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Clinical Pharmacokinetics in Patients with Liver Disease

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Summary

From considerations of hepatic physiology and pathology coupled with pharmacokinetic principles, it appears that altered drug elimination in liver disease may result from the following

mechanisms: reduction in absolute cell mass, in cellular enzyme content and/or activity, in portal vein perfusion due to extrahepatic/intrahepatic shunting, or of portal perfusion of hepatocyte mass due to decreased portal flow or sinusoidal perfusion; increase in arterial perfusion relative to portal perfusion; preferential perfusion of the sinusoidal midzone and terminal zones by arterioles; potential for direct mixing of arterial blood within the space of Disse; reduced exchange across the endothelial lining; and impaired diffusion within the space of Disse.

In general, oxidative drug metabolism is impaired in liver disease and the degree of impairment of oxidation differs between drugs but correlates best with the degree of sinusoidal capillarisation, i.e. the degree of access of the drug from the sinusoid to the hepatocyte. Drug conjugation appears to be relatively unaffected by liver disease, whereas elimination by biliary excretion correlates best with the degree of intrahepatic shunting and not with sinusoidal capillarisation. As the latter should impair hepatocyte access of all compounds similarly, a potentially important mechanism could be impaired access of oxygen to hepatocytes as oxidative metabolism is much more sensitive to oxygen supply than are conjugation or biliary excretion. This suggests a potentially important therapeutic role for agents which increase the hepatic oxygen supply.

Useful adjunctive strategies may also derive from the oxygen limitation hypothesis. Anaemia should be targeted as a critically important variable, as should oxygen-carrying capacity, i.e. modification of the smoking habit. Additionally, enzyme inducers such as barbiturates may be used if overriding hypoxic constraints are removed by oxygen supplementation. Agents likely to seriously compromise arterial perfusion of the hepatic vascular bed should be avoided, e.g. those causing postural hypotension or vasospasm. Vasodilators can be used to actively promote arterial perfusion.

While the effect of liver disease on drug handling is highly variable and difficult to predict, there are well recognised principles for modifying dosage. These include halving the dose of drugs given systemically (or of low clearance drugs given orally) and a 50 to 90% reduction in the dose of drugs with a high hepatic clearance given orally. Changes in the pharmacodynamic effects of drugs (either alone or in addition to pharmacokinetic changes) can also be profound, and awareness of this possibility should be increased.

As the liver is the main site of drug metabolism in the body, it would be expected that drug dosage may need to be reduced in patients with liver disease. A number of recent reviews have discussed the effects of liver diseases on pharmacokinetics and provided comprehensive information on changes observed with many drugs (Bass & Williams 1988; Howden et al. 1989; Secor & Schenker 1987; Wilkinson 1986). For detailed information on specific drugs, the reader is referred to these reviews, especially the article in the Journal by Bass and Williams in 1988.

Despite these extensive reviews, the mechanisms determining changes in the pharmacokinetics of drugs in liver disease are still poorly understood. There is little known about the effects of different liver diseases, as most information has come from patients with alcoholic cirrhosis. There is also a paucity of information on pharmacokinetic changes in a given disease over time, or on the changes that

occur in pharmacodynamic response (i.e. receptor sensitivity) to drugs in liver disease. The effect of a given disease on different drugs is highly variable, and the precise mechanisms underlying these changes are poorly understood.

In this review we examine the pathology of liver diseases in some detail and discuss the likely mechanisms of change in pharmacokinetics in animals and humans with hepatic impairment.

1. Structure and Function of Healthy Liver

The cell mass of the liver performs diverse metabolic and excretory functions with substrates being presented directly from the gut lumen (nutritional substrates, bacterial byproducts, xenobiotics), from the gut-related endocrine organs (gut peptides and various autacoids) and pancreas (insulin, glucagon) and indirectly from the general cir-

culation. The liver is exposed to a wide variety of potentially harmful influences (drugs, toxins, infectious and inflammatory disease) because of its strategic position in relation to the gut and its processing of 20 to 25% of the total circulation. A diverse range of disease processes in the liver derive from these noxious stimuli, resulting in loss of cell mass, circulatory disturbances, destruction of normal architecture and reduction in functional capacity.

Liver disease has general implications for health (nutritional and metabolic balance, maintenance of body fluid and electrolyte balance, coagulation control); however, pharmacologists have taken particular interest in the influence of liver disease on drug dosage requirements and drug action. This review focuses on those functions of the healthy liver which influence drug handling, and the various changes which result from liver disease.

1.1 Functional Anatomy of the Liver

The liver has a mass of 0.015 to 0.020 kg/kg bodyweight. In healthy humans, this mass consists of 1kg of mixed cell elements (see below) and 300ml of blood.

There is a dual blood supply delivering 1.2 to 1.5 L/min. In the healthy subject some 80% of the flow is part of a splanchnic portal circulation, while 20% derives from hepatic arteries delivering blood directly to the biliary tree and liver.

Vascular exchange occurs in modified capillary structures termed sinusoids, which are vascular spaces between plates of liver cells. The spaces are divided into inner and outer areas by an endothelial layer. Red blood cells and other formed elements are confined to the inner axial core by the epithelium, but the fluids in the outer space (space of Disse) are in free communication with the central flow (Greenway & Stark 1971). The inflow to the sinusoids derives from these 2 sources via 3 routes: portal venous input is direct from terminal branches of the portal vein; arterial input is both indirect from a sinusoidal network around tributaries of the biliary tree; and direct from branches of the hepatic artery entering via the sinusoidal

plates at various points along the length of the sinusoid.

Functional aggregates of sinusoids are defined by the terminal supply of branches of portal vein and hepatic artery (Campra & Reynolds 1982). This view of functional organisation supersedes the former orthodox view of a liver lobule defined at its outer limits by portal triads which focused on a 'central vein'. Venous drainage of the sinusoids is directly into a network of large venous elements forming a 3-dimensional 'basket-like network' over the surface of each functional aggregate of sinusoids.

The sinusoid represents a low pressure pathway, as evidenced by portal venous pressures of 8 to 10mm Hg and hepatic venous pressures of 1 to 2mm Hg. High flows of 1.0 to 1.5 ml/kg/min are needed to deliver the oxygen requirements as the portal venous blood is only 70 to 85% saturated. Hepatic arterial branches deliver blood with 100% saturation either directly to midzone and terminal sections of the sinusoid or into the peribiliary plexus. The hepatic artery represents a critical source of oxygen supply for the biliary tract (100% of supply) and an indispensable proportion of sinusoidal supply in most species, as demonstrated by ligation-survival studies.

1.2 Sinusoidal Structure and Physiology

In most species, sinusoidal flow is regulated only by variations in arterial inflow which can be modified by a wide variety of stimuli (Withrington & Richardson 1986). Insight into the regulation of sinusoidal flow has been obtained through observations with vasodilators given orally or into the portal vein. When hydralazine was administered into the gut of a dog and blood flow was measured (fig. 1) a rapid increase in hepatic arterial blood flow occurred, preceding the change in mesenteric artery blood flow by at least 1 circulation time (Heinzow et al. 1984). These observations indicate that arterial inflow into the sinusoid is regulated in part by vasoactive agents within the sinusoidal space. Further, they show that there is free exchange of vasoactive agents between the axial flow

Fig. 1. Influence of HABF on HABF between HABF and MABF

the length of the sinusoids are defined

inches of portal vein (Reynolds 1982). This supersedes the forlobule defined at its which focused on a one of the sinusoids is large venous elements 'net-like network' over 1 aggregate of sinusoids.

Flow pressure pathway, sinus pressures of 8 to 10 mm Hg, pressures of 1 to 2 mm Hg, and 1.5 ml/kg/min are requirements as the 0 to 85% saturated. After blood with 100% oxygen saturation into the peribiliary capillaries represents a critical part of the biliary tract (100% oxygen saturation). The proportion of sinusoids is demonstrated by

1 Physiology

Flow is regulated only by which can be modulated (Withrington & 1980). The regulation of flow is achieved through observation orally or into the mesenteric vein was administered. Flow was measured in hepatic arterial blood flow range in mesenteric vein circulation time measurements indicate that sinusoid flow is regulated within the sinusoidal space there is free exchange between the axial flow

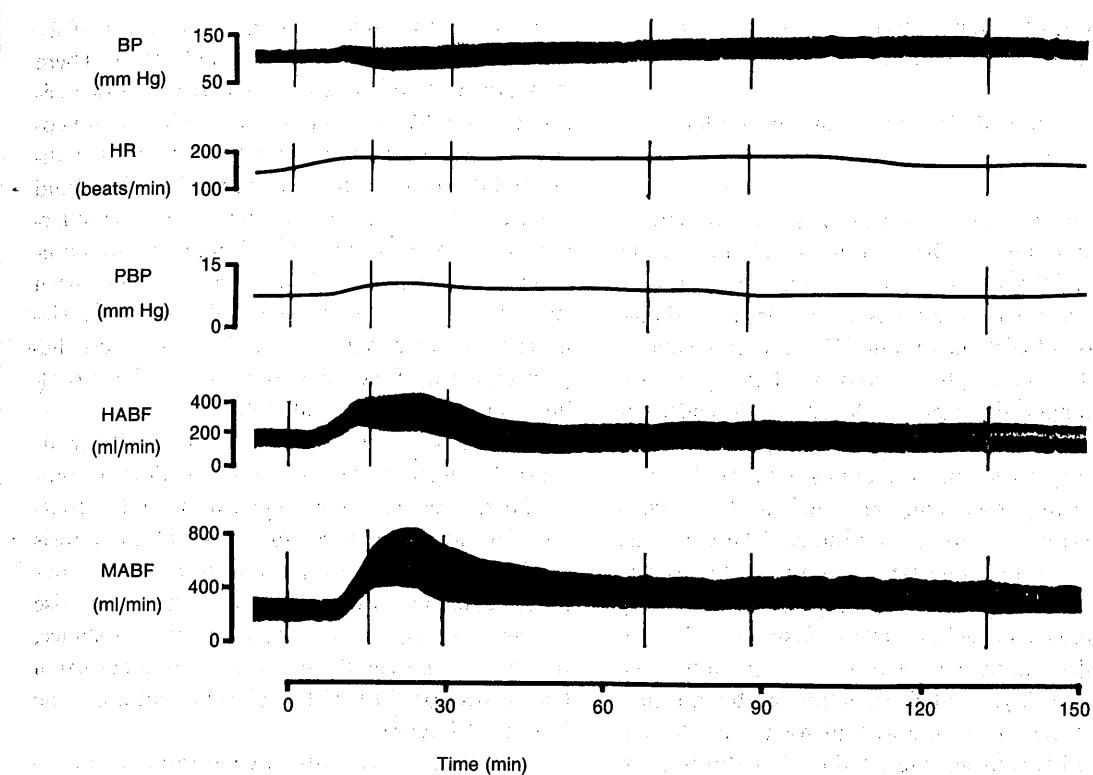


Fig. 1. Influence of oral hydralazine on systemic blood pressure (BP), heart rate (HR), portal pressure (PPB), hepatic artery flow (HABF) and mesenteric artery flow (MABF) in an anaesthetised dog, showing a difference in time of onset of effect between HABF and MABF (from Heinzow et al. 1984, with permission).

and the space of Disse, and this reaction of the arterial flow to portal administration of a vasodilator is also functional evidence of a substantial direct arterial inflow along the length of the sinusoid.

