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REVIEW ARTICLE

Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction

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Abstract The liver plays a central role in the pharmacokinetics of the majority of drugs. Liver dysfunction may not only reduce the blood/plasma clearance of drugs eliminated by hepatic metabolism or biliary excretion, it can also affect plasma protein binding, which in turn could influence the processes of distribution and elimination. Portal-systemic shunting, which is common in advanced liver cirrhosis, may substantially decrease the presystemic elimination (i.e., first-pass effect) of high extraction drugs following their oral administration, thus leading to a significant increase in the extent of absorption. Chronic liver diseases are associated with variable and non-uniform reductions in drug-metabolizing activities. For example, the activity of the various CYP450 enzymes seems to be differentially affected in patients with cirrhosis. Glucuronidation is often considered to be affected to a lesser extent than CYP450-mediated reactions in mild to moderate cirrhosis but can also be substantially impaired in patients with advanced cirrhosis. Patients with advanced cirrhosis often have impaired renal function and dose adjustment may, therefore, also be necessary for drugs eliminated by renal exctretion. In addition, patients with liver cirrhosis are more sensitive to the central adverse effects of opioid analgesics and the renal adverse effects of NSAIDs. In contrast, a decreased therapeutic effect has been noted in cirrhotic patients with β-adrenoceptor antagonists and certain diuretics. Unfortunately, there is no simple endogenous marker to predict hepatic function with respect to the elimination capacity of specific drugs. Several quantitative liver tests that measure the elimination of marker substrates such as galactose, sorbitol, antipyrine, caffeine, erythromycin, and midazolam, have been developed and evaluated, but no single test has gained widespread clinical use to adjust dosage regimens for drugs in patients with hepatic dysfunction. The semi-quantitative Child-Pugh score is frequently used to assess the severity of liver function impairment, but only offers the clinician rough guidance for dosage adjustment because it lacks the sensitivity to quantitate the specific ability of the liver to metabolize individual drugs. The recommendations of the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) to study the effect of liver disease on the pharmacokinetics of drugs under development is clearly aimed at generating, if possible, specific dosage recommendations for patients with hepatic dysfunction. However, the limitations of the Child-Pugh score are acknowledged, and further research is needed to develop more sensitive liver function tests to guide drug dosage adjustment in patients with hepatic dysfunction.

Keywords Drug dosage adjustment · Hepatic dysfunction · Liver disease · Drug clearance · Pharmacokinetics

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Introduction

The liver plays a central role in the absorption, distribution, and elimination kinetics of most drugs and many active or inactive drug metabolites. It is not only the most important biotransformation site, but parameters such as liver blood flow, binding to plasma proteins, and biliary excretion,

which can all potentially influence drug pharmacokinetics, depend on the normal functioning of the liver. In addition, patients with hepatic dysfunction may also be more sensitive to the effects, both desired and adverse, of several drugs. Dosage adjustment in patients with liver dysfunction is therefore essential for many drugs to avoid excessive accumulation of the drug, and possibly of active drug metabolite(s), which may lead to serious adverse reactions.

Hepatic pathophysiology

Any compound entering the body must eventually be eliminated by metabolism and/or excretion via the urine or bile/faeces. The liver is uniquely situated as an eliminating organ (hepatocellular uptake and metabolism, biliary excretion) between the upper gastrointestinal tract and the general circulation. Together with the small intestinal epithelium, the liver is responsible for the presystemic elimination (first-pass effect) of many potentially harmful exogenous substances including therapeutic agents, which are absorbed into the hepatic portal circulation from the small intestine after their oral ingestion [1]. Drug-metabolizing enzymes are found in most tissues of the body but the highest levels are located in the intestinal epithelial cells and in the liver [2, 3]. Compared to the intestinal epithelium, however, the liver expresses a much higher diversity of these drug-metabolizing enzymes. Drugs that are poorly metabolized remain in the body for longer periods of time and their pharmacokinetic profiles show much longer elimination half-lives than drugs that are rapidly metabolized.

The liver has a dual blood supply delivering approximately 1,500 ml/min in healthy adults partly via the hepatic artery (approximately 25%) and partly via the portal vein (approximately 75%). Exchange between substances in the circulation and the hepatocytes occurs in modified capillary structures termed sinusoids, which are vascular spaces between plates of hepatocytes [4, 5]. As blood passes through the liver, low-molecular-weight substances can enter the hepatocytes by passive diffusion or facilitated/active transport. Hepatic clearance of drugs is facilitated by the polarized nature of hepatocytes, which have distinct basolateral and apical (canalicular) domains that differ in protein and lipid composition. The uptake of drugs into hepatocytes may be mediated by the basolateral transport proteins belonging to the superfamily of solute carriers (SLC) [6, 7]. The biliary excretion of drugs and metabolites is mediated by unidirectional ATP-dependent export pumps belonging to the ATP-binding cassette (ABC) superfamily of transporters that reside on the canalicular membrane of the hepatocyte [6, 7]. Polar drug metabolites generated by hepatic drug-metabolizing enzymes may require a transport protein to facilitate basolateral efflux from the hepatocyte into sinusoidal blood for subsequent excretion in the urine (Fig. 1). The role of active transport of drugs and their metabolites in and out of hepatocytes was long underestimated but has recently received much attention.

Hepatic disease, and in particular cirrhosis, results in numerous pathophysiologic changes in the liver that may influence drug pharmacokinetics [8]. Histologically, cirrhosis is a diffuse process characterized by fibrosis and a conversion of normal liver architecture into structurally

