REVIEW ARTICLE

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Dose Adjustment in Patients with Liver Disease

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Abstract

Unfortunately, there is no endogenous marker for hepatic clearance that can be used as a guide for drug dosing. In order to predict the kinetic behaviour of drugs in cirrhotic patients, agents can be grouped according to their extent of hepatic extraction. For drugs with a high hepatic extraction (low bioavailability in healthy subjects), bioavailability increases and hepatic clearance decreases in cirrhotic patients. If such drugs are administered orally to cirrhotic patients, their initial dose has to be reduced according to hepatic extraction. Furthermore, their maintenance dose has to be adapted irrespective of the route of administration, if possible, according to kinetic studies in cirrhotic patients. For drugs with a low hepatic extraction, bioavailability is not affected by liver disease, but hepatic clearance may be affected. For such drugs, only the maintenance dose has to be reduced, according to the estimated decrease in hepatic drug metabolism. For drugs with an intermediate hepatic extraction, initial oral doses should be chosen in the low range of normal in cirrhotic patients and maintenance doses should be reduced as for high extraction drugs. In cholestatic patients, the clearance of drugs with predominant biliary elimination may be impaired. Guidelines for dose reduction in cholestasis exist for many antineoplastic drugs, but are mostly lacking for other drugs with biliary elimination. Dose adaptation of such drugs in cholestatic patients is, therefore, difficult and has to be performed according to

pharmacological effect and/or toxicity. Importantly, the dose of drugs with predominant renal elimination may also have to be adapted in patients with liver disease. Cirrhotic patients often have impaired renal function, despite a normal serum creatinine level. In cirrhotic patients, creatinine clearance should, therefore, be measured or estimated to gain a guideline for the dosing of drugs with predominant renal elimination. Since the creatinine clearance tends to overestimate glomerular filtration in cirrhotic patients, the dose of a given drug may still be too high after adaptation to creatinine clearance. Therefore, the clinical monitoring of pharmacological effects and toxicity of such drugs is important. Besides the mentioned kinetic changes, the dynamics of some drugs is also altered in cirrhotic patients. Examples include opiates, benzodiazepines, NSAIDs and diuretics. Such drugs may exhibit unusual adverse effects that clinicians should be aware of for their safe use. However, it is important to realise that the recommendations for dose adaptation remain general and cannot replace accurate clinical monitoring of patients with liver disease treated with critical drugs.

An alcoholic patient with physical signs of liver cirrhosis enters the hospital because of a seizure. After intravenous (IV) temazepam for the seizure, he is treated with oral clomethiazole as a prophylaxis for delirium tremens. After the first dose of clomethiazole, the patient experiences hypoventilation that results in global respiratory failure and eventually necessitates intubation and artificial ventilation. No further doses of clomethiazole are administered and sedation is achieved with IV midazolam. After extubation, prophylaxis for delirium tremens is performed with oral oxazepam, which is well tolerated by the patient and can be withdrawn gradually after 5 days.

The present article deals with the pharmacokinetic and pharmacodynamic changes of drugs in patients with chronic liver disease and should help to understand and avoid situations such as the one described.

1. Changes in Pharmacokinetics

Chronic liver disease, in particular liver cirrhosis, can modulate many factors determining the behaviour of drugs in the body. The most important alterations in the kinetic behaviour of drugs will be discussed in the following sections.

1.1 Drug Absorption

Since patients with liver cirrhosis are frequently affected by portal hypertensive gastropathy,[1] gastritis and/or ulcers of the upper gastrointestinal tract,[2,3] the absorption process of orally administered drugs might be altered. The extent of drug absorption could be decreased as a consequence of these pathologies or may be increased because of a high intestinal permeability in patients with portal hypertension.[4,5] However, the amount of drug absorbed is generally not affected in patients with cirrhosis,[6] whereas the rate of the absorption of orally administered drugs may be decreased. Delayed absorption, which is not explained by hypertensive gastropathy, gastritis or ulcers has, for instance, been shown for furosemide in patients with cirrhosis,[7,8] but not for torasemide, which is another loop diuretic used in patients with ascites.[9] The studies with furosemide suggest that impaired gastrointestinal motility may be a mechanism for delayed drug absorption in patients with cirrhosis. Cirrhotic patients have delayed gastric emptying,[10,11] which possibly results from a decreased action of gastrointestinal hormones such as secretin, glucagon, cholecystokinin or motilin.[12] Prokinetic agents such as erythromycin or cisapride, which act differently to the gastrointestinal hormones mentioned, can speed up gastric emptying in cirrhotic patients,[13,14] thus supporting the concept that the reasons for impaired gastric emptying in patients with cirrhosis are functional and not organic in nature. Impaired gastric emptying may be relevant for preparations with delayed drug release, since the action of these drugs may be delayed further in this

Table I. Substances investigated for quantification of liver function/liver metabolism

Substance (route of administration)	Hepatic extraction (%)	Metabolism	Clinical use	Reference
Serum bile acids (endogenous)	>90	Hydroxylation and conjugation, enterohepatic cycling	May be useful for estimation of porto-systemic shunt	20
Indocyanine green (IV)	90	Biliary excretion	Estimation of hepatic blood flow	21
Galactose (IV)	95	Rate-limiting step is phosphorylation	First-order elimination reflects 'functional hepatic capacity' Extrahepatic metabolism is problematic	22
Sorbitol (IV)	>80		Estimation of hepatic blood flow	23
Lidocaine (IV)	80	CYP3A		24
Dextropropoxyphene (PO)	70	CYP3A	Ratio norpropoxyphene/d-propoxyphene may be useful to estimate proto-systemic shunt	25
Erythromycin (IV)	30	CYP3A	CO_2 exhalation is used as a marker of CYP3A activity	26
Antipyrine (PO)	5	Different CYPs	Reflects activity of different CYPs	27
Aminopyrine (IV)	<30	Different CYPs	CO_2 exhalation is used as a marker of general CYP activity	28
Caffeine (PO, IV)	<30	CYP1A2, NAT2	CO_2 exhalation mainly measures activity of CYP1A2	29

CYP = cytochrome P450; **IV** = intravenous; **NAT2** = N-acetyltransferase type 2; **PO** = oral.

group of patients and may, therefore, be difficult to predict.