Functional exchange between the axial flow and the fluid spaces of the liver has been rigorously examined by the single-pass label dispersion technique. A mixture of labelled red blood cells (RBC), labelled albumin and labelled H_2O is injected as a bolus, and the concentration-time profile in the venous outflow examined. The relative dispersion of the outflow profile is a measure of confinement to the axial flow (RBC), penetration into the space of Disse (albumin) and diffusion into the cellular and intracellular space (H_2O). When a test substrate is injected along with these markers, a meas-

ure of the distributional space can be defined. Similarly, when the liver has been subject to a disease process, the nature of the physical changes can be quantified against healthy controls. Several groups have made major contributions to this field (Goresky 1963; Goresky et al. 1970; Gross et al. 1987; Huet et al. 1982; Plourde et al. 1988; Reichen 1989; Reichen et al. 1988).

The results with labelled water and labelled albumin indicate an extensive capacity for exchange of substances across the endothelial cell layer, with restriction only applicable to formed cellular elements and platelets. Diffusional processes appear to be relatively free. Ultrastructural, chemical and immunochemical study techniques indicate that the space of Disse is free of chemical constituents or

structural entities likely to impair the free diffusion of small and large molecules.

1.3 Functional Constraints on Sinusoidal Clearance

Extensive mathematical descriptions of hepatic sinusoidal function have been based on a wide variety of observations on the hepatic clearance of many test substances (Wilkinson 1987). Predictably, physiologists have tended to use endogenous substrates, while pharmacologists have generally used xenobiotic agents. Despite differences in interpretation of data and as to the priority of determining factors, most analyses have made common assumptions (Pang & Rowland 1977) concerning the operating conditions. These are as follows: (a) no limitation on oxygen or substrate supply to all systems; (b) ready access (including bulk fluid exchange) and free diffusion of substrate molecules and carrier macromolecule (if any) to the hepatocyte layer; (c) dissociation of bound substrate at the cell surface with dissociation rate well above other transfer rates; and (d) free diffusion of unbound substrate into the cell with free access to enzyme-based translocation or biotransformation processes.

2. Summary of Pathological Changes in Liver Disease

Various pathological processes are associated with liver disease syndromes. Common types follow infectious agents (viral, bacterial and parasitic), toxic-nutritional effects (alcoholism, halogenated hydrocarbons), circulatory change (cardiac failure, eclampsia), autoimmune inflammation and postviral syndromes. Most result in cell damage with cell death and/or pathological repair processes. The outcomes of the disease processes vary widely but there are elements common to all types of liver disease.

Changes in the sinusoids have been extensively documented (Gross et al. 1987; Huet et al. 1982; Plourde et al. 1988; Reichen 1989; Reichen et al. 1988; Villeneuve & Huet 1987). There is evidence

of change in the endothelial lining with loss of fenestration and development of basal laminae. There is enlargement of the space of Disse with deposition of complex macromolecules including mucopolysaccharides, collagen and fibrin with or without cellular proliferation including fibroblasts and Kupffer cells. These changes represent a 'capillarisation' of the sinusoids. The functional and pathological significance of these changes has been summarised as follows: 'the development of a significant blood hepatocyte barrier may cause hepatocellular dysfunction and eventually hepatocellular necrosis' (Horn et al. 1987).

Inflammation and repair results in diffuse fibrosis throughout the liver with or without cirrhosis, i.e. discrete bridging fibrosis from central (portal) triads to hepatic vein tributaries. Diffuse fibrosis results in increased resistance to flow, with a consequent rise in portal venous pressures. This rise in part compensates for the increased resistance, but there is an overall increase in arterial perfusion (50 versus 20% in healthy subjects) and a decline in overall flow rate.

Bridging fibrosis, with vascularisation of the fibrous bridges, represents cirrhosis. These vascular paths can be from artery or from portal vein branch to hepatic vein. The quantitative assessment of this process has varied widely as a function of both species and disease process (Groszman et al. 1972, 1976, 1977; Hoefs et al. 1978; Huet et al. 1976; Lebrec et al. 1976; Popper et al. 1952). Also recently identified is the presence of sinusoids with very high flows, the proportion of which increases greatly with the development of fibrosis and cirrhosis (Sherman et al. 1990). These 'fast sinusoids' represent functional rather than anatomical shunts in that it is the velocity, rather than the diameter, that is different in these vessels.

Raised portal venous pressures can result in changes in venous pathways outside the liver with development of extrahepatic shunts between the portal circulation and the general circulation. These portal-systemic shunts can develop at all anatomical junction points between the splanchnic circulation and the systemic circulation, i.e. at the lower end of the oesophagus (oesophageal-gastric var-

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lining with loss of features), at the anorectal verge (rectal haemorrhoids), around the umbilicus (caput medusae), in retroperitoneal tissue and via the diaphragm.

3. Potential Mechanisms of Altered Drug Disposition in Liver Disease

Known and inferred pathological changes might result in alteration in drug handling within the liver, and outside the liver due to secondary effects, e.g. altered concentration of binding proteins.

Within the liver, disease processes result in a varying mix of the following changes:

1. Reduction in absolute cell mass.
 2. Reduction in portal venous perfusion of hepatocyte mass due to extrahepatic shunting of portal blood.
 3. Reduction in portal venous perfusion of hepatocyte mass due to intrahepatic shunting of blood via cirrhotic shunts (portal triad to hepatic vein tributary).
 4. Reduction of portal perfusion of hepatocyte mass because of absolute reduction in portal flow due to increased vascular resistance.
 5. Reduction in portal perfusion of hepatocyte mass due to altered access from axial flow to the sinusoid (capillarisation).
 6. Increase in arterial perfusion of hepatocyte mass due to higher arterial inflow into the axial sinusoidal flow.
 7. Increase in direct arterial perfusion of the hepatocyte mass due to preferential perfusion of the sinusoidal midzone and terminal zones by arterioles.
 8. Potential increase in direct arterial perfusion of the hepatocyte mass due to direct proximity of arterial blood to the space of Disse and sinusoidal plates.
 9. Reduced exchange of water, proteins and small molecules across the endothelial lining of the axial space.
 10. Impaired diffusion of substrates within the space of Disse.
- There are a variety of disease processes which result in reduced biliary secretion, biliary tract stasis

and biliary tract infection, producing changes in the liver and liver function. Finally, liver disease results in changes in plasma protein binding and renal function which have indirect effects on drug clearance both within and outside the liver. Each of these processes requires detailed consideration for its potential effect on drug handling.

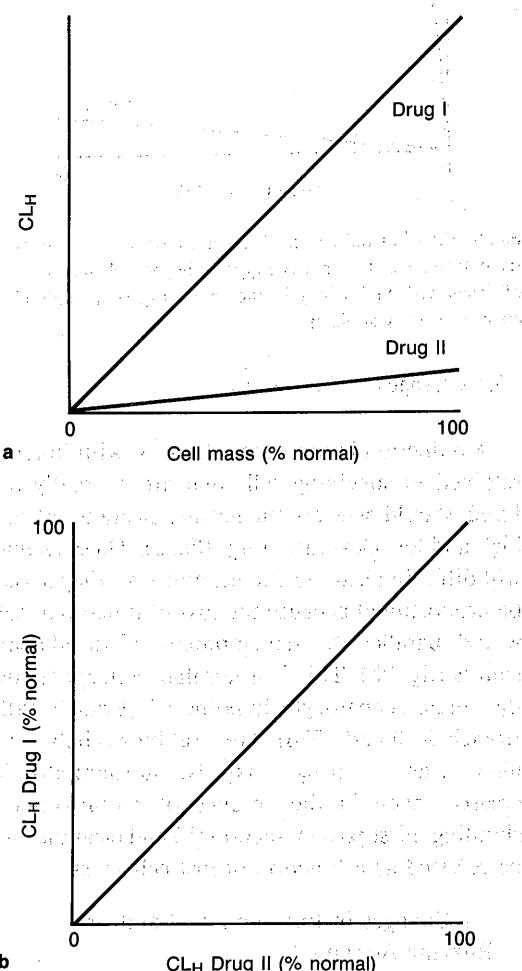


Fig. 2. Effect of reduction of absolute functioning cell mass on (a) hepatic clearance (CL_H) of drugs with high (drug I) and low (drug II) hepatic clearance in healthy subjects, (b) the relationship between hepatic clearances of drugs I and II.

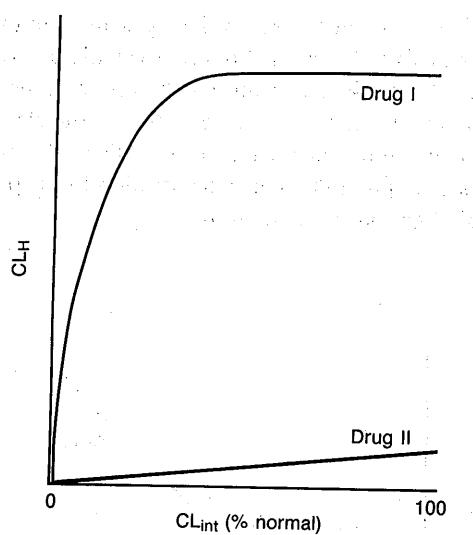


Fig. 3. Effect of reduction of hepatic enzyme content or activity [intrinsic clearance (CL_{int})] on hepatic clearance (CL_H) of drugs with high (drug I) and low (drug II) hepatic clearance in healthy subjects.

3.1 Changes in Cell Mass

A reduction in absolute cell mass, with function retained in surviving cells that are normally perfused, should decrease the hepatic clearance of both high and low clearance drugs (fig. 2). These changes will differ in absolute degree, although they should be proportional because the loss of functional cells would parallel the development of intrahepatic shunts (fig. 2b). This is a familiar concept termed the 'intact hepatocyte hypothesis' (Branch 1982; Branch & Shand 1976). The oral bioavailability of high clearance drugs may be substantially increased, even in the absence of portal-systemic shunting. First-pass extraction (E) and clearance will be reduced as a function of lost cell mass.

3.2 Changes in Enzyme Level and/or Enzyme Activity

Changes in enzyme level or activity due to alteration in the function of surviving cells have been termed the 'sick cell hypothesis'. This is seen as the major alternative to the 'intact hepatocyte hypothesis'.

There is direct evidence that there is a change in enzyme level and in the activity of drug metabolising enzymes in cirrhosis (Brodie et al. 1981; Cantrill et al. 1989; Farrell & Zaluzny 1983; Farrell et al. 1979, 1988), but it is not uniform among enzyme classes: for example, there are differences between the many [up to 200 (Brosen 1990)] individual cytochrome P450 enzymes (Murray et al. 1986). Additionally, hepatic active transport systems are affected (Reichen et al. 1987b). If the sick cell hypothesis were valid, the relationships shown in figure 3 would apply between systemic clearance and metabolic capacity (intrinsic clearance). A correlation between the hepatic clearances of high and low clearance drugs would not be evident.

