)- and *R*(+)-carvedilol is 0.71 and 0.84, respectively.[84] Thus, there is a reduction in the *R*/*S* isomer plasma concentration ratio following oral administration in cirrhosis. This means that any given plasma concentration of racemic drug reflects a higher plasma concentration of the *S*(–) isomer in patients with cirrhosis than in healthy individuals, with resultant greater β-blockade.

Ibuprofen is another drug which is administered as a racemic mixture, although therapeutic activity resides almost entirely with the *S* isomer. The *R* isomer undergoes irreversible inversion *in vivo* to the *S* isomer; the *R* isomer is known to form potentially toxic hybrid triglycerides.[85] Only slight changes in pharmacokinetics were seen in cirrhosis when racemic drug was analysed,[86] but when the individual isomers were measured, inversion of *R* to *S* was found to be impaired.[87] Elimination of the *S* isomer administered alone in cirrhosis was less impaired than when the racemic drug was administered. The authors concluded that use of the *S* isomer alone in cirrhosis might offer some clinical advantage.[87]

Another form of stereoisomerism is exemplified by mivacurium, a nondepolarising neuromuscular blocker comprising a mixture of *trans-trans* (57%), *cis-trans* (37%) and *cis-cis* (6%) isomers (the last isomer is largely inactive). Mivacurium is metabolised by plasma cholinesterase. In cirrhosis, the mean plasma clearance of both active isomers was reduced by half while that of the inactive isomer was unchanged.[88,89] Mean plasma cholinesterase activity was also reduced by half in patients with cirrhosis, and recovery from the neuromuscular blockade was significantly prolonged.[88,89] Use of a non-stereospecific drug assay gives a false picture of the effect of cirrhosis on mivacurium pharmacokinetics because of the undue influence of the inactive *cis-cis* isomer on the plasma profile of total drug.[88]

These findings suggest that changes in stereoselective drug metabolism may be an important source of change in the racemic drug concentration-response relationship in cirrhosis.

## 3. Renal Drug Elimination in Liver Disease

One of the main areas where our understanding of drug disposition in cirrhosis has advanced significantly in the past 5 years is the area of renal drug elimination. Previously it was known that renal drug elimination could be impaired in the hepatorenal syndrome (defined as renal impairment linked solely to liver impairment), but that this syndrome was present only in severe and rapidly advancing liver disease.[2] Evidence was then emerging that renal drug clearance could be impaired in patients with even moderate degrees of liver impairment, and that dosage of renally cleared drugs should be reduced if hepatic function is impaired.[2,8] There was also evidence that the observed serum levels of creatinine may underestimate the decline in renal function.[90,91]

### 3.1 Creatinine Clearance as a Marker of Renal Function in Liver Disease

The usefulness of creatinine clearance as a measure of renal function in cirrhosis was examined in

a recent, detailed investigation.[92] Serum creatinine level, 24-hour urinary creatinine excretion, and the renal clearances of intravenously administered inulin and aminohippuric acid were measured on 3 separate occasions in 56 patients with cirrhosis, 27 of whom had a reduced glomerular filtration rate (GFR). The sensitivity of serum creatinine level, calculated creatinine clearance (using the method of Cockcroft and Gault[93]) and measured creatinine clearance in predicting renal impairment was 18.5%, 51% and 74%, respectively.[92]

The serum creatinine level was above the normal limit in only 5 of the 27 patients with a reduced GFR. Other patients in the same group (81.5%) showed serum creatinine levels similar to those of healthy individuals, even when the GFR was lower than 60 ml/min per 1.73m$^2$ (fig. 4). Both the calculated and measured creatinine clearances predicted the GFR adequately in the normal GFR group, but overestimated the GFR in the renal impairment group. The authors concluded that the measured serum creatinine level was inaccurate in predicting GFR in cirrhosis because of reduced muscle mass and reduced conversion of creatine to creatinine resulting from hepatic impairment. The calculated creatinine clearance, which uses the serum creatinine level, was also inaccurate in predicting GFR because of use in the nomogram of bodyweight that was likely to be inflated due to the presence of ascites. The measured creatinine clearance was inaccurate because of an increased fractional tubular secretion of creatinine as the GFR deteriorated.[92]