1.2 Drug Distribution

In patients with liver cirrhosis who have oedema and/or ascites, the volume of distribution of hydrophilic drugs is increased. As a consequence, the loading dose of hydrophilic drugs may have to be increased in cirrhotic patients when a rapid action is needed (e.g. for β-lactam antibacterials or for digoxin). In cirrhotic patients with ascites, the initial administration of such drugs should, therefore, be performed according to bodyweight if a rapid and complete effect of the drug is desired.

On the other hand, an increase in the volume of distribution is associated with an increase in the elimination half-life of such drugs.[6] A slower elimination velocity in cirrhotic patients with ascites has indeed been demonstrated for furosemide[7,8] and for β-lactam antibacterials such as ceftazidime or cefprozil.[15,16] However, the influence of oedema and/or ascites on the elimination velocity of hydrophilic drugs used in this group of patients appears to be small and usually has no practical consequences.[8] Since many hydrophilic drugs are excreted non-metabolised primarily by the kidney, renal function should also be taken into consideration for such drugs. This aspect is discussed in section 1.4.

1.3 Hepatic Clearance

Although measurements of the creatinine clearance level can be used for dose adjustments in cases of impaired renal function,[17] there is no naturally occurring substance that can be used to estimate the hepatic clearance of drugs. The Child-Pugh score is composed of several clinical variables and is used widely for the assessment of prognosis in patients with liver cirrhosis,[18] but does not reflect the hepatic clearance or pharmacodynamics of drugs in these patients.[19] Regarding the lack of endogenous markers for the hepatic clearance of drugs, exogenous compounds might serve as an alternative. As shown in table I, the kinetics of several substances has been investigated, but none of them has gained general acceptance in the prediction of drug kinetics in patients with liver disease. Important reasons limiting the clinical value of these tests are that such tests

may be invasive and time consuming and that the hepatic metabolism of drugs may be too complex to be predicted accurately by such procedures. As discussed in the following sections, drugs can be metabolised by different enzymes (e.g. different cytochrome P450 [CYP] isoenzymes and different enzymes for drug conjugation) and can be excreted by the bile. One probe drug or exogenous substance is, therefore, most probably not sufficient to predict the kinetics of all drugs used in patients with cirrhosis. A cocktail of probe drugs could be used,[19] but analysis of the substances applied would be time consuming and might, therefore, not be helpful in most clinical situations.

Another possible way to predict the kinetic behaviour of drugs and to avoid dose-dependent drug toxicity in patients with liver disease is to classify drugs according to their handling by the liver. In order to understand the basis and consequences of this classification, the hepatic extraction (E) and hepatic clearance (Cl_{hep}) of drugs have to be defined. Cl_{hep} can be expressed for a given drug as the product of the blood flow across the liver (Q) and the extraction of this drug (E) during its first passage across the liver (equation 1):

$$Cl_{hep} = Q \times E = Q \times \frac{C_{in} - C_{out}}{C_{in}} \quad \text{(Eq. 1)}$$

where C_{in} is the concentration of the drug in the portal and C_{out} is the concentration of the drug in the liver veins. According to the venous equilibrium model (the concentration of a substance in the liver is assumed to be uniform and equal to the hepatic outflow concentration), E can also be expressed as (equation 2):[6]

$$E = \frac{f_u \times Cl_i}{Q + (f_u \times Cl_i)} \quad \text{(Eq. 2)}$$

where Cl_i is the intrinsic hepatic clearance and f_u is the fraction of a drug not bound to serum proteins (free fraction). Cl_i reflects the capacity of the liver to metabolise a certain drug independently of the blood flow across the liver.

Using this expression for E, Cl_{hep} can be written as (equation 3):

$$Cl_{hep} = \frac{Q \times (f_u \times Cl_i)}{Q + (f_u \times Cl_i)} \quad \text{(Eq. 3)}$$

For drugs with a high hepatic extraction (f_u x Cl_i) is >> Q and Cl_{hep} is approximating Q. These drugs are, therefore, called 'flow-limited' or 'high extraction'. Alternatively, for drugs with a low extraction, (f_u x Cl_i) is << Q and Cl_{hep} is approximating (f_u x Cl_i). These drugs are called 'enzyme-limited' or 'low extraction' and their Cl_{hep} is mainly determined by the capacity of the liver to metabolise such drugs. Many drugs are in between these two extremes and show properties of both groups (table II).

1.3.1 High Extraction Drugs

High extraction drugs undergo a high extraction during the first passage across the liver (≥60%) and, therefore, have a bioavailability of ≤40% (see figure 1). Since the blood flow across the liver is typically decreased in patients with liver cirrhosis,[30,31] the elimination of high extraction drugs is retarded in comparison to patients with normal liver function. In addition to decreased blood flow across the liver, patients with liver cirrhosis frequently have portosystemic shunts, which prevent the exposure of hepatocytes to drugs.[6,20] As a consequence, a variable amount of portal blood is not cleared by the hepatocytes, which potentially leads to a significant increase in the bioavailability of high extraction drugs that are administered orally (figure 2).

For example, the bioavailability of clomethiazole is 10% in healthy subjects and may increase to 100% in patients with liver cirrhosis.[32] This 90% increase in bioavailability is associated with a 10-fold higher drug exposure and eventually leads to adverse drug reactions, as demonstrated in the clinical example at the beginning of this article. Table III lists the observed increase in the bioavailability of some drugs in patients with liver cirrhosis compared with healthy subjects.