3.3 Changes in Sinusoidal Perfusion

Changes in sinusoidal perfusion should produce proportional changes in the hepatic clearance of those drugs whose hepatic clearance is high and therefore rate-limited by perfusion (drug I, fig. 4). For drugs of low hepatic clearance (drug II, fig. 4) the hepatic clearance, while independent of flow at near physiological hepatic flow rates, will become more dependent on flow rate as it decreases (Pang

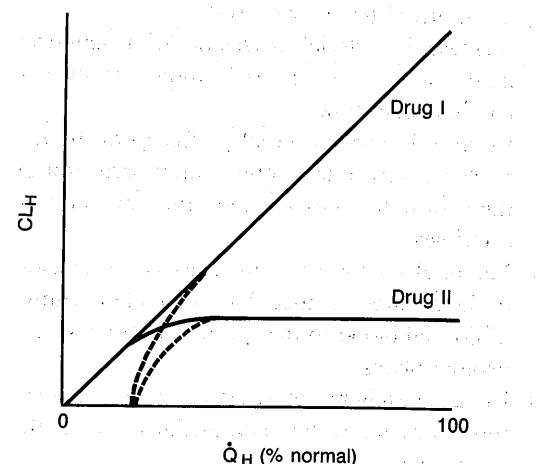


Fig. 4. Effect of reduction of hepatic blood flow (\dot{Q}_H) on hepatic clearance (CL_H) of drugs with high (Drug I) and low (Drug II) hepatic clearance in healthy subjects: --- indicates that changes secondary to reduced flow may affect relationships.

there is a change in the rate of drug metabolism (Brodie et al. 1981; Uzny 1983; Farrell 1987b). If the sick relationships shown [systemic clearance vs. hepatic clearance (drug I, fig. 4)] indicate differences between high and low flow rates, then it is evident.

When portal blood flow is directed away from exposure to hepatocytes, there are a number of potential consequences for the handling of high clearance drugs. Shunting of blood flow will not necessarily reduce systemic clearance unless there is a limitation on the reflex compensatory increase in arterial flow from the hepatic artery.

& Rowland 1977). At low flow rates this relationship becomes hypothetical because changes secondary to low flow supervene (e.g. collapse of sinusoids, reduction in oxygen delivery, etc.) [fig. 4].

3.4 Influence of Portal-Systemic Shunting

When portal blood flow is directed away from exposure to hepatocytes, there are a number of potential consequences for the handling of high clearance drugs. Shunting of blood flow will not necessarily reduce systemic clearance unless there is a limitation on the reflex compensatory increase in arterial flow from the hepatic artery.

When there is a relatively low pressure pathway available, there will be a reduction in perfusion flow (\dot{Q}_P) which is a direct function of the relative resistance of the 2 pathways. If the shunt flow is \dot{Q}_S and resistance in the shunt circuit is r_S while resistance in the perfusion circuit is r_P then total hepatic flow (\dot{Q}_H) is given by:

$$\dot{Q}_H = \dot{Q}_P + \dot{Q}_S$$

and

$$\dot{Q}_P/\dot{Q}_S = r_S/r_P$$

In an extreme case, reversal of flow in the portal vein has been documented in patients who have undergone a shunt procedure joining the portal vein directly to the inferior vena cava (mesocaval shunt). The diversion of blood will result in substantial changes in the oral bioavailability of high clearance drugs independent of the state of the hepatocyte or intrinsic clearance (CL_{int}). The relationship between bioavailability (F) and both shunt and perfusion flow has been previously described (McLean et al. 1979):

$$F = \dot{Q}_P/CL_{int} + \dot{Q}_S/(\dot{Q}_P + \dot{Q}_S)$$

3.5 Influence of Sinusoidal Capillarisation

Sinusoidal capillarisation, which results from loss of fenestration of the endothelium of the sinusoids, development of basal laminae and deposition of complex macromolecules in the space of Disse, is associated with a change from a flow-

limited to a diffusion-limited pattern of solute uptake by the sinusoids (Reichen 1989).

Reduction in the carrier protein exchange across the endothelium could have a major influence on drugs whose handling is affected by high protein binding (Blaschke 1977). This would be additive to any diffusional constraint caused by the accumulation of cells and extracellular matrix in the space of Disse. Accordingly, it would be predicted that the hepatic clearance of highly bound drugs should be reduced more than that of drugs with low binding, if diffusional constraints were applicable. Similarly, the oral bioavailability will be increased if diffusional constraints are rate-limiting.

Movement of drugs across the endothelial membrane would be facilitated by their lipophilicity. Accordingly, if access limited the rate of hepatic clearance, lipophilic drugs should be influenced less than those with lower lipid solubility. If these 2 potentially access-limiting factors were combined, it is possible to propose a hierarchy of effect, with the clearance of lipophilic drugs with high unbound fraction being relatively greater compared with that of drugs with relatively low lipid solubility and high protein binding.

Oxygen delivery could be compromised by the process of capillarisation if the critical diffusion distances were exceeded, as in lung pathology (Roughton & Forster 1957). In experimental preparations, limiting the oxygen supply to below 3.0 $\mu\text{mol}/\text{min}$ per gram weight of liver linearly reduces aromatic hydroxylation (Angus et al. 1989a), while glucuronidation is maintained until a critical threshold is reached of 2.0 $\mu\text{mol}/\text{min}$ per gram weight of liver (Angus et al. 1989b) [fig. 5]. Moreover, a reduced oxygen supply does not lower the hepatic clearance of the bile salt taurocholate (Jones et al. 1984). If the access of oxygen to the enzyme mass is applied as the rate-limiting constraint, rather than access of xenobiotic substrate to the enzyme mass, conjugation processes and bile salt excretion would be expected to be relatively unaffected, independent of the physicochemical properties of the drug substrate. Under these circumstances, administering vasodilators (e.g. nitrates, hydralazine, verapamil), which cause arteriolar di-

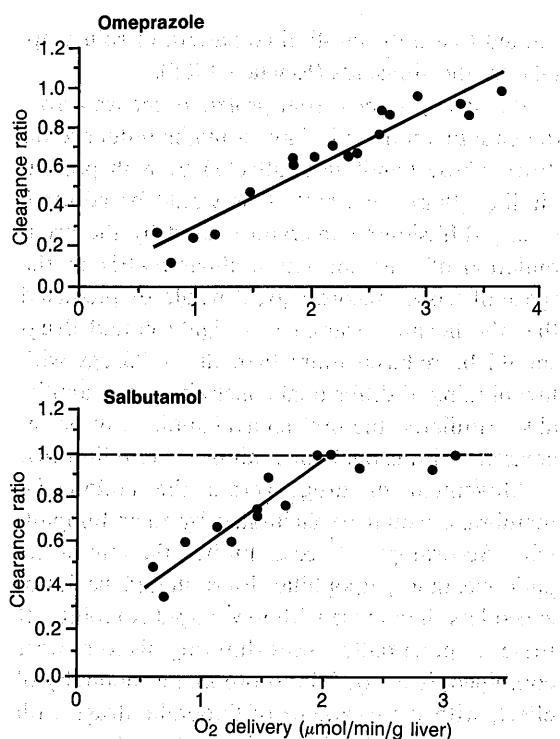


Fig. 5. Effect of oxygen delivery on drug clearance by the isolated perfused rat liver. Drug clearance is expressed as the ratio of clearance during the hypoxic : normoxic phases for each preparation. Omeprazole, metabolised primarily by oxidation, shows impairment of clearance as soon as oxygen delivery falls below the control value of $3.0 \mu\text{mol}/\text{min/g liver}$ (Angus et al. 1989a, with permission), whereas salbutamol (albuterol), metabolised primarily by glucuronidation, shows impairment of clearance only when oxygen delivery falls below about $2.0 \mu\text{mol}/\text{min/g liver}$ (Angus et al. 1989b, with permission).

the oxygen delivery to the liver. It has been suggested that a reduction in oxygen delivery, due to either a reduction in oxygenation and an increase in arterial flow, should increase the systemic clearance of drugs in cirrhotic subjects but not in healthy individuals. This increase in clearance could result from diffusion of oxygen across the walls of arterioles joining the midzone or pericentral zone. Alternatively, direct arteriolar perfusion of the space of Disse would explain such a change. Reichen and Le (1986) have reported increased oxygen consumption and clearance of phenazone (antipyrine) after administration of verapamil to the isolated perfused cirrhotic rat liver.

3.6 Influence of Biliary Obstruction on Drug Clearance

Fibrosis secondary to liver disease is known to reduce venous flow early in the disease process, as a result of low pressure gradients within the system.

Biliary drainage, like venous perfusion, operates under low pressures. The driving force to bile formation is the active secretion of bile acids and HCO_3^- , with osmotically determined water flow (Erlinger 1985; Poupon et al. 1976; Reichen & Simon 1982). Intrahepatic inflammation or extrahepatic obstruction can reduce bile flow, but it is not known whether biliary obstruction *per se* influences drug clearance, and, therefore, whether intact biliary drainage is part of the definition of a functional hepatic unit. It is more likely that biliary obstruction results in hepatocellular change with secondary modification of drug clearance.

3.7 Changes in Protein Binding and Drug Clearance

The plasma protein binding of many drugs is reduced in cirrhosis (Blaschke 1977; Tillement et al. 1978). The reduced binding correlates with the reductions in the plasma concentrations of albumin and α_1 -acid glycoprotein, the 2 main drug binding proteins in plasma (Kremer et al. 1988; Rothschild et al. 1988). Recent evidence suggests that the affinity of α_1 -acid glycoprotein for drugs is also lower in cirrhosis, indicating a qualitative change in the molecule (Aguirre et al. 1988). This is supported by immunochemical studies which have shown qualitative and quantitative changes to the structure of the sugar part of the glycoprotein molecule (Biou et al. 1987; Pedersen et al. 1987). The mechanisms of modification of hepatic drug clearance by protein binding have been extensively reviewed (Wilkinson 1987).

3.8 Hepatorenal Syndrome and Drug Clearance

Hepatorenal syndrome refers to renal impairment linked solely to liver impairment, i.e. when clinical, laboratory or anatomical evidence of other

ence of Biliary Obstruction on renal causes of renal failure are absent (Papper & Seldin 1973). This is normally thought of as a problem only secondary to liver disease is known flow early in the disease process, pressure gradients within the liver, like venous perfusion, open disease, has been shown to correlate with the driving force to bile secretion of bile acids (notically determined water solubility) and handling in patients with chronic stable cirrhosis (Blaschke 1977; Reichen & Ponson et al. 1976; Reichen & Blaschke 1977; Wensing et al. 1988) and cirrhotic rats (Wensing et al. 1988). While these changes may reflect an alteration in the handling mechanisms peculiar to Na⁺ balance, there remains a possibility of generalised change in tubular function. If this were so, xenobiotic clearance by the kidney which is dependent on tubular mechanisms could be altered in patients with even moderate degrees of liver impairment. It is more likely that biliary obstruction per se can reduce bile flow, but it is part of the definition of biliary obstruction that it is not due to hepatic inflammation or excretion. The driving force to bile flow can reduce bile flow, but it is part of the definition of biliary obstruction that it is not due to hepatic inflammation or excretion.