The implications of using creatinine as a marker of renal function in cirrhosis was highlighted recently. In a group of patients with cirrhosis, there was a mean 54% reduction in renal clearance of temafloxacin (about two-thirds of the dose excreted unchanged in healthy individuals), whereas the mean reduction in measured creatinine clearance was only 17%.[94] In addition to the altered renal disposition of creatinine in cirrhosis, the authors concluded that the low ratio of temafloxacin : creatinine renal clearance was also probably due to increased passive tubular reabsorption of the more nonpolar temafloxacin due to the reduced volume of distribution of unbound drug.[94]

### 3.2 Impaired Renal Drug Elimination in Liver Disease

There have been many studies in the past 5 years which have examined renal drug elimination in cirrhosis, but virtually all of these have used creatinine as a marker of renal function. These studies are listed in table II. In some of these studies, both

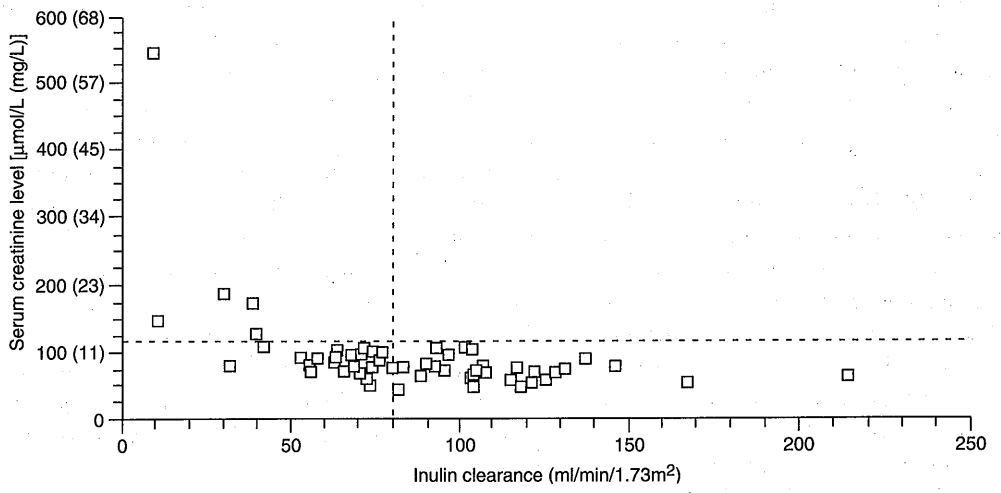


**Fig. 4.** Relationship between serum creatinine concentration and inulin clearance (mean values of triplicate measurements) in 56 patients with cirrhosis. Dashed lines represent the conventional limits of normal values (from Caregaro et al.,[92] with permission).

**Table II.** Renal drug elimination and creatinine clearance in liver disease

| Drug | Percentage reduction compared with healthy individuals | | Reference |
|---|---|---|---|
| | renal drug clearance | creatinine clearance | |
| **Both renal drug clearance and creatinine clearance normal** | | | |
| Azithromycin | None | None | 95 |
| Ceftazidime | None | None | 96 |
| Famotidine | None | None | 97, 98 |
| Perindoprilat | None | None | 79 |
| Pipecuronium | None | None | 99 |
| Rhein | None | None | 59 |
| Zidovudine and its glucuronide | None | None | 58 |
| **Renal drug clearance decreased and creatinine clearance normal** | | | |
| Cefpiramide | 52 | None | 69, 70 |
| Cetirizine | 62 | None | 100 |
| Cilazaprilat | 52 | None | 78 |
| Fluconazole | 56 | None | 101 |
| 7-Hydroxycoumarin | 30 | None | 34 |
| Lithium | 66 | None | 102, 103 |
| Ofloxacin | 32, 59 | None | 104, 105 |
| **Renal drug clearance and creatinine clearance both decreased** | | | |
| Enalaprilat | 17 | 37 | 77 |
| Famotidine | 52 | 43 | 106 |
| Fleroxacin and metabolites | 59 | 28 | 25 |
| Lomefloxacin | 40 | 35 | 107 |
| Rufloxacin | 67 | 56 | 108 |
| Temafloxacin | 54 | 17 | 94 |
| **Renal drug clearance normal and creatinine clearance decreased** | | | |
| Arginine vasopressin | None | 44 | 109 |