Therefore, for high extraction drugs that are administered orally, both the initial and the maintenance doses have to be reduced in patients with liver cirrhosis. However, the extent of this reduction cannot be predicted accurately since neither the portosystemic shunt nor the hepatic blood flow are usually known in a given patient. A conservative approach is to assume a 100% oral bioavailability of

Table II. Classification of drugs metabolised by the liver according to pharmacokinetic characteristics

Effect of porto-systemic shunts on bioavailability	Drug class	Examples of drugs (hepatic extraction value)[a]
Low hepatic extraction (<30%)/low protein binding (<90%)		
Not relevant	Analgesics	Paracetamol (acetaminophen)
	Antibacterial drugs	Doxycycline, metronidazole
	Antidepressants	Citalopram, fluoxetine, fluvoxamine, moclobemide
	Antiemetics	Metoclopramide
	Antiepileptics	Carbamazepine, ethosuximide, lamotrigine, levetiracetam, phenobarbital, primidone, topiramate
	Antihistamines	Diphenhydramine
	Antineoplastic and immunosuppressive agents	Cyclophosphamide, hydroxycarbamide (hydroxyurea), letrozole, melphalan, temozolomide
	Antiparkinson drugs	Pramipexole
	Antipsychotics	Risperidone
	Benzodiazepines	Alprazolam, bromazepam, clobazam, flunitrazepam, flurazepam, nitrazepam, triazolam
	Bronchodilators	Theophylline
	Corticosteroids	Methylprednisone, prednisone
	Tuberculostatic drugs	Isoniazid
	Other hypnotics and sedatives	Methaqualone, zopiclone
Low hepatic extraction (<30%)/high protein binding (>90%)		
Not relevant	Analgesics	Methadone
	Antiandrogens	Cyproterone
	Antibacterial drugs	Ceftriaxone, clarithromycin, clindamycin
	Anticoagulants	Phenprocoumon
	Antidepressants	Maprotiline, trazodone
	Antidiabetic drugs	Glipizide, tolbutamide
	Antiepileptics	Phenytoin, tiagabine, valproic acid
	Antiestrogens	Tamoxifen, toremifene
	Antihyperlipidemic drugs	Clofibrate, gemfibrozil
	Antineoplastic and immunosuppressive agents	Chlorambucil, mycophenolate mofetil
	Antiparkinson drugs	Sertindole
	Antipsychotics	Tolcapone
	Antiulcer drugs	Lansoprazole
	Benzodiazepines	Chlordiazepoxide, diazepam, lorazepam, oxazepam, temazepam

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Table II. Contd

Effect of porto-systemic shunts on bioavailability	Drug class	Examples of drugs (hepatic extraction value)[a]
	Corticosteroids	Prednisolone
	Tuberculostatic drugs	Rifampicin (rifampin)
	Other hypnotics and sedatives	Zolpidem
Intermediate hepatic extraction (30–60%)		
May be clinically relevant	Analgesics	Codeine (0.52), pethidine (meperidine) [0.52]
	Antiarrhythmics and anaesthetic agents	Amiodarone (0.54), lidocaine (0.4)
	Antibacterial drugs	Ciprofloxacin (0.4), erythromycin (0.38)
	Antidepressants	Amitriptyline (0.6), clomipramine (0.5), mirtazapine (0.43), nortriptyline (0.34), paroxetine (0.38)
	Antifungal agents	Itraconazole (0.4)
	Antihyperlipidemic drugs	Atorvastatin (0.55), pravastatin (0.32), simvastatin (0.35)
	Antineoplastic and immunosuppressive agents	Azathioprine (0.4), etoposide (0.48)
	Antiparkinson drugs	Entacapone (0.48)
	Antipsychotics	Amisulpride (0.52), clozapine (0.45), fluphenazine (0.47), haloperidol (0.55), olanzapine (0.4), zuclopenthixol (0.51)
	Antiulcer drugs	Omeprazole (0.35), ranitidine (0.48)
	β-adrenoceptor antagonists	Carvedilol (0.41)
	Calcium channel antagonists	Diltiazem (0.55), felodipine (0.56), nifedipine (0.33)
	Progestogens	Medroxyprogesterone (0.55)
	Prolactin inhibitors	Lisuride (0.53)
	Psychostimulants	Methylphenidate (0.54)
High hepatic extraction (>60%)		
Clinically relevant	Analgesics	Morphine (0.76), pentazocine (0.8), propoxyphene (n/a)
	Anthelmintics	Praziquantel (n/a)
	Antianginal agents	Isosorbide dinitrate (0.78), nitroglycerine (≈1)
	Anticholinesterases	Tacrine (n/a)
	Antidepressants	Dibenzepin (0.75), doxepin (0.72), imipramine (0.61), mianserin (0.67), sertraline (≈1), trimipramine (0.67), venlafaxine (0.73)
	Antihistamines	Promethazine (0.76)
	Antihyperlipidemic drugs	Fluvastatin (0.71), lovastatin (0.95)
	Antimigraine agents	Sumatriptan (0.82)

Continued next page

Table II. Contd

Effect of porto-systemic shunts on bioavailability	Drug class	Examples of drugs (hepatic extraction value)[a]
	Antineoplastic and immunosuppressive agents	Ciclosporin (0.72), fluorouracil (0.71), idarubicin (≈1), mercaptopurine (0.80), sirolimus (n/a), tacrolimus (0.75), vinorelbine (n/a)
	Antiparkinson drugs	Bromocriptine (0.60), levodopa (n/a), selegiline (≈1), biperiden (n/a)
	Antipsychotics	Chlorpromazine (0.68), chlorprothixene (n/a), flupentixol (n/a), quetiapine (0.91), perphenazine (0.8), sulpiride (n/a)
	β-adrenoceptor antagonists	Labetalol (0.67), metoprolol (0.67), propranolol (0.75)
	Calcium channel antagonists	Nicardipine (0.82), nisoldipine (0.96), verapamil (0.90)
	Hypnosedatives, antianxiety drugs	Buspirone (0.96), clomethiazole (0.9), midazolam (0.62), zaleplon (0.73)
	Phosphodiesterase inhibitors	Sildenafil (0.62)
	Prokinetic drugs	Cisapride (0.65)

a The values for hepatic extraction (E) were calculated using equation 5 (see section 1.3.5).