Protein Binding and

The binding of many drugs (Blaschke 1977; Tillement 1977) correlates with the concentrations of albumin, the 2 main drug-binding proteins (Kremer et al. 1988). Recent evidence suggests a glycoprotein for drugs, indicating a qualitative biochemical studies which and quantitative changes are part of the glycoprotein modification of hepatic binding have been examined (Pedersen et al. 1987).

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4. Methods and Observations with Drugs and Markers of Drug Disposition

The majority of published clinical pharmacokinetic studies in liver disease have used a relatively simple mechanistic framework to interpret their experimental findings. Thus, changes in the systemic clearance or systemic availability of orally administered drugs have been ascribed to a reduction in hepatic intrinsic clearance and/or effective hepatic blood flow. This approach was the basis for the intact hepatocyte and sick cell hypotheses (Branch 1982; Branch & Shand 1976). With our increasing understanding of the pathological changes and of the mechanisms by which these changes may alter drug disposition in liver disease, it is now possible to interpret experimental findings using a broader mechanistic framework. This section examines the results of some selected studies of drugs and other markers of drug disposition in terms of the mechanisms of altered drug disposition described in section 3. Blaschke (1977) classified the hepatic elimination of drugs according to whether hepatic blood flow, intrinsic clearance or unbound fraction was rate limiting; the same classification is used here, and the review concentrates on more recently published studies.

4.1 Capacity-Limited Binding-Insensitive Hepatic Elimination
Drugs in this category have a low hepatic intrinsic clearance relative to hepatic blood flow and are less than 30% bound to plasma proteins (Blaschke 1977). The hepatic clearance of such drugs is low and will be unaffected by changes in plasma protein binding or hepatic blood flow. Therefore, the interpretation of findings from studies of the disposition of these drugs in liver disease should be more straightforward than that for drugs with flow- or protein binding-limited hepatic clearance. The hepatic clearance of drugs with capacity-limited binding-insensitive hepatic elimination may still be affected in liver disease by loss of cell mass, reduction in enzyme mass per cell, alteration in the intrahepatic distribution of enzymes or sinusoidal capillarisation. Findings with typical drugs in this category are discussed below.

4.1.1 Phenazone
Phenazone is one of the standard model compounds for studying hepatic oxidative drug metabolism (Vesell 1979; Vesell & Page 1968) and has found widespread use in the study of the effect of liver disease on hepatic drug disposition. The clearance of phenazone following oral administration (and assuming complete bioavailability) has been measured in patients with a wide variety of hepatic disorders, but a reduction in clearance is usually observed only in severe disease. For example, there is little impairment in chronic persistent hepatitis, chronic active hepatitis, mild cirrhosis or hepatosplenic schistosomiasis (Daneshmend et al. 1982; Horvath et al. 1986; Villeneuve et al. 1987). However, phenazone clearance is reduced by 50 to 70% in advanced or decompensated cirrhosis (Daneshmend et al. 1982; Kawasaki et al. 1988; Kirch et al. 1989; McQuinn et al. 1988; Mehta et al. 1986; Pentikainen et al. 1986, 1989; Villeneuve et al. 1987) and in certain other severe disorders such as acute episodes of hereditary hepatic porphyria (Birnie et al. 1987).

In many of the studies cited above, phenazone was administered concurrently with another drug

that was under investigation, but in virtually every case the degree of impairment of phenazone clearance differed from that of the other drug studied, the impairment being smaller in some cases and greater in others than for the other drug. For example, the reduction of phenazone clearance in cirrhosis differed from that found for aminophenazone (aminopyrine) [Villeneuve et al. 1987], flecainide (McQuinn et al. 1988) and metronidazole (Daneshmend et al. 1982), even though these drugs are also eliminated by capacity-limited binding-insensitive hepatic oxidative metabolism. The reduction of phenazone clearance in cirrhosis was also greater than that of sulfadimidine, which was unchanged, or of the urinary excretion of menthol glucuronide, which decreased only slightly (Horvath et al. 1986). Thus, the acetylation of sulfadimidine and the glucuronidation of menthol appear to be much less affected by cirrhosis than the oxidative metabolism of phenazone. This is consistent with data from studies with other drugs that suggest that drug conjugation processes are relatively unaffected by liver disease (see section 4.1.5).

There are numerous other studies in which the clearance of phenazone was measured in cirrhosis together with the clearance of drugs that display capacity-limited binding-sensitive elimination, e.g. digitoxin (Kirch et al. 1989), mexiletine (Pentikainen et al. 1986) and midazolam (Pentikainen et al. 1989), or flow-limited elimination, e.g. galactose, indocyanine green (Kawasaki et al. 1988) and propranolol (Wood et al. 1978). In each case the reduction in phenazone clearance in cirrhosis differed from that of the other drug measured in the same patient, again the reduction being smaller in some cases and greater in others for the other drug. Moreover, although many of these studies found a good correlation between the reduction in phenazone clearance and that of other drugs in cirrhosis, the presence of such a correlation does not mean that the relative change in clearance was the same for each drug (Kawasaki et al. 1988; Morgan & Smallwood 1989).

Sotaniemi et al. (1986) used serum antigens related to collagen metabolism and basement membrane proteins to quantify hepatic fibrosis in al-

coholic liver disease. They found that the concentrations of these antigens correlated much better with phenazone clearance than with cellular cytochrome P450 level measured *in vitro*, and suggested that the creation of a mechanical barrier in the liver by the fibrotic process is more important in reducing the elimination of phenazone than a reduction in enzyme mass or activity. Total cytochrome P450 content is not, however, a very meaningful parameter with which to correlate drug metabolism. This is because cytochrome P450 is a large family of related oxidases which selectively catalyse different biotransformation reactions (Guengerich 1989). The regulation and expression of these enzymes involve several different mechanisms (Gonzalez 1990), so the effect of liver disease might not be expected to be the same for each enzyme. This is supported by the study of Murray et al. (1986). Thus, while the data of Sotaniemi et al. (1986) support the creation of a mechanical barrier as being responsible for impaired phenazone clearance in cirrhosis, they do not rule out the responsibility of a selective reduction in individual cytochrome P450 enzymes.

If impaired elimination was due to a reduced access of the drug to the hepatocytes, the impairment might be expected to be similar for most, if not all, drugs. This is clearly not the case. If the underlying mechanism is reduced access of oxygen to the hepatocyte, however (section 3.5), this could account for the variation in the impairment from drug to drug, depending on the sensitivity of the elimination process of each to a reduction in the oxygen supply (fig. 5) [Angus et al. 1989a,b; Aw & Jones 1982; Jones 1981].

4.1.2 Aminophenazone

Aminophenazone is also a standard model compound for studying hepatic oxidative drug metabolism, especially by using the convenient aminophenazone breath test (Hepner & Vesell 1974). The hepatic clearance of this drug is sufficiently low that it is not affected by gross changes in hepatic blood flow, such as that brought about by the creation of a portacaval shunt (Pomier-Layrargues et al. 1986). Like phenazone, aminophenazone clearance is re-

They found that the ligands correlated much better than with cellular mass measured *in vitro*, and suggested a mechanical barrier in liver disease is more important than phenazone than enzyme activity. Total cytochrome P450 is not, however, a very good marker to correlate drug use with cytochrome P450 oxidases which selectively transform reactions of metabolism and expression of several different mechanisms. The effect of liver disease may be the same for each drug. In the study of Murray & Sotaniemi et al., a mechanical barrier impaired phenazone clearance, but did not rule out the reduction in individual patients. This was due to a reduced number of hepatocytes, the impairment being similar for most, if not all drugs. If the reduced access of oxygen to the liver (Section 3.5), this could contribute to the impairment from the sensitivity of the enzyme to a reduction in the number of hepatocytes (Colli et al. 1989a,b; Aw & Vesell 1974). The enzyme activity is sufficiently low that it is not a significant factor in hepatic blood flow by the creation of sinusoidal capillarisation (Vesell 1974). The clearance is reduced only when cirrhosis is advanced (Monroe et al. 1980; Villeneuve et al. 1987), but the reduction is not the same as that of other drugs (Villeneuve et al. 1987).

In a rat model of cirrhosis, the aminophenazone *N*-demethylation rate measured *in vivo* by the aminophenazone breath test correlated with the hepatocellular volume measured morphometrically (Reichen et al. 1987a) and also with microsomal *N*-demethylase activity and cellular cytochrome P450 content (Gross et al. 1987). Subsequently this group repeated these experiments, but included an estimate of the degree of sinusoidal capillarisation. This was achieved by applying the multiple indicator dilution technique to the *in vitro* perfused liver of the animals after completion of the *in vivo* measurement (Reichen et al. 1988). The latter group found that sinusoidal capillarisation was the main determinant of aminophenazone clearance, being more important than enzyme activity or hepatocellular volume, and concluded that the apparent reduction of the intrinsic clearance of the drug in cirrhosis is primarily due to its restricted access to the hepatocyte via the space of Disse, rather than to loss of enzyme activity or cell mass.

4.1.3 Caffeine

Caffeine has also been used as a marker of hepatic oxidative drug metabolism (Desmond et al. 1980; Renner et al. 1984). As with phenazone and aminophenazone, caffeine elimination is impaired only in severe liver disease such as decompensated cirrhosis (Scott et al. 1988, 1989). Caffeine clearance in decompensated cirrhotic patients who are smokers is about double that of nonsmoking cirrhotic patients, in spite of a similar clearance of hexobarbital in both groups. This difference in caffeine clearance is similar to that between healthy smokers and nonsmokers (Joeres et al. 1988). Thus, despite the impairment of caffeine elimination in cirrhosis, the cirrhotic liver can still respond to the enzyme-inducing effect of smoking. This effect is thought to be specific for the cytochrome P450IA1 enzyme and supports the proposition that caffeine elimination is impaired in cirrhosis due to a loss

of cell mass, with the remaining cells being capable of normal function.

Although the clearance of caffeine is reduced in cirrhosis, the pattern of urinary excretion of its 11 metabolites is similar to that for healthy subjects (Scott et al. 1988). These authors concluded that the impairment of caffeine elimination in cirrhosis was due to a reduction either in hepatic caffeine uptake or in cell mass. A reduced hepatic uptake would be consistent with the presence of sinusoidal capillarisation.

4.1.4 Theophylline

The clearance of theophylline, which is metabolised primarily by hepatic oxidative enzymes, is reduced by 40 to 50% in patients with liver disease (Colli et al. 1988; Kraan et al. 1988). Clearance is reduced in compensated cirrhosis, in contrast to the drugs discussed above, and the impairment does not appear to be worse in decompensated cirrhosis (Colli et al. 1988). The reduction in clearance with intravenously administered theophylline (Kraan et al. 1988) was similar to that with orally administered drug. Although the 2 routes were not compared in the same subjects, this suggests that the route of hepatic drug input does not influence theophylline elimination in cirrhosis.