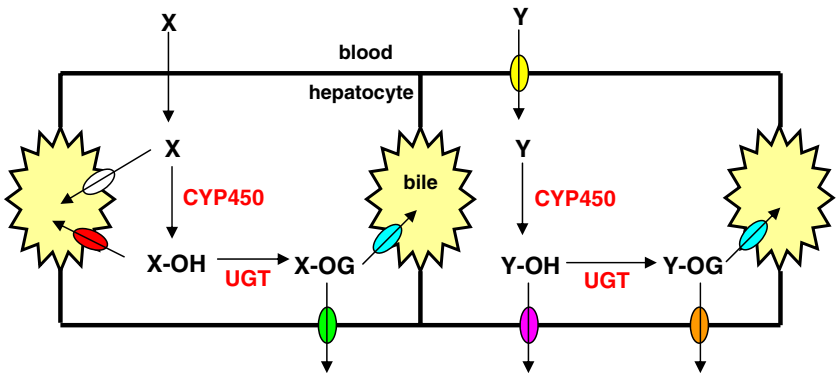

Fig. 1 Schematic diagram showing two adjacent hepatocytes and bile canaliculi. Hepatic uptake of drugs is mediated by SLC-type transporters (e.g., OATPs, OATs, OCTs, NTCP) in the basolateral (sinusoidal) membrane of hepatocytes. ABC transporters such as MRP2, MDR1, BCRP, BSEP, and MDR2 in the bile canalicular membrane of hepatocytes mediate the efflux (excretion) of drugs and their metabolites against a steep concentration gradient from hepatocyte to bile. Some ABC transporters are also present in the basolateral membrane of hepatocytes and play a role in the efflux of drugs and their metabolites back into blood. Drug uptake from the blood into the hepatocyte followed by metabolism and excretion into bile is a major determinant of the systemic clearance of many drugs. *Substance X* reaches the hepatocytes from blood by passive diffusion; *substance Y* is actively transported from blood into the hepatocytes. Both substances undergo sequential oxidation and glucuronide conjugation. CYP450, Cytochrome P450; UGT, UDP-glucuronosyltransferase; OAT, organic anion transporter; OATP, organic-anion-transporting polypeptide; MDR, MRP, multi-drug transport protein; NTCP, Na^+-taurocholate cotransporting polypeptide; BSEP, bile salt export pump; BCRP, breast-cancer-resistance protein; OCT, organic cation transporter

abnormal nodules. These modifications are associated with or are responsible for a reduction in liver blood flow, the presence of intra- and extrahepatic portal-systemic shunting, a capillarization of the sinusoids and a reduction in the number and in the activity of the hepatocytes [8]. From a theoretical and pathophysiological point of view, the evaluation of the respective roles played by each of these phenomena is of interest and has led to several theories, which have been summarized by Morgan and McLean [4]. The importance of the above-mentioned alterations in liver function may vary following the etiology of the cirrhosis, and there is marked interindividual variation in the rate of progression of the disease. Moreover, such progression will inevitably lead to the development of clinical manifestations, such as esophageal varices, edema, ascites, severe impaired parenchymal function, and hepatic encephalopathy, which may contribute to alterations in the pharmacokinetic and pharmacodynamic behavior of many drugs. Added to these features will be the effect of an impaired production of albumin, which results in reduced plasma binding of several drugs and thus an increased availability of the circulating drug pool for tissue uptake and pharmacodynamic effects. Impaired secretion of bile acids, bilirubin, and other organic anions is also observed in cirrhosis, mainly when its etiology is linked to lesions of the extrahepatic biliary tract [9]. Such impaired secretion is, however, also observed in intrahepatic processes that cause lesions without demonstrable mechanical obstruction of the biliary tract. In this case, changes in the membrane of biliary canaliculi and in their cytoskeleton, increased permeability of the paracellular pathway, changes in the activity of canalicular membrane transporters, or disturbed intracellular calcium homeostasis may be observed and could be responsible for an impaired biliary excretion of drugs and their metabolites. Cirrhosis may also exert a major influence on other organs such as the intestine, the lungs, and the kidneys. The function of these organs will be directly influenced by the modifications induced by cirrhosis on the vascular hemodynamics, such as the hyperkinetic state found in alcoholic cirrhosis or the potential occurrence of a hepatorenal syndrome, which is associated with a severe impairment of renal function.

Liver diseases without cirrhosis usually result in mild alterations in drug pharmacokinetics. Morgan and McLean, in their review of pharmacokinetic considerations in liver diseases, conclude that disease states such as chronic active hepatitis, primary or secondary liver cancer, and hepatosplenic schistosomiasis are not associated with significantly impaired hepatic elimination unless cirrhosis is present [4]. In this review most attention will be focused on the effect of cirrhosis and cholestasis on drug pharmacokinetics because these conditions may lead to situations where dosage adjustment is absolutely necessary to prevent excessive drug/metabolite accumulation and toxic effects.

Hepatic drug clearance

Although metabolic transformation occurring in the intestinal epithelial cells may significantly contribute to the presystemic elimination of drug substances administered orally, the total body clearance of a drug substance can generally be considered to be mostly dependent on hepatic and renal elimination mechanisms. For most drugs, however, hepatic metabolism is the major elimination pathway. To fully appreciate the impact of hepatic dysfunction on the pharmacokinetic behavior of a particular drug, a thorough understanding of the underlying determinants of *hepatic clearance* is absolutely necessary. Hepatic drug clearance (CL_H), defined as the volume of blood from which drug is removed completely by the liver per unit time, is a function of hepatic blood flow (Q_H) and the hepatic extraction ratio (E_H) of the drug [9, 10]:

$$CL_H = Q_H \times E_H \quad (1)$$

Since E_H depends on liver blood flow, the intrinsic clearance of unbound drug (CL_{int}), and the fraction of unbound drug in blood (fu), the following fundamental equation for CL_H has been derived:

$$CL_H = Q_H \times \frac{fu \times CL_{int}}{Q_H + fu \times CL_{int}} \quad (2)$$

This equation is based on the "well-stirred" or "venous equilibration" model, a kinetic model used most frequently to describe the relationship between hepatic drug clearance and the three primary determinants of hepatic drug elimination, i.e., blood flow, drug binding in blood, and the *intrinsic clearance* (activity of enzymes and transporters involved in the hepatic elimination of drugs by metabolism and biliary excretion) [11]. This model assumes that the liver is a single, well-stirred compartment and that drug in arterial blood entering the liver instantaneously equilibrates with that in the venous blood. The model provides insight into the influence of alterations of liver blood flow and intrinsic clearance on hepatic drug clearance and drug dosing. Drug substances can be categorized according to the efficiency of the liver in removing the substance from the circulation as having a high ($E_H>0.7$), low ($E_H<0.3$) or intermediate ($0.3<E_H<0.7$) hepatic extraction ratio. The hepatic clearance of highly extracted drugs approaches and becomes limited by liver blood flow:

$$E_H > 0.7 \text{ i.e. } Q_H << fu \cdot CL_{int} \rightarrow CL_H \cong Q_H \quad (3)$$

The hepatic clearance of these drugs is said to be blood-flow limited and is relatively insensitive to changes in binding of drug to blood components or enzyme/transporter activity, i.e., CL_{int}. Disease states associated with alterations in liver blood flow and porto-systemic shunting, such as cirrhosis, will have a significant impact on the hepatic

clearance of these drugs, especially when administered orally. Alternatively, the hepatic clearance of poorly extracted drugs is mainly influenced by changes in blood/plasma binding and the intrinsic hepatic clearance:

$$E_H < 0.3 \text{ i.e. } Q_H >> fu \cdot CL_{int} \rightarrow CL_H \cong fu \cdot CL_{int} \quad (4)$$

and is considered to be enzyme/transporter-capacity limited. Finally, the hepatic extraction efficiency of some drugs is intermediate, in which case the hepatic drug clearance is affected by changes in either one of its three primary determinants, i.e., Q_H, CL_{int} and fu.

