

# **Dose Adaptation of Drugs in Patients with Liver Disease**

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## Abbreviations

ADR	adverse drug reaction
ALT	alanine aminotransferase
ASAT	aspartate aminotransferase
AUC	area under the curve
BW	body weight
$Cl_{\text{hep}}$	hepatic clearance
$Cl_{\text{in}}$	intrinsic hepatic clearance
$Cl_{\text{sys}}$	systemic clearance
$C_{\text{max}}$	maximum concentration
CYP450	cytochrome P450 isoenzyme
$E_h$	hepatic extraction
ECG	electrocardiogram
EEG	electroencephalogram
F	bioavailability
$f_u$	unbound fraction
GI	gastrointestinal
h	hour
HAV	hepatitis A virus
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
i.v.	intravenous
INR	international normalized ratio
Q	blood flow across the liver
$Q_0$	extrarenal dose fraction
min	minutes
MEGX	monoethyl glycinexylidine
NSAID	non steroidal anti-inflammatory drugs
PB	Fraction bound to proteins (protein binding in %)
PD	pharmacodynamics
PK	pharmacokinetics
s	seconds
SD	standard deviation of the mean
TDM	therapeutic drug monitoring
$T_{\text{max}}$	time point of $C_{\text{max}}$
$t_{1/2}$	half live
ULN	upper limit of normal
$V_d$	volume of distribution



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# 1 Summary

A detailed introduction into the topic was obtained by developing a German-language online course named “Dose adjustment in Patients with Liver Disease” for the “Swiss Virtual Campus” in collaboration with PNN AG, a spin-off company of the ETH Zurich. This was followed by the German-language publication “Dosage Adaptation in Patients with Liver Disease” in “Grundlagen der Arzneimitteltherapie”, Documed, 2005, and an additional German-language online course for pharmacists named “Dose Adaptation of Drugs in Patients with Liver Insufficiency” published by PNN AG. The documents of these online courses and German publications can be found in the electronic appendix on CD-ROM.

This extensive introduction into the topic was followed by the actual investigational thesis.

The aim of the thesis was to define strategies for dose adaptation of drugs in patients with liver disease. The main focus was to compare the prediction of the kinetic behaviour as estimated using hepatic extraction with kinetic studies performed in patients with liver cirrhosis. For this purpose, the antineoplastic drugs and the central nervous agents on the market in Switzerland were studied.

In chapter 2 and 3, a general introduction and recommendation of dosing in liver disease is given.

Chapter 4 contains a more detailed description of the online course about dose adaptation in liver disease for the Swiss Virtual Campus.

Chapter 6 contains the results of the literature research for kinetic studies in liver disease subdivided into the class of antineoplastic drugs (chapter 6.1) and psychotropic drugs (chapter 6.2). For each drug, the pharmacokinetic information was collected and drugs were classified according to their bioavailability / hepatic extraction in order to predict their kinetic behaviour in patients with decreased liver function as illustrated in chapter 3. These predictions were compared with kinetic studies in patients with liver disease. Furthermore, both the dose dependent and liver specific adverse reactions were listed, the identified kinetic studies in liver disease summarized for each drug and specific dosing recommendations given.

In conclusion, there are currently not enough data for the safe use of cytostatics and psychotropic drugs in patients with liver disease. There are obvious gaps about the kinetic behaviour of drugs in patients with liver disease, in particular concerning data about hepatic extraction and kinetic studies of drugs with biliary elimination in patients with cholestasis.

Pharmaceutical companies should be urged to provide kinetic data (especially hepatic extraction) needed for the classification of such drugs. Kinetic studies should be conducted in patients with impaired liver function for drugs with primarily hepatic metabolism, allowing to give quantitative advise for dose adaptation.