4.1.5 Drugs Metabolised by Conjugation

All of the drugs discussed so far are metabolised by hepatic oxidation. It is clear that in advanced cirrhosis the hepatic elimination of such drugs is substantially impaired. For drugs metabolised by hepatic conjugation processes, the degree of impairment varies. In the case of conjugation by glucuronidation, there is general agreement that for the majority of drugs studied there is minimal impairment, which has led to the hypothesis that glucuronidation is relatively unaffected in liver disease (Secor & Schenker 1987; Wilkinson 1986).

In our review of the data we are aware of substantial difficulties and deficiencies. There is considerable between-subject variation in the populations studied. These differences include the stage and severity of the disease, the characteristics of the control group and the age of the subjects. The

difficulties are not aided by the small numbers of subjects usually studied. Moreover, oral administration is commonly used, adding some uncertainty to the interpretation of the data. In the majority of the studies, there has been no measurement of the pharmacokinetics of the glucuronide metabolite (or of any other metabolites), so that glucuronide formation has not been measured *per se*. In most instances, only the half-life or clearance of the parent drug was measured and partial clearances of metabolites were not. The best data would be those found when 2 drugs are administered to each subject such that there is a direct comparison of oxidative and conjugative metabolism, but no examples of this type have been found. In the absence of direct comparisons, studies in patients with unambiguously advanced disease and fractional metabolic clearances hold the next best discriminative value. In patients with advanced disease furosemide (frusemide) and ciramadol show normal glucuronidation (Hoyumpa et al. 1989; Villeneuve et al. 1986), whereas elimination of morphine and oxazepam (both metabolised mainly by glucuronidation) is impaired (Hasselstrom et al. 1990; Sonne et al. 1990). Where predominantly glucuronidated drugs have been studied in terms of parent drug elimination, the overall pattern is one of preservation of clearance. Moreover, glucuronyl transferase activity *in vitro* is normal in cirrhosis (Pacifici et al. 1990).

In cirrhosis, there is no evidence of impairment of the metabolism of temazepam (Ghabrial et al. 1986; Ochs et al. 1986), lorazepam (Krauss et al. 1978), ciramadol (Hoyumpa et al. 1989), furosemide (Villeneuve et al. 1986) or menthol (Horvath et al. 1986), all substances which are metabolised to the ether glucuronide. Oxazepam (Kraus et al. 1978; Shull et al. 1976; Sonne et al. 1990) and morphine (Crotty et al. 1989; Hasselstrom et al. 1990; Patwardhan et al. 1981) are also metabolised to the ether glucuronide and impairment of their metabolism is observed only in severe cirrhosis. However, there is impairment in cirrhosis, and in other liver diseases such as acute viral hepatitis, of the elimination of chloramphenicol (Narang et al. 1981) and paracetamol (acetaminophen) [Andreasen &

Hutters 1979; Benson 1983; Forrest et al. 1977, 1979; Jorup-Rönström et al. 1986], both of which are also metabolised predominantly to the ether glucuronide. In the case of ester glucuronides the elimination of zomepirac (Witassek et al. 1983) and naproxen (Williams et al. 1984) is significantly impaired in cirrhosis, while that of carprofen (Holazo et al. 1985) and ketoprofen (cited in Hoyumpa et al. 1989) is unchanged. Thus, on balance, there are sufficient data to strongly support the hypothesis that drug glucuronidation is relatively unaffected in cirrhosis.

A variety of mechanisms have been put forward to account for the persistence of glucuronidation in liver disease. These include: (a) activation of latent glucuronyl transferase enzyme(s); (b) the presence of extrahepatic gluconuridation which would be unaltered in liver disease (Hoyumpa et al. 1989); (c) the presence of a large reserve of intra- or extrahepatic glucuronyl transferase; (d) the location of glucuronidation in parts of the liver lobule less affected by liver disease; and (e) the reduction of enterohepatic recycling of the glucuronide, which might tend to increase the clearance of the parent drug and thereby offset the effect of decreased glucuronide formation (Ghabrial et al. 1986). These mechanisms will remain speculative until appropriate experimental data are available.

There are very few data available on other conjugation pathways in liver disease. Increased half-lives have been shown in cirrhosis for isoniazid (Acocella et al. 1972) and procainamide (Du Souich & Erill 1977), both of which are metabolised primarily by acetylation, and the acetylation of sulfadimidine appears to be impaired in cirrhosis (Horvath et al. 1986, 1988). The sulphate conjugation of ciprofloxacin was unchanged in cirrhosis even though there was a substantial concurrent reduction in the formation of 1 of the oxidative metabolites of the drug (Frost et al. 1989). However, there is evidence of impairment of paracetamol sulphation in cirrhosis (Forrest et al. 1979) and reduced sulphotransferase activity (Pacifici et al. 1990) in cirrhosis.

4.2. Capacity Hepatic Enzymes
Drugs in hepatic intrinsic flow, and arylalkylamine protein are some well-known because of the diazepam category hepatic the extent of as well as on cirrhosis, acetyltransferase squalene (Reichardt) hepatic uptake undergo carnitination, since limited to the effect of ion of drugs necessary to take it binding. The clearance of hepatic clearance called clearance 1977).

It is difficult to assess liver disease in this category. Intrinsic clearance unchanged, For example, clearance of toxin in cirrhosis (1989): while it could have been the patients received digitalis, reduced phenytoin and unchanged total 75%, indicating a significant decrease in hepatic clearance.

orrest et al. 1977, 1986), both of which relate to the ether glucuronides (Blaschke et al. 1983) and are significantly increased in carprofen (Holazo et al. 1986; Hoyumpa et al. 1986). In balance, there are drugs that support the hypothesis that some drugs are relatively unaffected by liver disease.

Several hypotheses have been put forward to explain the effect of glucuronidation on drug clearance. These include: (a) activation of microsomal enzyme(s); (b) the increase in the rate of glucuronidation which increases the clearance of drugs; (c) the increase in the rate of transferase; (d) the increase in the rate of metabolism of the liver by drugs; and (e) the increase in the rate of recycling of the glucose-6-phosphate pool thereby offset the decrease in the rate of formation (Ghoshal & Bhattacharya 1986). These mechanisms will remain speculative until further experimental work is done.

The effect of liver disease on other conjugated drugs is less clear. Increased half-lives have been reported for isoniazid and isoniazid sulphate (Du Souich et al. 1986) and for phenacetin (Metzger et al. 1986). Sulphate conjugation is increased in cirrhosis (Hoyumpa et al. 1986) and concurrent reduced oxidative metabolism has been reported (Pacifini et al. 1986). However, the effect of paracetamol on drug clearance is unclear (Pacifini et al. 1979) and remains to be clarified (Pacifini et al. 1986).

4.2 Capacity-Limited Binding-Sensitive Hepatic Elimination

Drugs in this category generally have a low hepatic intrinsic clearance relative to hepatic blood flow, and are normally more than 85% bound to plasma proteins (Blaschke 1977); nevertheless, there are some with a large hepatic intrinsic clearance because of very high binding to plasma protein [e.g. diazepam (Byrne et al. 1985)]. For drugs in this category hepatic clearance is low, and depends on the extent of protein binding of the drug in plasma as well as on the intrinsic clearance of the drug. In cirrhosis, access to the space of Disse and the hepatocyte surface is restricted for albumin in sinusoidal plasma due to capillarisation of the sinusoids (Reichen 1989). This should not affect the hepatic uptake of albumin-bound drugs that undergo capacity-limited binding-sensitive elimination, since in any case for these drugs uptake is limited to the unbound fraction. In order to assess the effect of liver disease on the hepatic elimination of drugs in this category it is therefore necessary to take into account changes in plasma protein binding. This is done by calculation of the intrinsic clearance of the drug which, for drugs of low hepatic clearance, can be approximated by the so-called clearance of unbound drug (Blaschke et al. 1977).

It is difficult to generalise about the effect of liver disease on the hepatic elimination of drugs in this category. Both unbound fraction and hepatic intrinsic clearance may be altered or both may be unchanged, or one or other of them may change. For example, there was no change in the hepatic clearance or unbound fraction of tianeptine or digitoxin in cirrhosis (Kirch et al. 1989; Royer et al. 1989); while the absence of change for tianeptine could have been because the disease was mild in the patients studied, disease in the patients who received digitoxin was sufficiently advanced to have reduced phenazone clearance by 50%. In a study of mexiletine in cirrhosis the unbound fraction was unchanged but hepatic clearance was reduced by 75%, indicating a corresponding decrease in intrinsic clearance (Pentikainen et al. 1986). In the case

of midazolam, erythromycin and naproxen, unbound fraction increased and intrinsic clearance decreased in cirrhosis (Barre et al. 1987; MacGilchrist et al. 1986; Pentikainen et al. 1989; Trouvin et al. 1988; Williams et al. 1984). With the first 2 drugs the reduction in intrinsic clearance was greater than the increase in unbound fraction, leading to a net reduction in hepatic clearance. However, in the case of naproxen the changes in both parameters were of similar magnitude, so that hepatic clearance was unchanged. Tolbutamide illustrates the remaining possibility, where unbound fraction increases in acute viral hepatitis but intrinsic clearance is unchanged. This results in an increase in the hepatic clearance of the drug (Williams et al. 1977).

4.3 Flow-Limited Elimination

Drugs that exhibit flow-limited hepatic elimination have a very high hepatic intrinsic clearance relative to hepatic blood flow and may be extensively bound to plasma proteins (Blaschke 1977). For such drugs the hepatic clearance is high, more than 70% of hepatic blood flow, and depends primarily on the latter. Of the pathological changes in cirrhosis (described in section 3) that can alter drug elimination, those expected to be most important for flow-limited drugs are changes in hepatic blood flow and relative contribution of portal venous and arterial flows, extrahepatic portovenous shunting and intrahepatic shunting, and sinusoid capillarisation. For flow-limited drugs highly bound to albumin or other proteins, hepatic elimination is not limited to the unbound portion but bound drug is also available for hepatic uptake. Sinusoidal capillarisation could also reduce hepatic uptake of these drugs by reducing the access of protein-bound drug in the sinusoid to the space of Disse. One of the main factors that has limited the interpretation of experimental findings with flow-limited drugs in liver disease has been the inability to unambiguously quantify the pathology present, especially that related to intrahepatic changes in blood flow. These difficulties are illustrated in the following examples.