n/a = value not available.

such drugs in cirrhotic patients. Accordingly, initial and first maintenance doses should be reduced, taking into account the assumed increase in bioavailability as follows (equation 4):

$$\text{Reduced dose} = \frac{\text{normal dose} \times \text{bioavailability}}{100} \quad \text{(Eq. 4)}$$

'Normal dose' is the starting dose in a patient without liver disease and 'bioavailability' is the percentage of a drug ingested orally that reaches the systemic circulation in a healthy person. The maintenance dose should be adjusted, taking into account the desired pharmacological effect and toxicity of the drug used. Using this approach, a possible reduction in drug clearance due to impaired hepatic blood flow is not considered, but may be negligible compared with the assumed increase in bioavailability.

On the other hand, for high extraction drugs that are administered intravenously, a normal initial dose can be administered and the maintenance doses have to be reduced according to hepatic clearance, which is reflected by blood flow across the liver. Theoretically, assessment of the hepatic blood flow using Doppler sonography might be helpful in this situation, but to the best of our knowledge, clinical studies supporting this hypothesis are so far lacking.

As shown in figure 3, a linear relationship has been described between the serum bile acid level and the extent of porto-systemic shunting in patients with liver cirrhosis.[20] The serum bile acid level may, therefore, be helpful for the initial dose adjustment of high extraction drugs. However, to the best of our knowledge, no studies are currently available to address this question.

1.3.2 Low Extraction Drugs with Low Binding to Albumin

Low extraction drugs undergo only a low extraction during the first passage across the liver (≤30%) and their hepatic clearance is mainly determined by the product of f_u x Cl_i. These drugs have a bioavailability that is ≥70% (unless dissolution in the gut and/or intestinal absorption are incomplete). Important examples of such drugs are listed in table II. As shown in figure 2, the bioavailability of low extraction drugs is not grossly affected by liver cirrhosis, but their clearance may be reduced depending on their hepatic metabolism (reflecting Cl_i) and binding

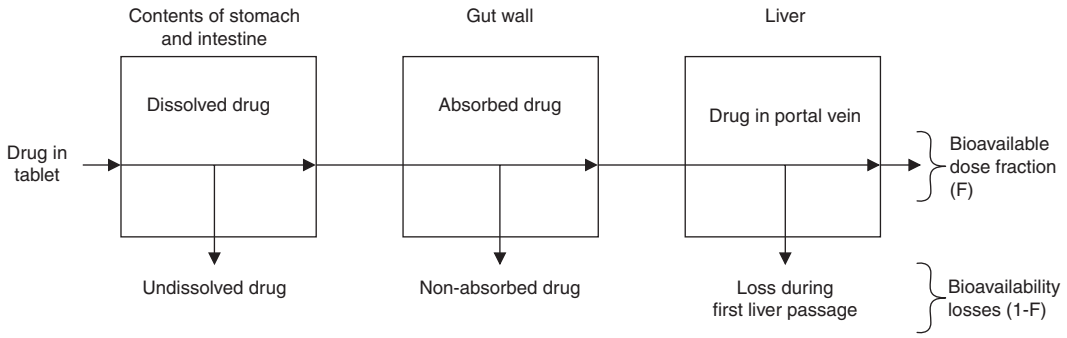

Fig. 1. Effect of liver cirrhosis on the bioavailability of high extraction drugs. After oral administration, only a fraction of a drug reaches the systemic circulation. Most of the drug not reaching the systemic circulation is either not absorbed or metabolised during the first passage across the liver. Patients with liver cirrhosis and/or portal hypertension can have intra- and extra-hepatic, porto-systemic shunts, which prevent the drug from reaching the hepatocytes and from being metabolised. Furthermore, important drug-metabolising enzymes have a reduced activity in cirrhotic livers. These are the two main factors that are responsible for an increase in the bioavailability of high extraction drugs in patients with cirrhosis.

to albumin (f_u). Accordingly, the maintenance dose of these drugs should be reduced, whereas therapy can be started with a normal dose.

Similar to high extraction drugs, it is impossible to predict precisely by how much the maintenance dose of the low extraction drugs has to be reduced. Studies that assessed the protein content and/or the activity of important drug-metabolising enzymes (CYPs and conjugation reactions) in livers from cirrhotic patients have shown that enzyme activities and protein content are reduced with increasing disease severity, as expressed by the Child-Pugh score, but with a large variability.[43-45]

The reduction in intrinsic hepatic clearance associated with liver cirrhosis appears, therefore, not only to be a function of the Child-Pugh score, but also of the metabolic reaction involved. Conjugation reactions such as glycosylation and transfer of sulfate groups (phase II reactions) are considered to be affected to a lesser extent by liver cirrhosis than CYP-associated reactions (phase I reactions).[6] For instance, the clearance of oxazepam[46] or temazepam,[47] two benzodiazepines that are only conjugated, is not reduced in patients with liver cirrhosis, whereas the clearance of diazepam[48,49] or midazolam,[37] both undergoing phase I and phase II reactions, is decreased. As discussed previously, the decrease in CYP activity and/or protein content is highly variable in patients with cirrhosis.[43,45,50-53] This variability can be explained, at least to some extent, by the different mechanisms that affect CYP activity and/or protein content, such as impaired transcription for CYP1A, CYP3A and CYP2C,[50,53] altered post-translational modification for CYP2E1[50] or increased sensitivity to cholestasis as described for CYP2E1 and CYP2C9.[43,50]