## 2 General Introduction

Liver insufficiency describes a partial or complete loss of liver function. Such functional deficiencies are mainly the result of “hepatic disease”, a general term integrating a set of diverse diseases and symptoms. Hepatic disease may be caused by viral, bacterial or parasitic infectious agents, xenobiotics, autoimmune diseases, genetic accumulation diseases (e.g. hemochromatosis, Wilson’s disease), enzyme birth defects (e.g.  $\alpha$ -1 antitrypsin deficiency) or liver stasis due to an obstructed liver vein.

The term “cirrhosis of the liver” for its part describes the shared consequence of such chronic liver diseases and becomes manifest in characteristic changes like cell death and pathological repair processes resulting in nodular regeneration, fibrosis and the generation of portasystemic shunts. Liver disease has general implications for health (nutritional and metabolic balance, maintenance of body fluid and electrolyte balance, coagulation control). Portasystemic shunts and the restricted metabolic capacity of the cirrhotic liver lead to alterations in the pharmacokinetics of predominantly hepatically eliminated drugs, which may result in toxically increased blood levels, thereby requiring a dose adjustment of these drugs (1, 2).

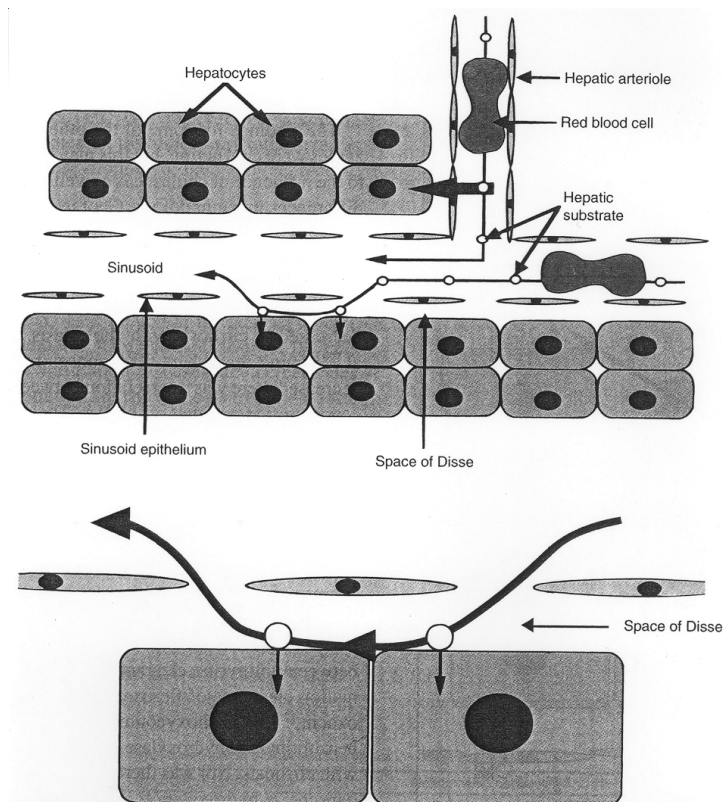
### ***2.1 Liver anatomy and function***

The liver lies in the right upper abdominal cavity, in contact with the diaphragm. In the adult, the liver weighs between 1.4 – 1.6 kilograms. It is perfused by 1.5 liter blood per minute and requires 20% of the total body oxygen supply for its numerous functions. The liver is situated in a strategically important position, since it is not only fed with oxygen rich blood by the hepatic artery (Arteria hepatica), but also by the portal vein (Vena portae), which carries to the liver the joined venous blood of the venous plexuses of all unpaired abdominal viscera such as the stomach, spleen, pancreas and intestine (3).

The two afferent blood vessels are accompanied by the leaving bile ducts (Ducti hepatici). The interior anatomy adheres to this trio known as Glisson trias, until the V. portae and the A. hepaticae branch out in all directions and discharge together in the capillaries hence containing mixed blood. These sinusoids run between the narrow

cell rows of hepatocytes, joining in a star formation at the Vena centralis, which collects the blood from the sinusoids and drains into the Vena hepatica (4).