4.3.1 Indocyanine Green

Indocyanine green is a highly plasma protein bound anionic dye which is taken up by the liver and excreted unchanged into bile (Cherrick et al. 1960). Its systemic clearance has been used for many years as a test of liver function (Brody & Leichter 1979; Caesar et al. 1961; Schenker et al. 1988; Wiegard et al. 1960; Williams et al. 1976). This compound has been viewed as having a high hepatic extraction ratio (> 0.7) and has therefore also found widespread use as a marker of hepatic blood flow, measured by applying the Fick principle (Caesar et al. 1961; Guechot et al. 1989; Huet & Villeneuve 1983; Pessayre et al. 1978; Pomier-Layargues et al. 1986; Poupon et al. 1981; Villeneuve et al. 1987; Vine et al. 1988; Wiegard et al. 1960). If indocyanine green is infused at rate R to steady-state, and the concentration is measured in a peripheral vein (C_v , equivalent to hepatic input) and hepatic vein (C_{Hv}), then according to the Fick principle, hepatic blood flow is given by:

$$\dot{Q}_H = R/(C_v - C_{Hv})$$

Skak and Keiding (1987) have shown that the hepatic extraction ratio of indocyanine green is lower than was previously thought, with values in healthy subjects ranging from 0.48 to 0.71. In theory, the application of Fick's principle is independent of the magnitude of the concentration drop across the liver ($C_v - C_{Hv}$), which is indicated by the hepatic extraction ratio. However, Skak and Keiding (1987) demonstrated that the experimental error associated with a low extraction ratio results in a systematic bias towards high calculated flow rates. Nevertheless, measurements of hepatic blood flow by this method in healthy subjects match well with other methods performed simultaneously (Huet & Lelorier 1980; Kawasaki et al. 1988; Keiding 1987; Zeeh et al. 1988). In patients with cirrhosis, however, the hepatic extraction ratio of indocyanine green is considerably reduced. In 52 patients with liver disease, the extraction ratio ranged from 0.02 to 0.69 (mean 0.34) [Skak & Keiding 1987]. Therefore, indocyanine green should not be used to measure hepatic blood flow in liver disease.

In hepatic cirrhosis the Fick principle gives an estimate of total, not functional, liver blood flow, since the hepatic venous concentration measurement takes place in mixed blood which includes that from functioning sinusoids as well as blood from possible intrahepatic vascular shunts. The use of the Fick principle to measure hepatic blood flow in cirrhosis compromises the interpretation of many published pharmacokinetic studies of flow-limited drugs in cirrhosis. For example, the reduced hepatic clearance in cirrhosis of several drugs was attributed principally to a reduction of hepatic intrinsic clearance because hepatic blood flow measured by the Fick principle was similar to healthy values (Barbare et al. 1985; Huet & Villeneuve 1983). However, a measure of functional hepatic blood flow is required to differentiate the effects of changes in blood flow and intrinsic clearance on hepatic clearance. It has been proposed that the hepatic clearance of a suitably high extraction ratio test substance should be used to assess the blood flow through functioning sinusoids (Blei 1986; Henderson et al. 1982; Kawasaki et al. 1988; Keiding 1987; Morgan & Smallwood 1989; Tygstrup & Winkler 1958; Zeeh et al. 1988). This is supported by the fact that hepatic blood flow in cirrhotic patients measured using the hepatic clearance of galactose and sorbitol was substantially lower than that measured simultaneously with indocyanine green using the Fick principle (Kawasaki et al. 1988; Zeeh et al. 1988).

In a recent study of cirrhotic patients, in which functional hepatic blood flow was measured by the hepatic clearance of galactose, the intrinsic clearance of indocyanine green was reduced from normal by 85%, and functional liver blood flow was reduced by 30% (Kawasaki et al. 1988). Using the multiple indicator dilution technique in 25 cirrhotic patients, Huet et al. (1982) found that the hepatic extraction of indocyanine green correlated with the extravascular space. They concluded from this that the reduced extraction of indocyanine green in cirrhosis may be due to restricted access of albumin-bound indocyanine green to the liver cell surface due to capillarisation of the sinusoids.

4.3.2 Galactose

Galactose 1-phosphate is a quantitative marker (Goresky et al. 1963). This compound is protein-bound, is phosphorylated and (Goresky et al. 1963) hepatic extraction ratio is still high. Hepatic clearance of galactose (clearance) has been measured as a measure of functional hepatic blood flow in disease (Henderson 1958) although this has been done in rats.

In a rat model, the galactose elimination test, was correctly determined using the technique (Reinhard 1988). In this, the main determinants of galactose clearance suggested that capillarisation are the main determinants of hepatic blood flow in cirrhosis.

In proposing the use of galactose to measure blood flow in cirrhotic patients, it is clear that healthy subjects have a higher hepatic blood flow than cirrhotic patients. However, the use of galactose to measure blood flow in cirrhotic patients has been suggested by Kawasaki et al. (1988) to be unreliable.

4.3.3 Proprietary products

In hepatic diseases, the use of propranolol to measure hepatic blood flow has been proposed by orally administered propranolol.

principle gives an , liver blood flow, ntration measurem- od which includes as well as blood ar shunts. The use heptic blood flow interpretation of many es of flow-limited , the reduced he- eral drugs was at- on of hepatic in- atic blood flow e was similar to 1985; Huet & Vil- sure of functional o differentiate the nd intrinsic clear- as been proposed suitably high ex- ld be used to as- tination sinusoids 2; Kawasaki et al. Smallwood 1989; et al. 1988). This atic blood flow in the hepatic clear- was substantially aneously with in- principle (Kawa-).

patients, in which measured by the intrinsic clear- reduced from nor- blood flow was 1988). Using the technique in 25 cir-) found that the green correlated concluded from of indocyanine restricted access reen to the liver of the sinusoids.

4.3.2 Galactose

Galactose has been used for many years as a quantitative marker of liver function (Tygstrup 1963). This compound, which is not plasma protein bound, is metabolised in the liver by phosphorylation and has free access to the space of Disse (Goresky et al. 1973). In healthy subjects the hepatic extraction ratio is 0.94 and, as the extraction ratio is still high in cirrhosis (0.79), the systemic clearance of galactose (which approximates hepatic clearance) has been recommended as an accurate measure of functional hepatic blood flow in liver disease (Henderson et al. 1982; Tygstrup & Winkler 1958) although significant extrahepatic elimination has been suggested (Keiding 1988).

In a rat model of cirrhosis, the efficiency of galactose elimination *in vivo*, using the galactose breath test, was correlated with hepatic haemodynamics determined using the multiple indicator dilution technique (Reichen et al. 1988). Multiple regression analysis indicated that sinusoidal capillarisation and portal blood flow were the main determinants of galactose elimination. The authors suggested that volume of flow and sinusoidal capillarisation are independent aspects of the reduction in functional hepatic blood flow, which is the main determinant of galactose elimination in cirrhosis.

In proposing, as a measure of functional hepatic blood flow in cirrhosis, the hepatic clearance of sorbitol (which has an extraction ratio of 0.96 in healthy subjects), Zeeh et al. (1988) assumed that sorbitol penetrates freely through capillarised sinusoids. However, the inability of galactose to cross capillarised sinusoids reported by Riechen et al. (1988) suggests that other markers of hepatic blood flow, including sorbitol, will behave likewise. Functional blood flow may therefore be more realistically measured in this way because it would not include flow through intrahepatic shunts or through capillarised sinusoids.

4.3.3 Propranolol

In hepatic cirrhosis the systemic clearance of propranolol decreases and the systemic bioavailability of orally administered drug increases (Hom-

eida et al. 1987; Pessaire et al. 1978; Watson et al. 1987; Wood et al. 1978). This phenomenon was initially attributed to a decrease in hepatic intrinsic clearance, because the decrease in total hepatic blood flow measured by the indocyanine green-Fick method was relatively small. The possibility of intrahepatic shunting was also considered, but measurement of shunt flow with $15\mu\text{m}$ microspheres (which cannot pass through normal sinusoids) in cirrhotic isolated perfused rat liver showed that shunt flow was small ($\approx 10\%$ of total flow) and could not account for the reduction in hepatic clearance (Wood et al. 1979). However, because the hepatic extraction ratio decreased with decreasing hepatic blood flow, the authors concluded that functional shunts of low resistance must be present in addition to anatomical shunts (Wood et al. 1979). This was supported by multiple indicator dilution studies in the isolated perfused rat liver where the intrahepatic shunt fraction measured with $15\mu\text{m}$ microspheres did not correlate with propranolol hepatic clearance, whereas the extravascular albumin space did (Reichen & Le 1983). This suggests that, as in the case of galactose, the principal determinant of propranolol elimination in cirrhosis is the degree of sinusoidal capillarisation.

Branch (1982) and McLean et al. (1979) have proposed methods for estimating functional hepatic blood flow and shunt fraction in cirrhosis. These methods, which are based on the intact hepatocyte hypothesis (section 3.1), assume that the change in hepatic clearance of both high (e.g. propranolol) and low (e.g. phenazone) intrinsic clearance drugs is proportional to the change in flow to functional hepatocytes, thus providing a measure of intrahepatic shunt function. These methods are probably not useful because the intact hepatocyte hypothesis does not appear to be valid (e.g. Kawasaki et al. 1988).

4.3.4 Lidocaine (Lignocaine)

Studies of lidocaine disposition in hepatic diseases such as chronic persistent hepatitis, chronic active hepatitis and hepatic cirrhosis show that the elimination of this drug is impaired only in cirrhosis, where the reduction in lidocaine clearance

and the increase in the systemic availability of orally administered drug become more pronounced as the severity of the disease worsens (Colli et al. 1988; Villeneuve et al. 1987). As with propranolol, this was attributed to a decrease in hepatic intrinsic clearance because the lidocaine clearance correlated with the calculated hepatic intrinsic clearance but not with total hepatic blood flow (measured with the indocyanine green-Fick method) [Huet & Villeneuve 1983; Pomier-Layrargues et al. 1986]. However, portasystemic shunting is probably also partly responsible because, after oral administration, peak plasma lidocaine concentration was much greater in decompensated cirrhotic patients than in control subjects, whereas no difference was found in peak theophylline concentrations (Colli et al. 1988). Using the multiple indicator dilution technique in isolated perfused cirrhotic rat liver, Varin and Huet (1985) found no evidence of portasystemic shunting with $15\mu\text{m}$ microspheres. The lidocaine data were consistent with restricted access to the hepatocytes. This was attributed to capillarisation of sinusoids and/or the development of small channels with poorly permeable walls, further evidence that the main determinant of the hepatic elimination of flow-limited drugs in cirrhosis is sinusoidal capillarisation.

4.3.5 Miscellaneous Drugs

A substantial increase in the systemic availability of orally administered drug has been observed in cirrhosis with other drugs such as pethidine (meperidine), pentazocine and dextropropoxyphene (propoxyphene) [Giacomini et al. 1980; Neal et al. 1979]. Systemic clearance of pethidine and pentazocine was reasonably well maintained, which Neal et al. (1979) suggested might have been due to the fact that in cirrhosis, hepatic arterial blood flow is equal to or even greater than that in healthy individuals. This possibility does not seem to have been pursued.

The hepatic extraction ratio of morphine was reduced by 25% in a group of cirrhotic patients (Crotty et al. 1989) but this impairment was not as great as that seen with lidocaine (Huet & Villeneuve 1983) or propranolol (Pessayre et al. 1978).