Several studies have shown that conjugation reactions can also be impaired in patients with liver cirrhosis. Reduced glucuronidation has been demonstrated for zidovudine,[54,55] diflunisal,[56] morphine,[57,58] mycophenolate mofetil,[59] lormetazepam[60] and lamotrigine.[61] The activity of sulfotransferases was also found to be reduced, whereas sulfatase activity appeared to be spared.[44]

Considering the large interindividual variability of the activity of drug-metabolising enzymes in cirrhotic patients, it is difficult to give general rules for the dose adjustment of low extraction drugs in this group of patients. For drugs that are new on the market, kinetic studies in patients with impaired hepatic function due to liver cirrhosis are requested by the drug agencies prior to approval. Dosing recommendations for most of these drugs can, therefore, be found in the physician's desk reference or similar publications, but usually only for patients with Child-Pugh class A or B, but not C.[62]

Despite the finding that conjugation reactions are also impaired in cirrhotic patients, it appears to be justified to preferentially recommend drugs that are mainly eliminated by conjugation, since only one metabolic pathway is involved. If no studies are available, we recommend using a maintenance dose

of 50% of normal in patients with Child-Pugh class A and of 25% in patients with Child-Pugh class B and to adjust this dose according to the pharmacological effect and toxicity. For Child-Pugh class C patients, we recommend the use of drugs whose safety has been demonstrated in clinical trials and/or whose kinetics is not affected by liver disease or for which therapeutic drug monitoring is available.

1.3.3 Low Extraction Drugs with High Binding to Albumin

Low extraction drugs with a high binding to albumin (≥90%) may represent an exception from the rule that hepatic clearance is mainly determined by the activity of drug-metabolising enzymes (Cl_i). In patients with reduced serum albumin levels, a frequent finding in patients with liver cirrhosis, the free fraction (and possibly also the free concentration) of such drugs is increased. Assuming that there is a first order reaction (the reaction velocity is proportional to the free drug concentration), such drugs may, therefore, be metabolised more rapidly in cirrhotic patients. According to equation 3, the hepatic clearance of such drugs may remain unchanged or may even be increased in cirrhotic patients. However, this argumentation is only valid when the total drug concentration (free and bound to albumin in this case) is considered. For the free concentration only, f_u would equal 1 and Cl_{hep} for low extraction drugs would approach Cl_i.

Importantly, in patients with hypoalbuminaenia, the total plasma concentration of drugs with a high binding to albumin is decreased when their free concentration is in the normal range (due to a decrease in drug concentration bound to albumin) [see figure 4 for an explanation]. In order to avoid toxicity by overdosing, free drug concentrations should be determined and used to guide the therapy of such drugs in cirrhotic patients, e.g. for phenytoin or valproate.

1.3.4 Intermediate Extraction Drugs

The hepatic clearance of drugs with a hepatic extraction between 30% and 60% ('intermediate extraction' drugs) is determined by both the blood flow across the liver and (f_u x Cl_i). Since the bioavailability of these drugs is ≥40%, the influence of porto-systemic shunts is less pronounced than with high extraction drugs (see table III). In general, the hepatic clearance of these drugs is reduced, which necessitates the adjustment of their maintenance dose. Treatment should be started with an initial dose in the low range of normal and mainte-

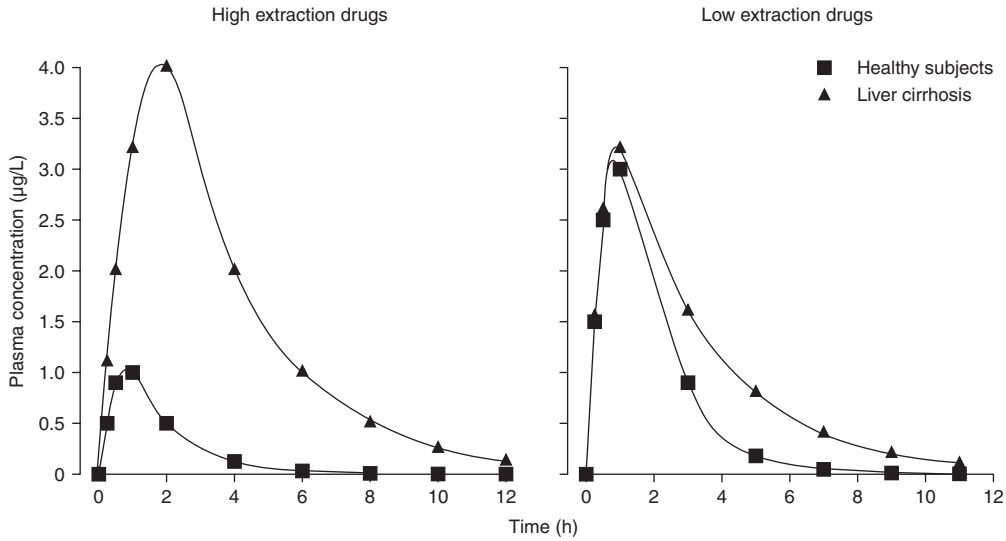

Fig. 2. Effect of liver cirrhosis on the kinetics of drugs with high or low hepatic extraction. For drugs with a high hepatic extraction, the maximal plasma concentration and bioavailability of the drug increases and elimination is slowed. For drugs with a low hepatic extraction, only elimination is slowed. Accordingly, for drugs with a high hepatic extraction that are administered orally, both initial and maintenance doses have to be reduced, whereas for drugs with a low hepatic extraction, only the maintenance dose has to be adapted.