Assuming that a drug is completely and exclusively eliminated by hepatic mechanisms and that all of the orally administered dose is absorbed into the intestinal epithelial cells from where it will pass into the portal circulation, it can be shown that the *oral clearance* is described by the following equation:

$$CL_{or} = \frac{D_{or}}{AUC_{0-\infty}} = fu \times CL_{int} \quad (5)$$

This means that irrespective of its hepatic extraction efficiency, the oral clearance of a drug is determined by its degree of binding to blood/plasma components and the intrinsic clearance of the elimination/transport process. For drugs administered intravenously, assuming that they are completely and exclusively eliminated by the liver, the intravenous or *systemic clearance* is mainly determined by liver blood flow for drugs with a high hepatic extraction ratio, and by the reversible binding to blood/plasma components and the intrinsic capacity of the liver to eliminate the drug in case of substances with a low extraction ratio. For drugs with an intermediate hepatic extraction ratio, the systemic clearance will be affected by fluctuations in all three primary determinants of hepatic drug clearance (Table 1).

Finally, for drugs that have high blood/plasma binding (≥90%), i.e., a low unbound fraction in blood (fu≤0.1), a significant decrease in their reversible binding to plasma proteins is often found in chronic hepatic disease. To correctly interpret the effect of liver disease on the pharmacokinetics and clinical efficacy and safety of these drugs, the *unbound clearance* should be determined.

Table 1 Determinants of systemic clearance (CL_{syst}) and oral clearance (CL_{or}) for high- and low-extraction-ratio drugs that are exclusively eliminated by hepatic mechanisms (metabolism, biliary excretion) and that, following oral administration, are completely absorbed from the gastrointestinal tract into the intestinal epithelial cells

E_H	CL_{syst}	CL_{or}
$E_H<0.3$	~$fu \times CL_{int}$	$fu \times CL_{int}$
$0.3<E_H<0.7$	$CL_H = Q_H \times \frac{fu \times CL_{int}}{Q_H + fu \times CL_{int}}$	$fu \times CL_{int}$
$E_H>0.7$	~Q_H	$fu \times CL_{int}$

Effect of liver dysfunction on pharmacokinetic processes

Absorption

Gastrointestinal dysfunction has been described in patients with liver disease and may contribute to the complications of cirrhosis [12]. Although studies with orally administered test substances, such as sugars, show an increased intestinal permeability, the consequences for intestinal absorption of drug molecules are not clear [13]. The effect of chronic liver disease on the bioavailability of orally administered drugs is, however, mainly the result of reduced presystemic hepatic metabolism.

As a consequence of the unique position of the liver in the circulatory system, all drugs absorbed from the gastrointestinal tract (with exception of the mouth and the lower part of the rectum) are exposed to the metabolizing enzymes and bile excretory transport systems of the liver before reaching the systemic circulation. Drugs with an intermediate to high hepatic extraction ratio will undergo an important presystemic elimination or 'first-pass effect' [1, 14, 15]. The fraction of an absorbed oral dose that escapes first-pass hepatic clearance, F_H, can be described by the following equation [16]:

$$F_H = 1 - f_H \times E_H = \frac{Q_H + fu \times CL_{int}(1 - f_H)}{Q_H + fu \times CL_{int}} \quad (6)$$

where f_H is the fraction of the mesenteric blood flow passing through the functioning liver. Cirrhosis may lead to porto-systemic shunts (reduction in f_H) and decreased activity of a number of important drug-metabolizing enzymes, i.e., a reduction in CL_{int} (see below), which will result in a substantial increase in the bioavailability of orally administered flow-limited drugs [14]. The oral bioavailability of a number of drugs with intermediate to high hepatic extraction ratios has indeed been shown to be significantly increased in patients with liver cirrhosis (Table 2). For example, the bioavailability of the sedative/hypnotic agent clormethiazole is increased more than 10-fold in patients with cirrhosis [17]. The increase in bioavailability in combination with the reduced systemic clearance of flow-limited drugs in patients with cirrhosis may lead to substantial increases in AUC, necessitating an important reduction in the administered dose. For example, carvedilol therapy should be started in cirrhotic patients at about one-fifth of the normal dosage [18].

Transjugular intrahepatic porto-systemic shunt (TIPS) is a side-to-side, nonselective porto-systemic shunt that is frequently used in cirrhotic patients to manage the

Table 2 Oral bioavailability is substantially increased in cirrhosis for drugs with a moderate to high hepatic extraction ratio

Drug	Normal	Cirrhosis	Fold increase	Reference
Carvedilol	0.19	0.83	4.4	[18]
Chlormethiazole	0.10	1.16	11.6	[17]
Labetalol	0.33	0.63	1.9	[19]
Meperidine	0.48	0.87	1.8	[20]
Metoprolol	0.50	0.84	1.7	[21]
Midazolam	0.38	0.76	2.0	[22]
Morphine	0.47	1.01	2.1	[23]
Nifedipine	0.51	0.91	1.8	[24]
Nisoldipine	0.04	0.15	3.8	[25]
Pentazocine	0.18	0.68	3.8	[20]
Propranolol	0.36	0.60	1.7	[26]
Verapamil	0.10	0.16	1.6	[27]

complications of portal hypertension such as variceal bleeding, ascites, and hepatic hydrothorax. Chalasani et al. showed that oral bioavailability of midazolam was significantly increased in cirrhotic patients with TIPS (0.76± 0.20) compared with both cirrhotic controls (0.27±0.14) and healthy volunteers (0.30±0.10) [28]. Following oral administration, midazolam is subject to presystemic CYP3A metabolism by both intestinal and hepatic tissues. However, first-pass intestinal metabolism is the major determinant of the oral bioavailability of midazolam [29]. The marked loss in first-pass metabolism of midazolam in the cirrhotic patients with TIPS was the result of diminished intestinal CYP3A activity. Consequently, cirrhotic patients with TIPS and other porto-systemic shunts may be particularly vulnerable to exaggerated effects of CYP3A substrates if the dose is not substantially reduced.