renal drug clearance and creatinine clearance were found to be within the normal range; in others, renal drug clearance was impaired but creatinine clearance was normal; and in a third group both renal drug clearance and creatinine clearance were found to be impaired (although not necessarily to the same degree).

Also given in table II is an example of a drug (arginine vasopressin) found to have renal clearance similar to that measured for healthy individuals in a group of patients with cirrhosis whose creatinine clearance was impaired.[109] Renal clearance of arginine vasopressin was normal because reduced glomerular filtration was compensated by increased tubular secretion.[109]

The data in table II indicate that, in general, if renal function is impaired in cirrhosis then renal drug clearance will be impaired. However, even if creatinine clearance is in the normal range this does not necessarily mean that renal drug clearance will be normal. Changes in the mechanism of renal drug elimination, i.e. in fractional secretion or reabsorption,[94,109] may also lead to greater differences in the effect of cirrhosis on renal drug clearance than predicted by true measures of GFR such as inulin.

A recent study in cirrhotic rats from our laboratory showed extensive tissue accumulation of chronically administered bismuth subcitrate resulting from reduced renal clearance.[74] As there are similarities between the disposition of bismuth and that of heavy metals such as mercury, arsenic and cadmium, occupational or environmental exposure to these metals may be particularly risky in patients with liver disease.[74]

Impaired renal function in liver disease is also important where the action of a drug is mediated via

an active metabolite eliminated renally.[32,68,72,78,79,110] This also applies to metabolites which can cause adverse effects. For example, symptoms in a patient with cirrhosis who was receiving pethidine were consistent with the convulsant actions of norpethidine (a renally excreted metabolite of pethidine), accumulation of which would probably have resulted from impaired renal elimination of the metabolite.[111]

Another factor which may complicate assessment of the effect of cirrhosis on renal drug clearance is the decrease in plasma drug binding which commonly occurs in cirrhosis.[2] For example, total renal clearance of cefpiramide is increased substantially in cirrhosis and cholestasis, but when corrected for the large increase in plasma unbound fraction, renal clearance of unbound drug is half the value found in healthy individuals.[69,70] An increase in unbound fraction could well account for observations of unchanged or increased total renal clearance in liver disease obtained in previous studies.[95,112,113]

In summary, a decrease in renal clearance of drugs or active drug metabolites normally cleared by the kidney is to be suspected when there are even moderate degrees of hepatic impairment. Therefore, the emphasis on modification of dosage in liver disease of drugs predominantly cleared by the liver must be extended to include renally cleared drugs. In assessing renal function in patients with hepatic impairment, it is important to realise that assessments based on creatinine, especially on serum creatinine concentration, may greatly overestimate renal drug clearance.

## 4. Drug Absorption in Liver Disease

Patients with cirrhosis frequently complain of gastrointestinal symptoms, such as anorexia, dyspepsia and abdominal distention.[114] Moreover, complications such as gastric ulcer or gastritis are frequently associated with cirrhosis.[115] Therefore, changes in rate and/or extent of drug absorption in cirrhosis might be anticipated; however, this has not been investigated systematically.