Table III. Comparison of the oral bioavailability of selected drugs in healthy control subjects and patients with liver cirrhosis

Drug	Bioavailability (fraction of 1)			Reference
	Control subjects	Cirrhotic patients	Increase (factor)	
Clomethiazole	0.10 ± 0.07	1.16 ± 0.25	11.6	32
Encainide	0.26 ± 0.20	0.76 ± 0.42	2.92	33
Flumazenil	0.28 ± 0.06	0.65 ± 0.26	2.32	34
Labetalol	0.33 ± 0.09	0.63 ± 0.19	1.91	35
Pethidine	0.48 ± 0.13	0.87 ± 0.27	1.81	36
Midazolam	0.38 ± 0.16	0.76 ± 0.37	2.00	37
Morphine	0.47 ± 0.14	1.01 ± 0.43	2.15	38
Nifedipine	0.51 ± 0.17	0.91 ± 0.26	1.78	39
Nisoldipine	0.04 ± 0.02	0.15 ± 0.10	3.75	40
Pentazocine	0.18 ± 0.05	0.68 ± 0.21	3.78	36
Propranolol	0.36 ± 0.02	0.60 ± 0.10	1.67	41
Verapamil	0.10 ± 0.02	0.16 ± 0.05	1.60	42

nance doses should be adjusted as described in section 1.3.2 for low extraction drugs. Examples of such drugs are listed in table II.

1.3.5 Problems in the Classification of Drugs According to Hepatic Extraction

In order to compare the prediction of the kinetic behaviour of drugs as estimated using hepatic extraction with kinetic studies performed in patients with liver cirrhosis, we recently studied the antineoplastic agents on the market in Switzerland (Krähenbühl S, unpublished data). Of the 64 antineoplastic drugs that were identified, the available kinetic data of only 49 were sufficient to allow a classification according to hepatic extraction. However, values for hepatic extraction (E) are published only for a minority of them. E, therefore, had to be estimated based on the bioavailability or by using the following equation (derived from the definition of E in section 1.3 and from the definition of Q_0) [equation 5]:

$$E = \frac{Q_0 \times CI_{sys}}{Q} \quad \text{(Eq. 5)}$$

where Q_0 is the fraction of a drug metabolised by the liver ($Cl_{hep} = Q_0 \times Cl_{sys}$), Cl_{sys} is the systemic clearance of the drug and Q is the liver blood flow. The values for Q_0 and Cl_{sys} can be obtained from different sources.[62-64]

Both approaches, whether using oral bioavailability as a surrogate for hepatic extraction or the calculation of hepatic extraction using equation 5, have their limitations. Oral bioavailability can be <100%, not only because of a first liver pass effect but also because of incomplete dissolution of tablets in the gut, incomplete absorption in the gut and/or degradation in the enterocytes (see figure 1). Enterocytes contain CYP3A4, which can metabolise CYP3A4 substrates such as midazolam[65] or ciclosporin[66] before they reach the liver. They also contain P-glycoprotein, which can transport drugs from the enterocytes back to the intestine (as shown for digoxin).[67] On the other hand, oral bioavailability can be measured directly in humans, which is difficult for hepatic extraction. A weakness of the calculation of hepatic extraction using equation 5 is that the systemic clearance of a drug is usually measured in plasma and not in blood. For substances with a different concentration in plasma and in erythrocytes (e.g. drugs that are trapped in erythrocytes such as ribavirin), the results of this approach will, therefore, be wrong. Thus, in our study on antineoplastic drugs (Krähenbühl S, unpublished data), we used both approaches and detected an acceptable agreement between them. The hepatic extraction of high extraction drugs in table II was calculated according to equation 5.

1.4 Renal Clearance

It is well established that patients with cirrhosis have reduced effective renal plasma flow and glomerular filtration rates, even in the absence of ascites.[68-70] On the other hand, several studies have shown that patients with liver cirrhosis tend to have low serum creatinine levels,[71-73] which indicates

that glomerular filtration rates cannot be estimated using the serum creatinine level. The low serum creatinine level in cirrhotic patients can be explained by impaired synthesis of creatine and a reduced skeletal muscle mass.[73] For the same reasons, calculation of the creatinine clearance using the Cockcroft formula[74] may overestimate the rate of glomerular filtration.[75-77]

Theoretically, the determination of the creatinine clearance based on urinary excretion of creatinine should yield accurate results, even in patients with impaired creatine synthesis and/or reduced muscular mass. Although one study has shown that the measured creatinine clearance reflects glomerular filtration in cirrhosis accurately,[75] other studies indicate that glomerular filtration is overestimated, in particular in patients with reduced glomerular filtration rates.[72,77-79] This finding has been explained by an increased secretion of creatinine in cirrhotic patients.[73,80] The serum cystatin C level, another endogenous marker for renal function, may reflect glomerular filtration more accurately in cirrhotic patients.[72]

Since the glomerular filtration rate is usually decreased in patients with liver cirrhosis, drugs with mainly renal elimination and a narrow therapeutic range should also be dosed with caution in this group of patients. A decreased renal elimination in cirrhotic patients has been shown for several drugs, including cefpiramide,[81] cilazapril,[82] fluconazole,[83] lithium[84,85] and ofloxacin.[86,87] As discussed previously, the serum creatine level is not accurate enough to be used as a marker for glomerular filtration in these patients. It should be replaced by the estimated or measured rate of creatinine clearance, but it has to be taken into account that creatinine clearance tends to overestimate glomerular filtration in cirrhotic patients.