As the degree of portasystemic shunting should have been similar in all 3 studies, Crotty et al. (1989) suggested that their findings with morphine, a drug metabolised primarily by glucuronidation, are consistent with the relative sparing of drug glucuronidation in cirrhosis. In a group of cirrhotic patients with more severe disease than the former group, morphine elimination was significantly reduced (Hasselstrom et al. 1990).

Although true cirrhosis is not associated with hepatosplenic schistosomiasis, hepatic fibrosis, portal hypertension and derangement of the hepatic microcirculation do occur (Dunn & Kamal 1981). Thus, studies in schistosomiasis of the hepatic elimination of the flow-limited drugs praziquantel and propranolol show a large increase in the systemic availability of orally administered drug, consistent with the presence of functional portasystemic shunting (Homeida et al. 1987; Watt et al. 1988).

Currently there are few data from which to evaluate the possible effect of the protein binding of drug in sinusoidal plasma in limiting the passage of drug through the defenestrated sinusoidal wall in cirrhosis. However, 1 study with testosterone, which has a hepatic extraction ratio far exceeding the unbound fraction, suggests that the access of protein-bound testosterone is not limited in cirrhosis (Guechot et al. 1989).

4.3.6 First-Pass Effect in Cirrhosis

Drugs with a high hepatic clearance will have a low systemic availability on oral administration, that is, they will exhibit a substantial first-pass effect. Portasystemic shunting of blood in cirrhosis can increase the bioavailability of orally administered drug substantially, while having a lesser effect on hepatic clearance because of maintained or even increased hepatic arterial flow. Moreover, the increase in bioavailability and decrease in hepatic clearance will have a multiplicative effect on the total area under the concentration-time curve (AUC) of orally administered drug (Blaschke & Rubin 1979). For example, a 50% decrease in pentazocine clearance and a 4-fold increase in its bioavailability in cirrhosis resulted in an 8-fold in-

crease in (Neal et al. 1979). It is required in effect to produce a

4.4 Bilirubin

Bile acids in healthy subjects. They are in conjugated form in serum. Their concentration (M) is Poupon et al. (1984) that intrinsically of serum in cirrhosis. It is concluded that the terminal half-life (al. 1984) of shunting of albumin. The acids correspondingly. Using a rat model, in a rat model (1988) also measured the terminal half-life of capillarisation of acid level of indocyanine excreted in urine. The elimination of intrahepatically. There is an effect of liver drugs which drug in seen in some others (Kraus et al. 1988).

4.5 Summary

The overall view is that the effect of

ic shunting should be considered. Crotty et al. (1979) found that morphine was extensively metabolized by glucuronidation, resulting in sparing of drug glucuronide formation in the group of cirrhotic patients. More than the former, the latter was significantly reduced.

4.4 Biliary Elimination

Bile acids are removed from portal blood in healthy subjects by flow-limited hepatic elimination. They are excreted in bile either unchanged and/or in conjugated form. In cirrhosis, plasma bile acid concentrations are elevated due to impaired elimination (Meischer et al. 1983; Ohkubo et al. 1984; Poupon et al. 1981). Poupon et al. (1981) found that intrinsic clearance was the main determinant of serum bile acid concentrations in patients with cirrhosis. In contrast, Meischer et al. (1983) concluded that intrahepatic shunting was the main determinant, and this was supported by Ohkubo et al. (1984) who obtained a measure of intrahepatic shunting using radioactive macroaggregates of albumin. The latter authors found that serum bile acids correlated well with the degree of shunting.

Using the multiple indicator dilution technique in a rat model of hepatic cirrhosis, Reichen et al. (1988) also found that the degree of shunting, as measured by $15\mu\text{m}$ microspheres, was the main determinant of bile acid concentrations. Sinusoidal capillarisation was not a determinant of serum bile acid levels, in contrast to findings in humans with indocyanine green. With the latter, which is also excreted in bile, the main determinant of hepatic elimination is sinusoidal capillarisation rather than intrahepatic shunting (Huet et al. 1982).

There is little information available on the effect of liver disease on the hepatic elimination of drugs which are eliminated primarily as unchanged drug in bile. Impairment of elimination has been seen in some cases (Saudek et al. 1989), but not in others (Krakamp et al. 1989).

4.5 Summary of Experimental Findings

The observations with drugs and markers reviewed in this section indicate a wide diversity in the effect of liver disease on hepatic elimination.

This is no doubt due in part to the fact that 'liver disease' is an umbrella term for a wide variety of syndromes resulting from infection, noxious xenobiotics, circulatory disturbances, autoimmune activity or postviral events (section 2). It is also clear that the stage of disease is also an important variable in determining the effect on hepatic elimination. In some cases (e.g. theophylline), a progressive decrease in drug elimination was seen which paralleled the decline in functional status defined by clinical indices such as the Child-Turcotte score. However, in most studies, impaired elimination was seen only in advanced (i.e. decompensated) cirrhosis, suggesting that studies of drug disposition that use only patients with compensated cirrhosis are inadequate for extrapolation to the whole range of pathological change. In particular, there is a need for more information about patients with severe disease. Ideally, there should be an attempt to include several markers (see below) to reduce the chance of a 'false negative' result and also to facilitate the comparison of results among different studies.

The experimental findings also highlight the shortcomings of the proposed use of drugs or other compounds as markers of liver function. Galactose (Tygstrup 1963), indocyanine green (Caesar et al. 1961; Wiegard et al. 1960), bile acids (La Russo et al. 1975), phenazone (Vesell & Page 1968), aminophenazone (Hepner & Vesell 1974), caffeine (Desmond et al. 1980), phenacetin (Breen et al. 1984), lidocaine (Oellerich et al. 1990), erythromycin (Watkins et al. 1990) and diazepam (Hepner et al. 1977) have each been proposed as predictors of drug elimination in individual patients. However, although the results of these tests may correlate, the correlations are not strong enough to be of predictive value (e.g. Barbare et al. 1985; Colli et al. 1988; Holstege et al. 1989; Kawasaki et al. 1988; Kraan et al. 1988; Marchesini et al. 1990; McGilchrist et al. 1986; Villeneuve et al. 1987; Wensing et al. 1990a). Whether a satisfactory single substrate test or group of substrate tests will emerge is yet to be seen.

The experimental observations reviewed in this section indicate that oxidative drug metabolism is

impaired in cirrhosis but the impairment is highly variable between drugs. Metabolism by glucuronidation tends to be well maintained for the majority of drugs studied to date. In nearly every case where the extent of sinusoidal capillarisation has been included in the analysis, the degree of impairment of drug elimination (i.e. of aminophenazone, caffeine, phenazone, indocyanine green, propranolol and lidocaine) has correlated best with this variable. Exceptions are galactose, where portal flow was equally as important as sinusoidal capillarisation, and bile acids where shunting was the main determinant. Although most of these findings have been obtained with models of cirrhosis in the rat which differ significantly from human cirrhosis, similar observations of a high correlation between the extent of sinusoidal capillarisation and drug elimination have been made in humans (Huet et al. 1982; Sotaniemi et al. 1986). The variation in the effect of cirrhosis on drug oxidation and glucuronidation is consistent with the multiplicity of cytochrome P450 enzymes (Brosen 1990; Guengerich 1989; Gonzales 1990), with each enzyme being affected to a different degree. However, the correlations between the elimination of oxidised drugs and the extent of sinusoidal capillarisation and between the relative sparing of glucuronidation and the lack of dependence of biliary excretion on sinusoidal capillarisation are also consistent with the hypothesis that restricted access of oxygen to the hepatocyte from capillarised sinusoids may be an important underlying mechanism. This hypothesis is based on the observation that oxidative drug metabolism is more sensitive to reduced hepatic oxygen supply than conjugation or biliary excretion (Angus et al. 1989a,b; Aw & Jones 1982; Jones 1981; Jones et al. 1984) [fig. 5].

Clarification of the importance of oxygen supply in cirrhosis awaits further experimentation, but the hypothesis broadens the framework for interpreting experimental studies and has important therapeutic implications (discussed in section 6).

4.6 Renal Elimination

All of the drugs discussed so far in this section are normally eliminated from the body by predominantly hepatic processes. However, in view of the

impairment of renal function that can accompany hepatic cirrhosis, such as reduced sodium and water excretion, with concomitant impaired creatinine clearance (section 3.8), it is important also to examine renal drug excretion in cirrhosis.

4.6.1 Diuretics

Diuretics such as furosemide are commonly used in patients with cirrhosis to relieve ascites. Renal clearance accounts for about half of the total clearance in healthy subjects. Some earlier studies suggested that furosemide elimination was normal in cirrhosis (e.g. Fuller et al. 1981; Keller et al. 1981; Verbeeck et al. 1982), but it is clear that, at least in cirrhotic patients with ascites resistant to diuretics, the renal clearance of furosemide is impaired (Gonzales et al. 1982; Villeneuve et al. 1986). In these patients the renal clearance of this agent is reduced in parallel with creatinine clearance, but because nonrenal clearance is unaltered, the decrease in total clearance is not sufficient to warrant a reduction in dosage (Villeneuve et al. 1986).

A similar decrease in renal clearance in parallel with reduced creatinine clearance was also seen in cirrhosis with the diuretic bumetanide (Marcantonio et al. 1983). Nonrenal clearance of this drug was also reduced, leading to a substantial reduction in total clearance. The renal and nonrenal clearances of torasamide were also reduced in cirrhosis, although creatinine clearance was not measured (Brunner et al. 1988). In contrast, the renal clearance of amiloride was unchanged in cirrhosis, but there was evidence of a reduction in nonrenal clearance (Spahn et al. 1987). The significance of the unchanged renal clearance is uncertain because creatinine clearance was not measured.

Although the renal clearance of diuretics is impaired in cirrhosis, the alteration in pharmacodynamic response of the renal tubule to these drugs (see section 5) is probably of more clinical significance.

4.6.2 Histamine H₂-Receptor Antagonists

Histamine H₂-receptor antagonists (e.g. cimetidine, ranitidine, famotidine) are widely used in the treatment of peptic ulcer disease, oesophagitis and

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5. Mechanisms of Drug Action

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gastritis, all of which are common in the cirrhotic patient. More than 50% of the total clearance of H₂-receptor antagonists is via the kidney, although nonrenal elimination is also significant.

In compensated cirrhosis with normal renal function there is no impairment of the renal, nonrenal or total clearance of these agents (Schentag et al. 1981; Smith et al. 1984; Sonne et al. 1981). In advanced cirrhosis with normal creatinine clearance, there is a decrease in nonrenal clearance and an increase in the systemic availability of orally administered drug (Grahnen et al. 1984; Gugler et al. 1982; Morgan & Stambuk 1986; Young et al. 1982); when advanced cirrhosis is accompanied by impaired renal function, the renal clearance of cimetidine and ranitidine is reduced in parallel with the reduction in creatinine clearance (Cello & Oie 1983; Morichau-Beauchant et al. 1986; Smith et al. 1984; Villeneuve et al. 1983). Moreover, the ratio of the renal clearance of cimetidine to creatinine clearance was reduced from 3.7 in healthy subjects to 1.22 in cirrhotic patients. This indicates that the decrease in renal cimetidine clearance is not due solely to the decline in glomerular filtration rate, but also to impairment of the active renal tubular secretion (as given by the cimetidine/creatinine clearance ratio) [Villeneuve et al. 1983].