Plasma protein binding and distribution

Since only the unbound drug is capable of entering and leaving the tissue compartments, the distribution of a drug within the body depends on its reversible binding to blood cells, plasma proteins, and tissue macromolecules [30]. Many drugs that are highly bound to albumin or α_1-acid glycoprotein have a significantly higher fu in patients with chronic liver disease [30, 31]. Mechanisms for decreased binding of certain drugs to plasma proteins include (1) reduced albumin and α_1-acid glycoprotein synthesis leading to low levels of these important binding proteins in plasma of patients with chronic liver disease, (2) accumulation of endogenous compounds, such as bilirubin, inhibiting plasma protein binding of certain drugs, and (3) possible qualitative changes in albumin and α_1-acid glycoprotein [30]. As a result of the lower plasma binding, the distribution volume of certain drugs may be larger in these patients. Moreover, water-soluble drugs will have a significant increase in their volumes of distribution in patients with ascites possibly necessitating larger loading doses. For example, the apparent volume of distribution of the β-lactam antibacterial cefodizime was shown to be three times larger in patients with cirrhosis compared to healthy individuals [32]. Chronic liver disease, such as cirrhosis, is more likely to be associated with altered drug binding than are acute conditions such as viral hepatitis [31].

The unbound fraction in blood/plasma is also an important determinant of the oral clearance of blood-flow-limited drugs, and of the oral and systemic clearance of capacity-limited drugs (Table 1). To correctly interpret the effect of liver disease on the plasma or blood clearance of capacity-limited drugs exhibiting high blood/plasma protein binding, one should take alterations in fu into account [30]. Failing to do so has led on many occasions to misinterpretations of the experimental data.

The importance of plasma protein binding determinations in the evaluation of the effect of chronic liver disease on drug pharmacokinetics is clearly illustrated by using naproxen, a capacity-limited compound with high plasma binding, as an example. Williams et al. studied the effect of alcoholic cirrhosis on the oral pharmacokinetics of naproxen following single-dose and multiple-dose administration [33]. Plasma protein binding of naproxen was decreased in alcoholic cirrhosis resulting in unbound plasma fractions 2 to 4 times higher in these patients compared to healthy subjects. If only the plasma clearance based on total (i.e., bound plus unbound) drug concentrations (CL/F in this case) is considered, no statistically significant difference was apparent between control subjects and cirrhotic patients. One might therefore erroneously conclude that alcoholic cirrhosis is not affecting the metabolism of naproxen. CL/F, however, is related to CL_u/F and fu by the following equation:

$$CL/F = \frac{CL_u/F}{fu} \quad (7)$$

The decrease in hepatic metabolic capacity, as reflected by CL_u/F, is obscured by a simultaneous increase in the fraction of unbound drug if total plasma clearance is the sole parameter used to assess hepatic metabolic function. The marked reduction (-60%) in CL_u/F of naproxen in patients with alcoholic cirrhosis, however, shows that metabolism of this drug is significantly impaired in these patients. In the same study, a small increase in distribution volume of naproxen was found in the presence of alcoholic cirrhosis. Naproxen is a drug with a very small distribution volume of approximately 0.15 L/kg. For drugs with such small distribution volumes, important alterations in plasma protein binding will only be associated with relatively unimportant changes in Vd [34].

Since the oral clearance of all drugs, i.e., those with flow-limited and as well as those with capacity-limited elimination, and the systemic clearance of capacity-limited drugs are influenced by changes in fu, a classification into binding-sensitive (fu<0.1) and binding-insensitive drugs (fu>0.1) is useful [35]. While categorization of drugs based on hepatic extraction ratio and unbound fraction in blood/plasma will be helpful when describing the potential effect of liver disease on drug pharmacokinetics, the variable nature of liver disease, possible extrahepatic contribution to metabolism, and altered drug pharmacodynamics, make predictions from such classifications to individual drug and patient situations extremely tenuous. An understanding of the fundamental pharmacokinetic principles related to hepatic drug clearance, however, will be helpful to correctly interpret the results of pharmacokinetic observations in patients with liver disease and to understand the general guidelines concerning dosage adjustment in these patients.

Elimination

Metabolism

The liver is the main organ involved in drug metabolism. The hepatic intrinsic clearance (CL_{int}) represents the ability of the liver to clear unbound drug from the blood when there are no limitations of flow. CL_{int} depends on metabolic enzyme activity and the activity of sinusoidal and canalicular transporters (Fig. 1) [7, 36]. The importance of hepatic transport proteins in hepatobiliary drug disposition has been recognized only recently. Many aspects of this evolving field and the impact on pharmacotherapy remain to be elucidated. It has long been realized that chronic liver disease in general is associated with impaired metabolism of a number of drugs. Indeed, in chronic liver disease, a reduction in absolute liver cell mass or a decrease in enzyme activity due to alteration in the function of surviving cells may lead to impaired drug metabolism [4, 5]. In addition, as a result of sinusoidal capillarization, the uptake of certain drugs and of oxygen across the capillarized endothelium may be impaired, which may contribute to reduced hepatic drug metabolism in chronic liver disease [4, 5, 37]. The microsomal mixed-function oxidase system, located in the smooth endoplasmic reticulum of hepatocytes, is responsible for phase I oxidative metabolism. This system consists of two enzymes: cytochrome P450 (CYP450) and NADPH-dependent cytochrome P450 reductase. These enzymes require two additional components to function: nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen. As a result, CYP450 enzymes are in general more sensitive than the phase II conjugating enzymes due to the lack of oxygen that results from shunting, sinusoidal capillarization, and reduced liver perfusion [5, 37].

Studies assessing the protein content or the activity of important drug-metabolizing enzymes in livers from cirrhotic patients have shown that, in general, enzyme activities and protein content are reduced with increasing disease severity [e.g., 38–42]. However, these studies also seem to indicate a selective regulation of the various drug-metabolizing enzymes in patients with chronic liver disease. Indeed, chronic liver diseases are associated with variable and nonuniform reductions in CYP450 activities that do not correlate with reduced hepatic blood flow. For example, in the same cohort of patients with mild to moderate chronic liver disease, the oral clearance of S-mephenytoin was significantly reduced (to 20% of the control value) whereas the oral clearance of debrisoquine was not affected [43, 44]. Among extensive metabolizers (all study subjects were extensive metabolizers), S-mephenytoin is almost exclusively metabolized by CYP2C19 and debrisoquine is a probe for CYP2D6 activity. Similarly, Frye et al. used a validated cocktail approach to study the effect of liver disease on multiple CYP450 enzymes [45]. A mixture of caffeine, mephenytoin, debrisoquine, and chlorzoxazone was orally administered to measure the in vivo activity of CYP1A2, CYP2C19, CYP2D6, and CYP2E1, respectively, in healthy subjects and patients with different aetiologies and severity of liver disease. The results confirmed that CYP450 enzyme activity is differentially affected by the presence of liver disease.