The endothelial tissue of the liver sinusoids is equipped with Kupffer cells which play a role in the recycling of red blood cells and the cellular defense of the innate immune system. Typically, liver sinusoids do not own a basement membrane. This, together with the prominent fenestrae in the endothelium, allows the free flow of plasma but not cellular elements (5). The plasma is thus in direct contact with hepatocytes in the subendothelial space of Disse. This space is crucial for the exchange of material between the sinusoids and the hepatocytes, and may be obliterated in liver disease (figure 2.1).



**Figure 2.1** Schematic representation of the relationships between the hepatic sinusoid, the space of Disse and hepatocytes in the healthy liver. Top: the anatomy of the junction between a hepatic arteriole and the sinusoid in addition to the macroscopic relationships. Bottom: the free exchange of fluid and substrate(s) between the sinusoidal lumen and the space of Disse (Morgan et al., 1995).

The space of Disse also contains Ito cells which store fat or fat soluble vitamins. Ito cells seem to play a major role in the generation of fibrosis and cirrhosis of the liver.



The hepatocytes are connected by gap junctions and equipped with microvilli that point into the space of Disse with the objective of surface area amplification and optimization of exchange. The intercellular space of the hepatocytes is welded together by tight junctions to form the canaliculi (Canaliculi biliferi), into which the bile product of the hepatocytes is secreted. Where the hepatocytes are intact and the junctions tight, no bile reaches the sinusoidal blood (4).

By way of the hepatic artery (A. hepatica) and the portal vein (V. portae) the liver is provided with the required substrates for its numerous synthetic, metabolic and secretory functions. In addition, the liver detoxifies both naturally occurring and foreign substances (xenobiotics) in the body. For all substances resorbed in the gastrointestinal tract, the liver operates as a barrier prior to the systemic circulation, and is more or less passable, depending on the chemical characteristics of the substance. For substances which directly enter into the systemic circulation, e.g. by intravenous application, or which have reached the systemic circulation after the first liver passage, the liver – in addition to the kidneys and the lungs – again plays a pivotal role in the elimination process (3).

## ***2.2 Liver diseases relevant for drug metabolism***

### **Liver cirrhosis**

Cirrhosis often represents the final common pathway of a number of chronic liver diseases. The development of cirrhosis is characterized by the appearance of fibroblasts and collagen deposition in the liver. This is accompanied by a reduction in liver size and in the formation of nodules of regenerated hepatocytes. These modifications are associated with - and may be responsible for - a reduction in liver blood supply, the presence of intra- and extrahepatic portal-systemic shunting, capillarization of the sinusoids (loss of fenestrae in sinusoidal epithelia) and a reduction in the number and in the activity of the hepatocytes (1). Loss of functioning hepatocellular mass and capacity may lead to jaundice, edema, coagulopathy and a variety of metabolic abnormalities which may contribute to alterations in the pharmacokinetic behavior of many drugs; fibrosis and distorted vasculature lead to portal-hypertension and its sequelae, including gastro-esophageal varices and porto-systemic shunts. Ascites and hepatic encephalopathy results from both

hepatocellular insufficiency and portal-hypertension (4, 6). Cirrhosis can alter the relationship between serum drug concentration and response. A general principle is that the pharmacological response to a drug is a function of its free concentration in blood. An increase in the free fraction of some drugs, as a result of a reduced serum albumin concentration, is one of the well-known effects of cirrhosis (7).

### **Alcoholic liver cirrhosis**

Alcoholic cirrhosis is the most common type of cirrhosis. With continued alcohol intake and destruction of hepatocytes, fibroblasts appear at the site of the injury and deposit collagen. With continuing hepatocyte destruction and collagen deposition, the liver shrinks in size and acquires a nodular appearance. Alcoholic cirrhosis may be clinically silent, and many cases (10 to 40%) are discovered incidentally.

Although patients with liver cirrhosis may stabilize if drinking is discontinued, over a period of years, patients may become emaciated, weak, and chronically jaundiced. Ascites and other signs of portal hypertension may become increasingly prominent. Progressive renal dysfunction often complicates the terminal phase of the illness (4).