In conclusion, it appears that in patients with severe liver disease there will be a reduction in renal drug clearance only if renal function is impaired. The reduction may not be reflected well by the decline in creatinine clearance, however, because actual creatinine clearance may be overestimated from serum creatinine measurements in patients with cirrhosis, particularly those with ascites (Echizen & Ishizaki 1988; Hull et al. 1981; Papadakis & Arief 1987); such patients may have a decreased creatinine production due to diminished muscle mass. A reduced renal drug clearance in cirrhosis despite an apparently normal serum creatinine has been observed (Hoyumpa et al. 1989).

5. Mechanisms of Altered Pharmacodynamic Response

In addition to changes in the hepatic and renal elimination of drugs in hepatic disease, there may also be substantial changes in pharmacodynamic

response. For example, there appears to be greater cerebral sensitivity to strong analgesics, antianxiety and hypnotic drugs but a decreased renal response to diuretics (Bass & Williams 1988; Davey 1988; Secor & Schenker 1987; Wilkinson 1986). Therefore, in adjusting drug dosage in hepatic disease, both pharmacokinetic and pharmacodynamic changes must be taken into account.

There are several mechanisms by which changes in pharmacodynamic response can occur. Broadly, these can be classified into mechanisms involving changes in access of drug to the site of drug action, which is a pharmacokinetic mechanism, and mechanisms involving a change in pharmacodynamic response at the receptor level.

5.1 Altered Drug Access to Site of Action

5.1.1 Altered Plasma Protein Binding

As discussed in section 3.7, the plasma protein binding of drugs can change in hepatic cirrhosis. For drugs with capacity-limited binding-sensitive (restrictive) hepatic elimination kinetics, a change in the bound fraction of drug in plasma at steady-state will have the greatest impact on the total plasma concentration, whereas the unbound concentration, which is responsible for the pharmacological effect, will remain unchanged. By contrast, for drugs with flow-limited, nonrestrictive hepatic elimination kinetics, a change in the protein bound fraction will result in a significant change in plasma unbound drug concentration, with little change in total concentration (Rowland & Tozer 1989; Smallwood et al. 1988). Therefore, the amount of unbound drug available for tissue uptake is altered, with potential for an altered pharmacological response. For example, the plasma protein binding of testosterone increases in cirrhosis due to an increase in the concentration of sex hormone binding globulin (SHBG), apparently resulting in a reduction in testosterone uptake by the brain in this disease (Sakiyama et al. 1982).

5.1.2 Altered Blood-Brain Barrier Permeability

There is some evidence to suggest that the permeability of the blood-brain barrier is altered in hepatic cirrhosis and that this may be at least partly

responsible for the altered response of the central nervous system to certain drugs. For example, there appears to be enhanced cerebral uptake of cimetidine as the cerebrospinal fluid/plasma cimetidine concentration ratio in cirrhotic patients is about twice that in healthy subjects (Kimmelblatt et al. 1980; Schentag et al. 1981). In patients with hepatic encephalopathy, positron emission tomographic (PET) studies showed a substantially greater cerebral benzodiazepine uptake, indicating either greater density or affinity of benzodiazepine receptors in the brain, or enhanced permeability of the blood-brain barrier (Samson et al. 1987). However, a subsequent study found a decreased clearance and increased unbound fraction of this drug (flumazenil) in cirrhosis, which could account for the greater cerebral uptake (Pomier-Layrargues et al. 1989).

Animal models have also generally shown evidence of an increase in the permeability of the blood-brain barrier in hepatic failure (Horowitz et al. 1983; Livingstone et al. 1977; Zaki et al. 1984). However, there was no evidence of an altered blood-brain barrier permeability to theophylline in the rat (Ramzan et al. 1987), whereas the permeability to propranolol appeared to be decreased (Lin et al. 1988).

5.2 Altered Receptor Response

Patients with hepatic cirrhosis exhibit an increased cerebral sensitivity to benzodiazepines (Branch et al. 1976; McConnell et al. 1982), in addition to the higher blood benzodiazepine concentrations that can result from impaired hepatic elimination. Studies using objective measures of central nervous system performance show greater impairment in cirrhotic patients than in healthy subjects, despite similar plasma drug concentrations (Bakti et al. 1987; MacGilchrist et al. 1986). On the basis of animal experiments it was suggested that this was due to an increase in the number of γ -aminobutyric acid (GABA) and benzodiazepine binding sites in hepatic encephalopathy (Schafer et al. 1983; Zeneroli 1985). However, more recent studies in animals and in cirrhotic patients

who died in hepatic encephalopathy have not confirmed these receptor changes (Butterworth et al. 1988; Maddison et al. 1987).

Alteration of β -adrenoceptor responsiveness appears to be associated with cirrhosis. Cirrhotic patients are less sensitive to the chronotropic effects of isoprenaline (isoproterenol), and the decrease in sensitivity correlates with the severity of disease (Caujolle et al. 1988; Ramond et al. 1986). Cirrhotic patients with advanced disease showed a reduction in β -adrenoceptor density in mononuclear cells (Gerbes et al. 1986). Therefore, β -adrenoreceptors may be down-regulated in advanced cirrhosis.

On the other hand, studies with a variety of other cardiovascular drugs (e.g. enalapril, encainide, nifedipine, nimodipine, nisoldipine) show no alteration in receptor response. At a given plasma concentration of the active moiety, the measured pharmacodynamic effect in cirrhotic patients was the same as that measured in healthy subjects (Bergstrand et al. 1986; Gengo et al. 1987; Kleinbloesem et al. 1986; Ohnishi et al. 1989; van Harten et al. 1988). All of these drugs have an impaired hepatic clearance in cirrhosis, which can lead to an increased clinical response.

As well as the impairment of tubular secretion that occurs with diuretics (section 3.8), studies with furosemide, triamterene and bumetanide show that the kidney is also less sensitive to these agents in cirrhosis (Dao & Villeneuve 1988; Keller et al. 1981; Marcantonio et al. 1983; Villeneuve et al. 1984). Villeneuve et al. (1986) found that the rate of urinary excretion of furosemide to achieve 50% of the maximum response was the same in cirrhotic patients and in healthy subjects, although the maximum response was reduced in cirrhosis. Moreover, the reduction in maximum response was greater than the reduction in creatinine clearance. They concluded that the sensitivity of the renal tubules to furosemide was unchanged in cirrhosis, and that the reduced response was due to a reduction in both the number of nephrons and the maximum response per nephron.

6. Use of Drugs in Patients with Liver Disease

The major problem in the pharmacokinetics of drugs in patients with liver disease is the mechanism of drug disposition. In addition to the effects of impaired hepatic function, shunting of blood through the portal vein, and changes in the distribution of drugs between the central and peripheral compartments, there are changes in the pharmacokinetic properties of drugs. These changes are mainly due to the reduced ability of the liver to metabolize drugs, and to the increased permeability of the blood-brain barrier.

6.1 Therapeutic Agents in Hepatic Failure

The classical therapeutic agents used in hepatic failure include corticosteroids, diuretics, and albumin. These agents are effective in the treatment of hepatic encephalopathy, ascites, and edema. They are also used to reduce the risk of variceal hemorrhage and to prevent hepatic encephalopathy.

It is not clear whether these agents are effective in the treatment of hepatic failure. Some agents, such as diuretics, are effective in the treatment of ascites and edema, but they may cause adverse effects, such as hypotension and electrolyte imbalances. Other agents, such as corticosteroids, are effective in the treatment of hepatic encephalopathy, but they may cause side effects, such as hypertension and diabetes.

In summary, the therapeutic agents used in hepatic failure are effective in the treatment of ascites, edema, and hepatic encephalopathy, but they may cause side effects. It is important to monitor the patient's response to these agents and to adjust the dose accordingly.

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6. Use of Therapeutic Drugs in Patients with Liver Disease

The major aim of this review is to determine the mechanisms of alteration in drug handling and effect. In addition to the well accepted mechanisms of impaired hepatic elimination of portal-systemic shunting and reduced intrinsic clearance, sinusoidal capillarisation is a major factor. A reduction in hepatic oxygen supply associated with sinusoidal capillarisation represents a potential unifying principle of clearance limitation which has not been identified previously. This principle embodies a relative maintenance of conjugation mechanisms and active transport systems compared with clearance processes heavily dependent on oxygen supply (i.e. oxidation). If this is the case, then there are therapeutic implications resulting from the substantial potential to increase oxygen supply.

6.1 Therapeutic Strategies to Improve Liver Function

The classes of agents likely to decrease arteriolar tone and increase oxygen supply include drugs which modify autonomic neurone function as well as direct-acting arteriole dilators (Ballet 1990; Reichen 1990). Specific arteriolar dilators such as hydralazine and verapamil are potentially the most efficacious.

It is not sufficiently recognised that drug use can adversely affect liver function. Maintenance of hepatic artery perfusion is clearly important: drugs which cause postural hypotension or depletion of vascular volume may produce deleterious effects on liver function. Anaemia, hypoxaemia and carboxyhaemoglobinæmia should be minimised if oxygen delivery is rate-limiting. Oxygen supplementation may be needed in severe liver dysfunction.

In summary, a comprehensive approach to therapeutic drug use in liver disease requires awareness of a 3-way interaction between drug dosage, liver function and systemic cardiorespiratory status.

6.2 Modification of Drug Dosage

Well recognised principles of dosage adjustment can be endorsed (Bass & Williams 1988; Howden et al. 1989; Secor & Schenker 1987; Wilkinson 1986) but the mechanisms underlying these are updated with recognition of the importance of capillarisation processes giving functional shunts as opposed to cirrhotic shunting.

Drugs with high hepatic extraction should be used orally in greatly reduced doses (Blaschke & Rubin 1987) – i.e. 10 to 50% of the normal dose. This restriction applies to liver disease without cirrhosis. High clearance drugs with high protein binding are likely to be maximally influenced by the process of capillarisation. The dosage of drugs administered parenterally, or low clearance drugs used orally, should be reduced by some 50% if the clinical stigmata of liver disease are apparent.

6.3 General Principles of Drug Use in Patients with Liver Disease

Drug use in patients with liver disease must take into account 3 general principles: (a) pharmacokinetics are modified; (b) drugs may modify the functional status of the liver; and (c) pharmacodynamics may be modified.

Altered drug handling is well recognised, and the principle of reduced oral and systemic dosage regimens is well known. However, there is still a scarcity of information available on specific dosage requirements in classes of liver disease without cirrhosis. The importance of drug administration for the functional status of the liver is best illustrated by the potential critical dependence of the functional state on oxygen supply via arterial inflow, which is not widely appreciated. Care in the choice of drugs aimed at preserving splanchnic arterial perfusion therefore appears to be important. Notwithstanding these 2 principles, the influence of the disease on pharmacodynamic drug response can lead to some of the more profound adverse drug effects, and awareness of this possibility should be increased.

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