The authors propose that a "sequential progressive model of hepatic dysfunction" may provide a means to characterize quantitative liver function (Fig. 2). According to this model, if a patient is evaluated at an early stage of hepatic disease, then clearance of a drug metabolized by CYP2C19 can be expected to be reduced, whereas the clearances of drugs metabolized by CYP1A2, CYP2D6, and CYP2E1 will exhibit normal or nearly normal values. At the other end of the clinical spectrum of hepatic function, a patient with decompensated end-stage liver disease will have reduced clearances by CYP1A2, CYP2C19, CYP2D6, and CYP2E1. At an intermediate level of severity of liver disease, the clearances of drugs will be more or less reduced according to the specific CYP450 isoform involved in their elimination. Consequently, the effect of a decrease in hepatic function on the clearance of a particular drug may be anticipated from knowing the individual drug-metabolizing enzymes involved in the metabolism of the drug under normal circumstances and the sensitivity of the enzymes to the disease process. Although the results of several studies clearly indicate a selective regulation of activity for different CYP enzymes in the presence of chronic liver disease, the mechanisms responsible for this differential effect remain unknown.

CYP3A is the most abundant CYP450 subfamily. It plays a major role in human drug metabolism catalyzing the biotransformation of more than 50% of drugs commonly

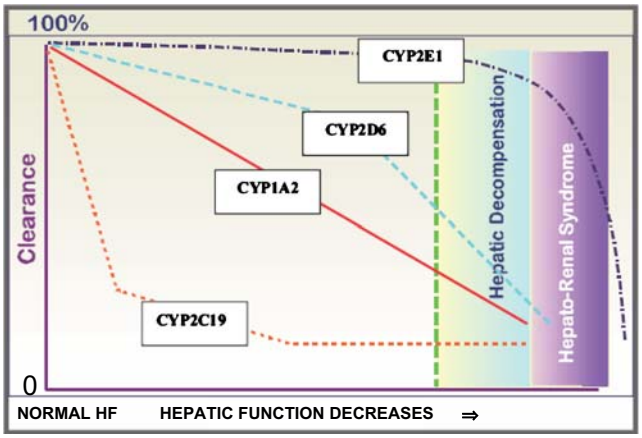

Fig. 2 Sequential progressive model of hepatic dysfunction. The *ordinate* shows how plasma clearance, starting at 100% when hepatic function is normal (*normal HF*), decreases for substances eliminated predominantly by metabolism via individual CYP450 isoforms in the liver. CYP450 enzyme activity in general decreases as liver function decreases. However, some CYP450 isoform enzyme activities show relative preservation as liver function deteriorates (e.g., CYP2E1 and to a lesser extent CYP2D6), whereas others (e.g., CYP2C19) are particularly sensitive to the presence of liver disease. In general, patients with hepatic decompensation suffer from the hepato-renal syndrome. (Reprinted with permission from the American Society for Clinical Pharmacology and Therapeutics from Frye et al. [45])

used. While CYP3A4 is usually the most abundant CYP450 isoform in human liver, CYP3A5 is expressed in only a fraction of Caucasians and may constitute 17–50% of the CYP3A enzymes in those who express it [46, 47]. CYP3A4 and CYP3A5 have largely overlapping substrate specificity. Among patients with cirrhosis, several pharmacokinetic studies have shown a decrease in the clearance of drugs metabolized by CYP3A4/3A5 such as midazolam, nifedipine and everolimus [22, 24, 28, 48].

Conjugation reactions such as glucuronidation are often considered to be affected to a lesser extent by liver cirrhosis than CYP450-mediated reactions [42, 49, 50]. This idea is mainly based on the results of early pharmacokinetic studies with benzodiazepines, which showed that the clearance of oxazepam, lorazepam, and temazepam, which are mainly eliminated by glucuronidation, is not reduced in patients with liver cirrhosis, whereas the clearance of diazepam and midazolam, both undergoing phase I reactions, is decreased [22, 28, 49, 51–54]. The mechanism involved in the sparing of glucuronidation in cirrhosis has not been elucidated, but several theories have been proposed. One of these theories suggests that there is activation of latent UDP-glucuronosyltransferase (UGT) enzymes during liver injury [49]. Examination of cirrhotic human livers revealed an up-regulation of UGT activity in remaining viable hepatocytes [55]. Another possible explanation for the relative sparing of glucuronidation in liver disease may be increased extrahepatic metabolism in case of cirrhosis. Extrahepatic glucuronidation seems to contribute substantially to the overall clearance of, for example, morphine and may be increased in patients with liver dysfunction [49, 56]. However, despite the consistent results of many early studies, there is now experimental evidence that glucuronidation may not be spared in cirrhosis to the same degree as originally predicted. Several more recent studies have shown impaired glucuronidation of drugs such as morphine, diflunisal, lormetazepam, oxazepam, lamotrigine, zidovudine, and mycophenolate mofetil in patients with advanced cirrhosis [23, 57–63]. It seems that most studies that found preservation of drug glucuronidation had used patients with only mild to moderate liver disease [49].

It is possible that liver disease has a differential effect on the various UGT isoforms, as was shown for the CYP450 enzymes, and that some UGT enzymes may be more resistant to hepatic injury [64]. Congiu et al. examined the mRNA levels of various UGT isoforms in liver samples of patients with differing degrees of fibrosis [65]. However, the results did not show a reduction in the mRNA of total UGT nor of individual UGT isoforms. The data did indicate, however, that there is the potential for decreased drug glucuronidation in the liver of patients with an active inflammatory condition and some hepatic fibrosis, but glucuronidation may recover once the inflammation subsides. Clearly further studies are needed to better understand the effects of liver disease on drug glucuronidation.

For some drugs a full appreciation of factors influencing the hepatic clearance of drugs requires knowledge of the impact of both uptake transporters and biliary transporters and their interplay with drug-metabolizing enzymes. Currently, the ability to translate, in a practical manner, the rapidly increasing amount of information on the in vitro transport of drugs in cell systems to whole-organ models is limited by our incomplete knowledge of the abundance of specific transporters in the human liver and its associated variability [66, 67].