Although it is well established that liver disease can be associated with impaired renal function, it is less clear whether impaired renal function may also affect the hepatic metabolism of drugs. Indeed, in patients with renal failure, CYP-associated drug metabolism has been shown to be impaired,[88] in particular for CYP2D6. Similar observations have been reported for rats with renal failure, where several CYPs show a reduced hepatic expression.[89] The clinical relevance of these findings has been demonstrated among others for metoclopramide (a CYP2D6 substrate), which reveals an overproportional reduction in total body clearance in patients with renal failure.[90]

1.5 Cholestasis

Cholestasis can impair the activity of several CYPs, for instance CYP2C[50] and CYP2E1.[43] In patients with cholestasis, drugs that are metabolised by CYPs can, therefore, have a diminished hepatic clearance, potentially requiring adjustment of their dose.

Although it is conceivable that drugs with predominant biliary elimination may have a decreased clearance in patients with cholestasis, it is surprising that kinetic studies exist for only a few of such drugs. Kinetics and dynamics have been investigated in cholestatic patients, particularly for antineoplastic agents (including vinca alkaloids,[91,92] doxorubicin and derivatives[93-95] and dactinomycin).[96] These studies resulted in recommendations for dose adjustment according to the serum bilirubin level and/or activity of alkaline phosphatase.[96] However, it remains unclear whether these two parameters are the best markers for dose adjustment in patients with cholestasis or whether other enzyme activities and/or the serum bile acid level would be more accurate. Considering the impact of cholestasis on the kinetics and dynamics of antineoplastic drugs (Krähenbühl

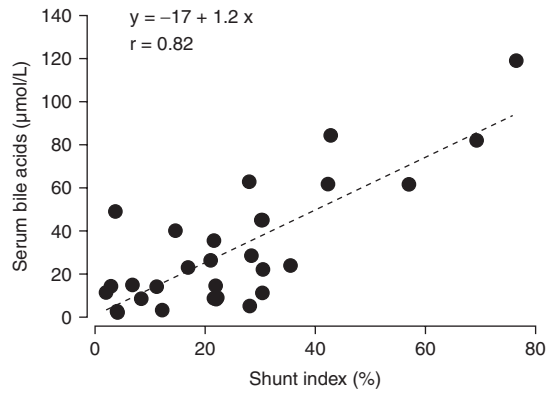

Fig. 3. Relationship between serum bile acid level and the hepatic shunt index. As described by Ohkubo et al.,[20] there is a linear relationship between these two variables. The determination of the serum bile acid level may, therefore, be suitable for predicting the proper dosing of drugs with a high hepatic extraction in cirrhotic patients.

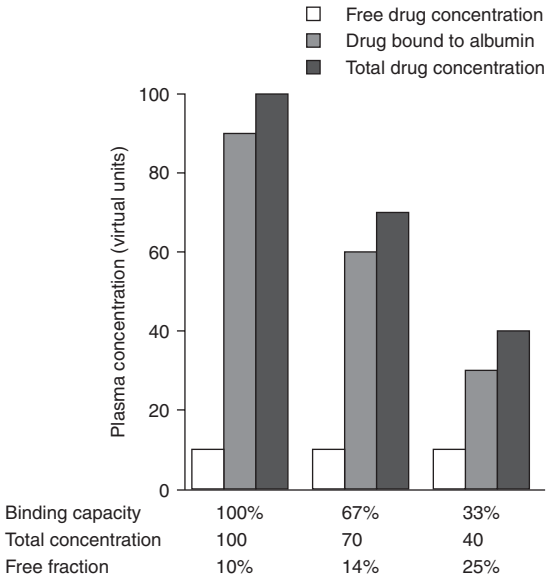

Fig. 4. Effect of the serum albumin level on the total serum concentration and free fraction of drugs with high albumin binding. The free concentration of a drug with high binding to albumin (≥90% at a normal serum albumin level) is kept constant at a plasma concentration of 10. Under normal conditions (binding capacity 100% at a normal serum albumin level), 90% of the drug is albumin-bound and 10% is free. The total plasma concentration is 100. When the serum albumin level is lowered by one-third (binding capacity 67%), the free concentration remains at 10. The free fraction increases to 14% and the total serum concentration decreases to 70. After lowering the serum albumin level to 33% of normal (binding capacity 33%), the free concentration remains 10, the free fraction increases to 25% and the total serum concentration of the drug drops to 40. When the free fraction of a drug is above normal, the reason for this finding should be sought and the free drug concentration should be used for therapeutic drug monitoring.

S, unpublished data), it is crucial that kinetic studies in cholestatic patients are also performed with other drugs that exhibit a predominant biliary excretion and/or enterohepatic cycling, e.g. phenprocoumon, mycophenolate mofetil and others.

2. Liver Disease and Adverse Effects of Drugs

Dose adaptation in patients with liver disease is aimed at reducing the dose-dependent adverse effects of drugs (type A reactions). In contrast to type A reactions, adverse drug reactions independent of the dose (idiosyncratic or type B reactions) may not be avoidable by dose reduction.

Considering systemic adverse effects, the usefulness of dose adaptation in patients with liver disease is most clearly evident for antineoplastic agents, which are generally associated with dose-dependent, systemic adverse effects. For some of them, as discussed, recommendations for dose adaptation in patients with liver disease have been established.[96]

Regarding adverse effects that affect the liver itself, most such events are type B reactions.[97] Only a few drugs reveal a dose-dependent hepatic toxicity, including methotrexate,[98] paracetamol (acetaminophen)[99,100] and isoniazid.[101,102] Therefore, patients with pre-existing liver disease who are treated with one of these drugs may be at a higher risk for hepatic toxicity than patients without liver disease. For methotrexate, alcoholic patients have an increased risk of developing liver fibrosis and cirrhosis.[98] The mechanism for this increase in methotrexate toxicity is not completely clear, but may be due to the presence of two different agents that are associated with liver fibrosis and possibly cirrhosis.[98] Similarly, alcoholic patients are more susceptible to the hepatotoxic effects of paracetamol. An important factor for this finding is the induction of CYP2E1 by alcohol, which increases the generation of N-acetyl-p-benzoquinone imine, a toxic metabolite of paracetamol.[99,100] For isoniazid, both pre-existing liver cirrhosis and ingestion of too much alcohol appear to be risk factors for hepatic toxicity.[101,102] Since isoniazid is also metabolised by CYP2E1, increased hepatic toxicity in alcoholics may also be due to the induction of CYP2E1 by alcohol.[103]