Evidence has been presented of prolonged orocaecal transit and a trend towards a delay in gastric emptying in cirrhosis,[116] but neither cirrhosis nor ascites significantly influenced gastric emptying in patients who were chronic alcoholics.[117] Isobe et al.[118] recently investigated gastric emptying using a scintigraphic technique in patients with cirrhosis but without alcoholic liver disease, diabetes or other diseases known to independently affect gastric emptying. They found that the mean half-time for gastric emptying was nearly double that found in a healthy control group, and that this half-time correlated with the plasma retention of indocyanine green 15 minutes after intravenous administration in the cirrhotic group. They showed that the delay in gastric emptying was not due to autonomic nervous dysfunction, but was more likely to be due to the action of abnormal levels of gastrointestinal peptides such as glucagon, cholecystokinin or motilin.[118]

Based on the hypothesis that malabsorption of furosemide (frusemide) and other drugs may occur in patients with oedematous disorders such as congestive heart failure and cirrhosis. Fredrick et al.[119] examined furosemide absorption in a group of patients with cirrhosis. Extent of absorption was normal, but absorption rate (as given by the mean absorption time) was significantly slower than for healthy people. As oedema was not present in some of the patients with slowed absorption, the authors concluded that the change in absorption was due to disease-induced alterations in gut motility. This is consistent with the findings of Isobe et al.[118] and of Chesta et al.[116]

Further work is necessary to define the effects of liver disease on drug absorption. One difficulty will be the potentially confounding effects of a concomitant decrease in systemic drug clearance, which could mask a decrease in extent of oral absorption, and the presence of hepatic shunts, which could mask a decrease in rate of drug absorption.

## 5. Pharmacokinetics in Liver Disease Without Cirrhosis

Most of the emphasis in this review and others published has been on changes in drug disposition in chronic liver disease when cirrhosis is present.

However, chronic liver disease, which arises from such causes as infection, noxious agents, circulatory changes, autoimmune disturbance or postviral syndrome, is a progressive disease. Pathology ranges from fatty liver in the early stages, to chronic active hepatitis as the disease progresses, and then to cirrhosis when the disease is at an advanced stage.

When drug disposition has been examined in patients with chronic active hepatitis without cirrhosis, either rates of drug elimination were intermediate between those of healthy individuals and patients with cirrhosis,[29,68,120-123] or rates of drug elimination rate were the same as for healthy individuals.[18,28,114,121] It seems reasonable to conclude from this that, at most, there is a mild reduction in drug elimination in chronic active hepatitis but the reduction is not enough to warrant a reduction in dosage. Only when the disease progresses to cirrhosis and there is a clear reduction in drug elimination, does a reduction in drug dosage become necessary.

There is little information on hepatic drug elimination in primary or secondary liver cancer. Early studies produced conflicting evidence on the effect of liver cancer on hepatic drug metabolism.[125-127] It has been suggested that a primary malignancy may itself cause changes in drug metabolism independent of coexisting liver metastases, and that liver metastases from different primary malignancies might affect drug metabolism in different ways.[128]

Several recent studies of phenazone, aminophenazone and doxorubicin (adriamycin) elimination in patients with metastatic liver disease without cirrhosis showed that hepatic clearance in these patients was similar to that for healthy individuals.[28,128,129] Total phenazone clearance in metastatic liver disease was decreased in another study; however, the patients in this study also had cirrhosis.[130]

When expressed in terms of residual parenchymal cell mass, there was no difference in values between healthy individuals and those with metastatic disease.[130] This is consistent with the findings of Robertz-Vaupel et al.,[128] who used computed tomography in patients without cirrhosis to show that there is substantial liver enlargement in metastatic liver disease, but that a large proportion of functional liver parenchyma still remains. As a result of this, drug elimination is not impaired. This is reflected in findings of normal CYP enzyme concentrations and normal *in vitro* drug metabolising enzyme activity in hepatic parenchymal samples from patients with metastatic liver disease.[125,128] Limited studies in patients with primary liver carcinoma without cirrhosis suggest that phenazone clearance may be unaffected in these patients.[28,125] However, epirubicin clearance and the rate of formation of monoethylglycinexylidide from lignocaine are reduced in hepatocellular carcinoma, and the clearance of epirubicin correlates strongly with serum AST and serum albumin levels.[131]

While there has been some evidence in metastatic liver disease of altered formation of several drug metabolites in the presence of overall unchanged parent drug elimination,[128,129] drug elimination in primary and secondary liver cancer appears to be unaffected in most cases, provided that cirrhosis is absent. More detailed investigation of drug elimination in liver carcinoma will be required to confirm these trends.