Biliary excretion

Common bile duct stones, sclerosing cholangitis, or cancer of the biliary tree or the pancreas can obstruct bile flow and produce extrahepatic cholestasis. Intrahepatic cholestasis due to functional derangement of the hepatocanalicular bile secretory system may be induced by certain drugs such as erythromycin, phenothiazines, and anabolic steroids [68]. Reduced formation or secretion of bile into the duodenum will lead to a decreased clearance of substances, both endogenous and exogenous, that are eliminated by biliary excretion. Because of technical difficulties in collection of multiple bile samples and the exact measurement of bile flow, detailed information on the contribution of biliary excretion to the overall elimination of most drugs in

humans is scarce. Studies in patients undergoing surgery for obstruction of the common bile duct have clearly shown that the biliary excretion of antibiotics, such as ampicillin, piperacillin, certain cephalosporins, clindamycin, and ciprofloxacin, was markedly impaired in patients with obstructed biliary tract [69–74]. Drugs and drug metabolites normally excreted to a significant extent via the bile may therefore accumulate in patients with obstruction of the common bile duct. In addition, biliary obstruction may lead to hepatocellular damage with impairment of metabolic drug clearance. Indeed, the activity of several CYPs, for example CYP2C and CYP2E1, has been shown to be impaired in livers removed at transplantation from patients with end-stage cirrhosis with and without cholestasis, whereas CYP3A protein was significantly reduced only in the cirrhotic livers without cholestasis [38]. Consequently, drugs that depend to a significant extent on hepatic metabolism for elimination may require dosage adjustment in patients with cholestasis.

Reduced transporter expression may contribute to impaired excretory liver function in patients with cholestatic liver diseases [75, 76]. However, recent experimental studies suggest, that, particularly with prolonged cholestasis, maintenance or even up-regulation of hepatocellular efflux pumps may reflect adaptive and compensatory mechanisms limiting hepatocellular accumulation of potentially toxic biliary constituents [77]. How these potential alterations by chronic liver disease of hepatic uptake transporters and efflux pumps may affect the hepatic elimination of drug substances remains to be determined.

Renal excretion

Advanced hepatic disease is commonly complicated by impaired renal function. The hepatorenal syndrome may be defined as unexplained progressive renal failure occurring in patients with chronic liver disease in the absence of clinical, laboratory, or anatomical evidence of other known causes of renal failure. Reduced renal excretion has been reported for a number of drugs mainly excreted in unchanged form by the kidneys such as the diuretics furosemide and bumetanide, the H_2-receptor antagonists cimetidine and ranitidine, and the antiepileptic levetiracetam, in patients with advanced cirrhosis accompanied by impaired renal function [78–82]. Due to reduced muscle mass and impaired metabolism of creatine to creatinine in a number of patients with severe liver disease, estimations of creatinine clearance based on serum creatinine measurements (e.g., Cockroft-Gault method) in these patients are often inaccurate [83]. Even measured creatinine clearance has been shown to overestimate true glomerular filtration rate by a factor of two [84, 85]. In a group of patients with cirrhosis, Granneman et al. [86] showed an average 54% reduction in temafloxacin renal clearance, whereas the average reduction in measured creatinine clearance was only 17%. The measured creatinine clearance seems to be inaccurate because of an increased fractional tubular secretion of creatinine in patients with cirrhosis as the glomerular filtration rate deteriorates [87]. The serum cystatin C level, another endogenous marker for renal function, may reflect glomerular filtration more accurately in cirrhotic patients [83]. In any case, in patients with advanced chronic liver disease, dosage modification is not only necessary for drugs predominantly cleared by the liver but may also be indicated for renally cleared drugs.

Altered pharmacodynamics in liver disease

Before considering the effects of cirrhosis on changes in pharmacodynamics, it must be emphasized that in numerous studies such changes have been investigated without considering the potential contribution of alterations in the pharmacokinetic parameters of the drugs. In particular, several studies have reported changes in pharmacodynamics without taking into account alterations in plasma protein binding of drugs, which is a common feature in cirrhosis. Altered plasma protein binding may lead to a profound change in the unbound drug plasma concentration and subsequently alter the pharmacodynamics of these drugs [30]. Patients with cirrhosis, however, may display an altered therapeutic response unrelated to changes in the pharmacokinetic behavior of the drug. Theoretically, altered pharmacodynamics could result from changes in drug receptor binding, in the affinity of a drug for its receptor, or in the intrinsic activity of the receptor.

The most important changes in pharmacodynamics observed in cirrhosis are those associated with β-adrenoreceptor antagonists, diuretics, opioid analgesics, anxiolytics, and sedatives. A decreased therapeutic effect is observed with β-adrenoreceptor antagonists and diuretics whereas the opposite effect is found with analgesics, anxiolytics, and sedatives.

Theoretically, a decreased therapeutic effect may be observed with all β-adrenoreceptor antagonists since there is a close correlation between the degree of liver insufficiency and the decrease in the sensitivity to the chronotropic effects of isoproterenol [88, 89]. Moreover, in case of advanced cirrhosis, a reduction in β-adrenoreceptor density has been found in mononuclear cells [90]. It is thus tempting to speculate that β-adrenoreceptors could be less sensitive in cirrhosis, and this phenomenon has been demonstrated with different β-adrenoreceptor antagonists such as propranolol [88] or metipranolol [91].

With regard to diuretics, a decreased pharmacodynamic effect has been observed with furosemide [92, 93],

triamterene [94, 95], torasemide [96, 97], and bumetamide [98]. In comparison to healthy individuals, a higher tubular concentration of diuretics is needed in cirrhotic patients to excrete a given amount of sodium. However, due to reduced hepatic clearance in cirrhosis a higher concentration of the diuretic may reach the kidney, thereby offsetting pharmacodynamic alterations except in cirrhotics with diuretic-resistant ascites. In these patients, the reduced pharmacodynamic effect could be due to a reduction in both the number of nephrons and the maximum response per nephron as suggested by Villeneuve et al. [93].

In contrast to β-adrenoreceptor antagonists and diuretics, an enhanced therapeutic effect is observed in cirrhosis with opioid analgesics, anxiolytics, and sedatives. For these drugs, it has been shown that, at similar plasma drug concentrations, an increased cerebral effect is observed in cirrhotics in comparison to healthy subjects [99–101]. Moreover, encephalopathy may be precipitated when "therapeutic" doses of these drugs are administered to patients with cirrhosis. Various hypotheses such as alterations in blood-brain-barrier permeability and an increased GABA-ergic tone or an increased number of GABA receptors have been proposed to explain the increased sensitivity of cirrhotics to certain centrally acting drugs. Accumulation of endogenous non-benzodiazepine GABA-A receptor ligands has been suggested to explain the notion of increased GABA-ergic tone and would explain the beneficial effect of the selective benzodiazepine antagonist flumazenil in patients with hepatic encephalopathy [102].

Patients with liver cirrhosis are more sensitive to the renal adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are known to precipitate renal failure in patients with cirrhosis and ascites [103]. Although no clinical data have been published for selective COX-2 inhibitors, it seems prudent to avoid this class of drugs in cirrhotic patients with ascites since COX-2 inhibitors have been shown to impair renal perfusion in salt-depleted, healthy subjects [104].