The occurrence of hepatic microvesicular steatosis that is associated with the ingestion of drugs is a typical type B reaction. Microvesicular steatosis is a life-threatening condition caused by impaired β-oxidation of liver mitochondria[104,105] and has been described in patients treated with valproic acid,[106] analgetic doses of aspirin (acetylsalicylic acid),[106] certain opiates [107] or the uricosuric benzbromarone.[108] Since microvesicular steatosis is considered to be more frequent in patients with a pre-existing mitochondrial disorder, e.g. a defect in β-oxidation or in the urea cycle, or a mitochondrial cytopathy,[109] certain pre-existing liver diseases may also be risk factors for type B reactions.

Although, as described previously, pre-existing liver disease and also enzyme polymorphisms[110,111] or specific HLA genotypes[112,113] can represent risk factors for drug-induced liver disease, it is important to realise that hepatic injury is not the typical adverse reaction associated with the drugs used in patients with liver cirrhosis. The drugs used in this group of patients (in particular diuretics and centrally active drugs) much more often impair renal function and/or induce encephalopathy (see section 3).

3. Pharmacodynamics

Patients with liver cirrhosis have been reported to be more sensitive to the central adverse effects of morphine[57,114] and benzodiazepines,[115,116] and to renal adverse effects of NSAIDs,[117] whereas the sensitivity to the natriuretic effect of loop diuretics was found to be reduced.[6]

An early study described precipitation of hepatic encephalopathy after IV administration of morphine in patients with decompensated liver cirrhosis at low doses (8mg IV).[114] In contrast, in a more recent study, none of six cirrhotic patients developed encephalopathy after the IV administration of higher doses of morphine.[118] Since several studies have shown that the oral bioavailability of morphine is increased and its elimination is impaired,[38,58,119] morphine should be used with caution in patients with cirrhosis, irrespective of the presence of an increased sensitivity to central adverse effects.

Patients with liver cirrhosis appear to be extremely sensitive to the sedative effects of benzodiazepines.[115,116] In these patients, benzodiazepines may induce encephalopathy, which can be reversed by the administration of benzodiazepine antagonists.[120] Although impaired hepatic metabolism has been demonstrated in patients with cirrhosis for midazolam[115] and diazepam,[48,49,116,121] no such changes were detected for oxazepam,[46] temazepam[47] or triazolam,[122] which suggests that the increased sedation of benzodiazepines in cirrhotic patients is partially due to pharmacodynamic alterations.

Despite their disadvantages, benzodiazepines are difficult to replace as sedatives in cirrhotic patients. Antipsychotic agents undergo extensive hepatic metabolism and can also cause neurological adverse reactions.[123] Contrary to the benzodiazepines, they have the disadvantage that they cannot be antagonised. Clomethiazole, a sedative used widely for the prevention of delirium tremens in Europe, has a high first liver pass effect with an unpredictable oral bioavailability in cirrhotic patients[32] (see table III). As illustrated in the introduction of this article, an unexpectedly high bioavailability can result in toxic drug concentrations with life-threatening respiratory depression. Considering benzodiazepines, substances with a long half-life should be avoided and those eliminated by conjugation only, e.g. oxazepam or lorazepam, should be preferred.

In comparison to healthy individuals, a higher tubular concentration of diuretics is needed in cirrhotic patients to excrete a given amount of sodium. This has been shown for the loop diuretics torasemide,[124,125] bumetanide[126] and furosemide.[125,127,128] For torasemide, a diuretic that is metabolised by the liver, the kidney compensates for reduced hepatic metabolism in patients with cirrhosis. A larger proportion of the drug is, therefore, eliminated by the kidney and leads to an apparently normal pharmacological effect in cirrhotic patients.[124]

NSAIDs are known to precipitate renal failure in patients with cirrhosis and ascites.[117] Patients with portal hypertension have a low peripheral resistance and hyperdynamic circulation due to an increased production of vasodilating substances such as nitric oxide.[129] In order to prevent a large drop in the arterial pressure, the renin angiotensin aldosterone and the sympathetic nervous system are activated, which leads to renal arterial vasoconstriction. For the maintenance of a sufficient filtration pressure, local production of vasodilatory prostaglandins is necessary for dilating the renal arteries. After ingestion of NSAIDs, renal production of prostaglandins is abolished and eventually leads to renal failure in cirrhotic patients. Although no clinical data have been published for selective cyclo-oxygenase (COX)-2 inhibitors, and renal function was not impaired by the administration of a selective COX-2 inhibitor in cirrhotic rats,[130] it is 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.[131]

4. Conclusions

The most dangerous drugs in patients with liver cirrhosis are those with a low hepatic extraction and a narrow therapeutic range. If such drugs are administered orally, both initial and maintenance doses have to be reduced by ≥50% of the normal dose, depending on the severity of liver disease, hepatic extraction and metabolism, and toxicity of the drug. If such drugs are administered parenterally, only the maintenance dose has to be adapted according to hepatic clearance. For most other drugs metabolised by the liver (intermediate or high hepatic extraction agents), only the maintenance dose has to be adjusted.

It is important to realise that renal function can be impaired in cirrhotic patients despite normal serum creatinine levels. If no immediate pharmacological effect is needed, drug therapy should be started cautiously in this group of patients and titrated individually until the desired pharmacological effect is achieved or toxicity appears. Obvious gaps in our knowledge about the kinetic behaviour of drugs in patients with liver disease include data about hepatic extraction and kinetic studies of drugs with biliary elimination in patients with cholestasis.

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