Hepatosplenic schistosomiasis is a disorder which is associated with hepatic fibrosis, portal hypertension and oesophageal varices, but it is not a 'true' cirrhosis because there is minimal hepatocyte dysfunction until the disease is advanced.[132] Several studies have shown that clearance of drugs such as theophylline, metronidazole and oxamniquine is unaffected in patients with hepatosplenic schistosomiasis without cirrhosis.[134-136] However, the systemic availability of oral propranolol was increased in a similar group of patients, and this was attributed to extra- or intra-hepatic shunting.[132]

In conclusion, it would appear from the material presented here concerning drug disposition in a variety of liver diseases that these liver diseases are not associated with significantly impaired hepatic elimination unless cirrhosis is also present.

## 6. Pharmacodynamics in Liver Disease

At the time of our previous review,[2] it was widely recognised that cirrhosis could be associated with changes in pharmacodynamics, i.e. changes in response to a given concentration of drug in plasma. It was considered that such changes could result from altered drug access to the site of action (e.g. decreased plasma protein binding, decreased blood-brain barrier permeability) or from altered receptor sensitivity. Pharmacodynamic changes of clinical significance included increased cerebral sensitivity to strong analgesics, anxiolytics and hypnosedatives, and decreased sensitivity to diuretics and β-agonists. However, there was no alteration in receptor response to a variety of cardiovascular drugs in cirrhosis.[2]

Investigations of pharmacodynamics in cirrhosis published over the last 5 years are summarised in table III. The majority of these studies, which examined anxiolytics, antiarrhythmics, neuromuscular blockers and antihistamines, found that receptor sensitivity in patients with cirrhosis was the same as for healthy individuals. For example, the relationship between ACE inhibition and plasma cilazaprilat concentration was the same in patients with cirrhosis and healthy volunteers.[78] These data do not exclude the possibility of alterations in other drug effects (such as renal pharmacodynamics), and in this particular case dosage does need to be reduced because of reduced renal clearance.[78]

Two studies reported a decrease in receptor sensitivity in cirrhosis (table III). There was decreased receptor sensitivity to the nonselective β-blocker metipranolol due to down-regulation of β-receptors as a consequence of chronic sympathetic activation in cirrhosis.[141] Diuretic resistance to torasemide was observed in the form of a shift to the right of the sodium *vs* drug urinary excretion rate curve (fig. 5).[113] These studies support previous observations of decreased sensitivity to β-agonists and diuretics in cirrhosis.[2]

Whether patients with cirrhosis display an altered therapeutic response also depends on whether there is a change in the pharmacokinetics of the drug. Table III indicates that, for some of the drugs for which receptor sensitivity was unchanged, there was either no or insufficient change in plasma drug concentrations to cause a change in therapeutic response in cirrhosis. For the other drugs for which receptor sensitivity was un-