Liver function assessment

Child-Turcotte's classification as modified by Pugh has been used extensively in clinical practice to categorize patients according to the severity of liver function impairment [105]. The Pugh modification of the Child-Turcotte's scale was initially designed to stratify the risk of portocaval shunt surgery in cirrhotic patients but has also been shown to correlate with survival and the development of complications of cirrhosis. The Child-Pugh classification incorporates five variables to assess the severity of liver disease: serum bilirubin, serum albumin, prothrombin time, the presence of encephalopathy, and the presence of ascites (Table 3). Disease severity is then classified as mild (class A), moderate (class B), or severe (class C) (Table 3). This classification scheme is useful in following an individual patient's disease course and in comparing patient groups, and may offer the clinician some guidance for dose adjustment. Another classification scheme, the model for end-stage liver disease (MELD), is based on serum bilirubin concentration, serum creatinine, the international normalized ratio (INR) of prothrombin time, and the underlying cause of liver disease [106]. The MELD score accurately predicts 3-month mortality among patients on a liver-transplant waiting list and has been adopted to use for allocating priorities in patients awaiting liver transplantation [107]. However, unlike in renal patients, where estimates of glomerular filtration rate (creatinine clearance, inulin clearance) correlate with kinetic parameters of drug elimination such as renal clearance, these classification schemes lack the sensitivity to quantitate the specific ability of the liver to metabolize individual drugs.

In addition to the Child-Pugh and MELD classification schemes, dynamic liver function tests have been developed in an attempt to better predict individual drug handling in patients with hepatic dysfunction. These tests rely on the oral or intravenous administration of an exogenous substance, which is mostly, or better exclusively, eliminated by the liver. The test is based on the determination of the plasma disappearance of the probe (i.e., clearance) or the appearance of a metabolite in plasma, urine, or even in expired air in the case of a breath test [108, 109]. The exogenous substances used as model substrates to measure the individual's ability to eliminate drugs can be broadly classified into blood-flow-limited model substances (high extraction ratio) and capacity-limited model substances (low extraction ratio).

As previously outlined, reduced liver function occurring in cirrhosis appears to be the result of multiple factors, especially hepatocellular dysfunction and portal-systemic shunting. From a clinical point of view both these factors are of importance when predicting the appropriate dose of various medications to be given to cirrhotic patients. The

Table 3 Child-Pugh classification and scoring of the severity of liver disease

Clinical/biochemical indicator	1 point	2 points	3 points
Serum bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (s > control)	<4	4–6	>6
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate

Points are summed, and the total score is classified according to severity as follows: 5–6 points = group A (mild), 7–9 points = group B (moderate), 10–15 points = group C (severe)

degree of portal-systemic shunting remains difficult to evaluate mainly due to various technical problems and to the unpredictable influence of reduced liver cell function on the extraction of test compounds characterized by a high extraction ratio, such as indocyanine green [110, 111], galactose [112], and sorbitol [113]. These three substances have a high hepatic extraction ratio and their clearance therefore will be blood-flow dependent. It has been proposed that the simultaneous measurement of hepatic extraction of sorbitol and indocyanine green will give an estimate of the degree of sinusoidal and vascular shunting [114]. However, it is not clear to what extent hepatic-uptake mechanisms, which may be significantly altered in chronic liver disease, may be affecting the hepatic clearance of these blood-flow-limited model substances [5].

"Metabolic" liver cell dysfunction can be assessed by the use of test substances whose metabolic elimination by the liver is minimally influenced by total hepatic blood flow or portal-systemic shunting, such as antipyrine, caffeine, and midazolam [115–117]. In humans antipyrine is eliminated exclusively by biotransformation and at least six hepatic CYP450 isoforms, i.e., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18, and CYP3A4, contribute to its metabolism [118]. Antipyrine clearance, therefore, depends on the activity of multiple CYP450 isoforms and as such is responsive to environmental, host, and genetic factors and thus shows a high interindividual variability even in healthy subjects. On the other hand, caffeine is largely eliminated by CYP1A2 metabolism and can be used to quantify CYP1A2 activity. Ratios of paraxanthine (a caffeine metabolite) to caffeine in plasma are significantly reduced in patients with liver impairment and correlate linearly with Child-Pugh scores [41]. Midazolam is almost exclusively eliminated by CYP3A-catalyzed biotransformation [117]. However, CYP3A4 is the predominant CYP450 isoform in the intestine and contributes substantially to the presystemic clearance of CYP3A substrates following their oral administration. Therefore, orally administered CYP3A-selective substrates measure not only hepatic CYP3A activity but also intestinal CYP3A activity. If midazolam is to be used as an in vivo marker for hepatic CYP3A activity then it should be administered intravenously [117].

$^{14}CO_2$ Breath tests have also been developed for substrates, such as aminopyrine, erythromycin, and caffeine [119]. The test compound, in which the ^{12}C-atom of a functional group has been replaced by a ^{14}C-atom, undergoes metabolic breakdown leading to the production of $^{14}CO_2$ which can be measured in the expired air. These three substances have a relatively low hepatic extraction ratio, and their metabolism therefore is thought to be mostly dependent on hepatic metabolic capacity. The results of these breath tests have been shown to correlate with the Child-Pugh classification [41, 120]. Erythromycin is used as a CYP3A probe and following intravenous administration of ^{14}C-erythromycin, the breath test should quantify hepatic CYP3A activity. However, results obtained by using erythromycin and midazolam to determine CYP3A activity do not always correlate [121, 122]. Unlike midazolam, erythromycin is a substrate for P-glycoprotein (a transmembrane efflux pump found in enterocytes and hepatocytes), and it has been suggested that the erythromycin breath test reflects P-glycoprotein function [123]. Consequently, it is important to be aware that the intrinsic metabolic clearance of a substance by the liver may be the result of the combined activities of uptake transporters, efflux pumps, and metabolizing enzymes. For example, the overlap in substrate specificity between CYP3A and P-glycoprotein has been well documented [67, 124]. Therefore, to accurately measure CYP3A activity, a selective CYP3A substrate such as midazolam should be used that has no P-glycoprotein affinity.

The formation of monoethylglycinexylidide (MEGX) from lidocaine, a flow-limited drug substance (E_H~0.7), is another frequently used dynamic liver function test [125]. The test is simple and consists in measuring the plasma concentration of MEGX usually 30 min after intravenous administration of a low lidocaine dose (1 mg/kg). It was long thought that the biotransformation of lidocaine to MEGX was exclusively catalyzed by CYP3A. However, more recent studies have clearly shown that, besides CYP3A, CYP1A2 also contributes to the formation of MEGX [126]. The MEGX test, therefore, does not exclusively measure CYP3A activity. The MEGX test has also been shown to correlate with the Child-Pugh score [82, 127].