**Table III.** Pharmacodynamics in cirrhosis

| Drug | Effect | Comment | Reference |
|---|---|---|---|
| **Unchanged sensitivity and unchanged pharmacokinetics** | | | |
| Adinazolam | Central effects | Effect due to *N*-demethyl metabolite | 136 |
| Cilazapril | ACE inhibition | Effect due to cilazaprilat | 78 |
| Enalapril | ACE inhibition | Effect due to enalaprilat | 77 |
| Encainide | ECG intervals | Effect due to active metabolites | 32 |
| Perindopril | ACE inhibition | Effect due to perindoprilat | 79 |
| Triazolam | Postural sway | | 140 |
| **Unchanged sensitivity, changed pharmacokinetics** | | | |
| Cetirizine | Antihistamine | Increased plasma concentrations | 100 |
| Mivacurium | Muscle relaxant | Decreased plasma cholinesterase activity | 138, 139 |
| Nicardipine | Antihypertensive | Increased plasma concentrations | 33 |
| Pipecuronium | Muscle relaxant | Slower onset of effect | 88 |
| Rocuronium | Muscle relaxant | Slower onset and offset of effect | 140 |
| Spiralapril | ACE inhibition | Lower plasma concentrations of spiralaprilat | 68 |
| **Decreased sensitivity, changed pharmacokinetics** | | | |
| Metipranolol | β-Blockade | Increased plasma concentrations of active moiety | 141 |
| Torasemide (torsemide) | Diuretic | Increased urinary excretion rate | 113 |

*Abbreviations:* ACE = angiotensin converting enzyme; ECG = electrocardiogram.

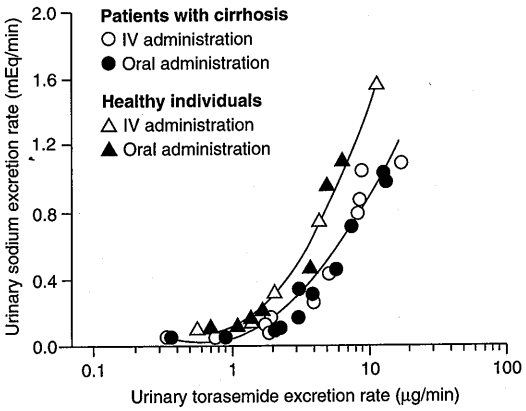


**Fig. 5.** Comparison of the relationship between urinary sodium and torasemide excretion rates after intravenous (IV) and oral administration of torasemide 10mg to patients with cirrhosis and to healthy individuals. Each point represents the mean value in a collection interval, while the curve represents the line of best fit (from Schwartz et al.,[113] with permission).

changed, there was a change in plasma drug concentrations leading to an altered therapeutic response (table III). While detailed studies of the relationship in cirrhosis between plasma concentrations of oral anticoagulants and pharmacodynamic effect (inhibition of synthesis of clotting factors) are not available, an enhanced effect of a given anticoagulant concentration would be expected in light of the reduced levels of vitamin K–dependent clotting factors in cirrhosis.[142]

Changes in plasma protein binding, which is commonly decreased in cirrhosis,[14,15] must be taken into account when assessing the significance of changes in systemic clearance of total drug in cirrhosis. Some studies have found a modest decrease or no change in systemic clearance of total drug in cirrhosis, but when the concomitant decrease in plasma protein binding was taken into account, a substantial decrease in clearance of unbound drug was apparent.[60,69,70] The significance of this is that the unbound plasma drug concentration will be greater than in healthy individuals, and a greater pharmacodynamic effect will therefore result.

A number of recent studies with drugs such as methohexitone, azithromycin, flunitrazepam and nefazodone have found no difference in the systemic clearance of total drug in cirrhosis; however, the degree of plasma protein binding of these highly bound drugs was not measured.[95,118,143,144] Without protein binding data, the clearance of unbound drug, on which decisions to change dosage should be based, cannot be determined. It is possible that clearance of unbound drug was decreased in these studies but was not reflected in a decrease in clearance of total drug because of an increase in plasma unbound fraction (because total clearance = unbound fraction × unbound clearance). Similarly, with cefodizime, clearance of total drug was increased in cirrhosis,[145] but if this were due to a decrease in plasma protein binding (which was not measured), no alteration of dosage would be warranted.

Changes in plasma protein binding were thought to be important in a study of the diuretic torasemide in patients with cirrhosis.[113] Resistance to diuretic action was found (fig. 5) along with a greater excretion rate of torasemide into the urine due to an increased renal clearance of the drug. Plasma protein binding of torasemide was reduced in these patients, and the authors concluded that the increased renal clearance was probably due to increased tubular secretion of drug resulting from the decreased plasma binding. The greater urinary excretion rate compensated for the decreased receptor sensitivity, and this resulted in there being no difference in the diuretic response (rate of sodium excretion) between patients with cirrhosis and healthy individuals (fig. 6).

## 7. Conclusions

Hepatic drug handling mechanisms are altered sufficiently in chronic liver disease with cirrhosis to warrant dosage reduction, but not sufficiently to warrant dosage reduction if cirrhosis is absent. The changes in patients with cirrhosis involve altered hepatic blood flow and extraction, and therefore dosage requirements for drugs of both high and low hepatic clearance are affected. Caution is warranted in drawing general conclusions from individual studies about the pharmacokinetics of specific







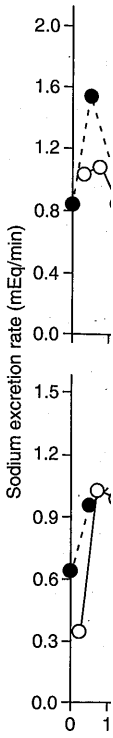


**Fig. 6.** Comp
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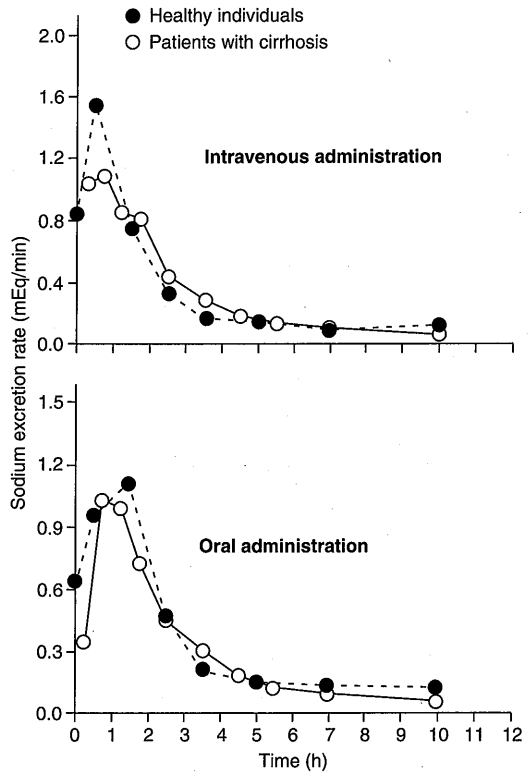


**Fig. 6.** Comparison of urinary sodium excretion rates versus time after intravenous (**top**) and oral (**bottom**) administration of torasemide 10mg to patients with cirrhosis and to healthy individuals, showing similarity of pharmacodynamic effects between healthy people and those with cirrhosis. In patients with cirrhosis, the greater urinary excretion of drug compensated for the relative resistance to diuretic effect (from Schwartz et al.,[113] with permission).

drugs, because results from such studies are highly dependent on the severity of disease in the patient group studied. In some of the studies reviewed here, the patient group represented a range of disease severity, judged on clinical and biochemical criteria, while in other studies disease severity was either uniformly mild or uniformly severe. In other studies disease severity was not specified. It is possible that the absence of a significant effect of cirrhosis on pharmacokinetics in a particular study could have been due to the use of a patient group with mild disease (i.e. Child class A).

Chronic liver disease with cirrhosis also influences the dosage requirements of those drugs where the parent drug or active metabolite(s) are excreted principally by the kidney via a reduction in renal clearance. A reduction in dosage of up to 90% could be required for such drugs, but the decrease in renal clearance is not reliably correlated with the decrease in creatinine clearance. In addition to altered pharmacokinetics, altered pharmacodynamics may also occur.

'Safe' drug use in patients with liver disease requires an awareness of the possibility of multiple interactions between changes in hepatic and renal disposition and pharmacodynamics. The material reviewed in this update affirms the view that in chronic liver disease with cirrhosis, dosage reduction is the general rule, regardless of the route of elimination of drug or metabolite.

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