The results of various dynamic liver function tests have been compared to the Child-Pugh classification to assess the functional reserve of the liver and the progression of the patient's liver dysfunction. It has not been clearly demonstrated that the use of one of these tests is better than the Child-Pugh classification for these goals. In addition, several studies have shown that, when performed in the same group of patients, a significant correlation is found between a test using a low-extraction drug (e.g., antipyrine, caffeine) and a test using a high-extraction drug (e.g., indocyanine green, galactose) [128–130]. These observations are consistent with the intact hypothesis theory, which states that chronic liver disease is associated with a reduced number of hepatocytes that function normally and are normally perfused, as well as with the development of intrahepatic porto-systemic shunting [44].

The challenge is to develop a dynamic liver function test that measures the residual elimination capacity of the liver in a patient with hepatic dysfunction which serves as the cornerstone for dosage adjustment, in analogy to the creatinine clearance test used for drug dosage adjustment

in renal patients. So far, the usefulness of these dynamic liver function tests for dosage adjustment purposes in patients with hepatic dysfunction is rather limited, and clinicians rely more on the Child-Pugh score, which may not be better but is readily available for liver patients.

Dosage adjustment in patients with hepatic dysfunction

Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have published a guidance for industry on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function [131, 132]. These guidelines recommend that a pharmacokinetic study be carried out during development of a medicinal product that is likely to be used in patients with impaired hepatic function and when hepatic impairment is likely to significantly alter the pharmacokinetics of the drug substance or its active metabolite(s). The primary objective of such a study is to identify patients at risk and to assess whether a dosage adjustment is required for patients with impaired hepatic function. These guidelines recommend that the Child-Pugh classification be used to categorize patients according to their degree of hepatic impairment. In addition, they encourage the use of exogenous markers to assess the elimination capacity of the patients by different mechanisms.

According to a recent survey, the number of medications found to contain specific recommendations for dosage adjustment based on hepatic function as determined by the Child-Pugh score is still rather limited [133]. Moreover, in many cases when the pharmacokinetics of a medicinal product are studied during development, patients with a Child-Pugh classification C, i.e., with severe hepatic disease, are not included. However, the practical and ethical problems associated with giving investigational drugs that have no potential to confer benefit to patients with severe liver disease merit careful consideration. In any case, characterization of the status of hepatic function would benefit by being quantified on the basis of an independent measure of metabolism of a marker known to be influenced by liver disease in addition to clinical assessment by a semi-quantitative Child-Pugh score.

When no recommendations for dosage adjustment in patients with hepatic dysfunction based on their Child-Pugh score are available, the following general considerations will be helpful. It is assumed that the drug is mostly eliminated by hepatic mechanisms (metabolism, biliary excretion).

1. Drugs with a relatively high hepatic extraction ratio: The oral bioavailability of these drugs can be drastically increased in patients with chronic liver disease, and the dosage should be reduced accordingly. Following systemic administration (iv, im, sc, etc.), the plasma clearance may be reduced if hepatic blood flow is decreased.
2. Drugs with a low hepatic extraction and high plasma protein binding (>90%): The oral and intravenous clearance of these drugs is determined by the intrinsic capacity of the hepatic elimination mechanisms and the unbound drug fraction in blood or plasma. The intrinsic clearance will be reduced to a degree determined by the functional status of the liver and the specific metabolic pathway(s) involved in the elimination of the drug. Because the unbound fraction of drug in blood or plasma may be significantly increased in patients with chronic liver disease, pharmacokinetic evaluation should be based on unbound blood/plasma concentrations, and dosage adjustment may be necessary even though total blood/plasma concentrations are within the normal range.
3. Drugs with a low hepatic extraction ratio and low plasma protein binding (<90%): The oral and intravenous clearance of these drugs is determined by the intrinsic capacity of the hepatic elimination mechanisms and the unbound drug fraction in blood or plasma. The intrinsic clearance will be reduced to a degree determined by the functional status of the liver and the specific metabolic pathway(s) involved in the elimination of the drug. Fluctuations in the unbound drug fraction in blood or plasma are rather small and will not significantly affect blood/plasma clearance of the drug. Dosage adjustment may be necessary and should be aimed at maintaining normal total (i.e., bound plus unbound) plasma concentrations.
4. The elimination of drugs that are partly excreted in unchanged form by the kidneys will be impaired in patients with the hepato-renal syndrome. It should be taken into account that creatinine clearance significantly overestimates glomerular filtration rate in these patients.
5. The volume of distribution of hydrophilic drugs may be increased in patients with chronic liver disease who have edema or ascites. As a consequence, the loading dose may have to be increased in these patients if a rapid and complete effect of the drug is required. Since many hydrophilic drugs are eliminated primarily in unchanged form by the kidneys, renal function should be taken into consideration.
6. Extreme caution is recommended when using drugs with a narrow therapeutic index in patients with liver disease and when administering any drug to patients with severe liver dysfunction (Child-Pugh class C).

In conclusion, drugs must be given with caution to patients with severe hepatic insufficiency such as is the case

in cirrhosis. Before administering drugs that are largely eliminated by hepatic mechanisms, their potential therapeutic benefits must be carefully counterbalanced with their risk for serious toxic reactions. This is especially true for drugs with a narrow therapeutic index and for sedatives, central analgesics, and anxiolytics, which may precipitate the occurrence of hepatic encephalopathy. If these drugs are needed by the cirrhotic patient, they should be started at a low dose which may subsequently be titrated to obtain the desired therapeutic effect.

A guide to drug dosage in hepatic disease describing the effect of (mostly) cirrhosis on the pharmacokinetic behaviour of more than 100 drugs including recommendations for dosage adjustment has been published by Hebert [134]. It constitutes a valuable information base when selecting a drug and its proper dosage regimen for a patient with liver disease. In addition, more recent review articles have described the effect of liver disease on the pharmacokinetics of drugs, some of which focused on specific drug classes, such as opioids, cardiovascular drugs, antiretroviral agents, and antineoplastic drugs [35, 135–142]. For the safe use of antineoplastic drugs in patients with liver disease, the authors of the review article conclude that not enough data are available in the scientific literature [142]. They recommend that pharmaceutical companies should provide pharmacokinetic data in patients with impaired liver function, especially for drugs that are primarily eliminated by metabolism, to allow quantitative advice for dose adaptation.

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