### **Viral hepatitis**

Hepatitis is an inflammatory condition of the liver that is caused by viruses or hepatotoxins. Viral hepatitis is a systemic infection affecting the liver predominantly which is in almost all cases caused by one of five viral agents: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV) and hepatitis E virus (HEV). Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce a clinically similar illness. This ranges from asymptomatic and unapparent to fulminant and potentially fatal acute infections common to all types, on the one hand, and from subclinical persistent infections to rapidly progressive chronic liver disease with cirrhosis and even hepatocellular carcinoma (8). Several informative studies about the effects of acute viral hepatitis on drug disposition were conducted (9-11). A small number of patients were studied during the time when they had acute viral hepatitis and subsequently after recovery. The drugs that were administered included phenytoin (9), tolbutamide (10), warfarin (11) and lidocaine

(12). The most consistent finding was that the plasma protein binding of both phenytoin and tolbutamide was reduced during acute hepatitis. No consistent changes were observed in warfarin and lidocaine kinetics during acute viral hepatitis. The reason for this difference is not clear. In general, drug elimination during acute viral hepatitis is either normal or only moderately impaired. Observed changes tend to be variable and related to the extent of hepatocellular damage incurring. If the acute hepatitis resolved, drug disposition returns to normal. Drug elimination is likely to be impaired most significantly in patients who develop chronic hepatitis B virus-related liver disease, but even then only late in the evolution of this disease (13).

## **Cholestasis**

Cholestasis is the result of impaired hepatobiliary transport of substances and water and may be classified as extra- or intra-hepatic.

Extra-hepatic cholestasis encompasses conditions with physical obstruction of the bile ducts, which is usually located outside the liver. In intra-hepatic cholestasis, there is no demonstrable obstruction of the major bile ducts. Causes are e.g. drug-induced cholestasis or hormones (14). Prolonged cholestasis can lead to biliary cirrhosis; the time taken for its development varies from months to years.

Cholestasis causes the retention in the blood of all substances normally excreted in the bile. In patients with cholestasis, the clearance of drugs with predominant biliary elimination is reduced, serum bile acids are increased. It appears that drugs metabolized by CYP's may also have a diminished hepatic clearance in patients with cholestatic liver disease, potentially needing adjustment of their dose (15-17).

## **2.3 Assessment of liver function**

Although there are numerous causes of hepatic injury, it appears that the functional consequences are determined more by the extent of the injury than by the cause. At this time there is no generally available test that can be used to correlate changes in drug absorption and disposition with the degree of hepatic impairment. Measurements such as creatinine clearance have been used successfully to adjust dosing regimens for drugs eliminated primarily by the kidneys. Similar measures of hepatic function have been sought using endogenous substances affected by the liver such as bilirubin and albumin, or functional measures such as prothrombin time,

or the ability of the liver to eliminate marker substrates such as antipyrine (18), indocyanine green (18), monoethylglycine-xylidide (MEGX) (19), and galactose (20). Despite extensive efforts, no single measure or group of measures has gained widespread clinical use to allow estimation in a given patient of how hepatic impairment will affect the pharmacokinetic and/or pharmacodynamic of a drug. The primary problem shared by all these test substrates is the considerable intersubject variability in their clearance, both in healthy individuals and in patients with liver disease, usually leading to considerable overlap between these two groups (21-23). Another difficulty is represented by some confounding factors in the interpretation of the pharmacokinetic results of CYP-dependent test substrates, such as influence of genetics, age, gender, environmental factors and the concomitant administration of other drugs that modify the activity of the metabolizing enzymes in the liver (7).

An useful classification scheme that is used most commonly in studies designed to formulate drug dosing recommendations for patients with liver disease is the Pugh modification of Child's classification of liver disease severity (Table 2.1) (24). The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5 to 15. Child-Pugh class is either A (a score of 5 to 6), B (7 to 9), or C (10 and above).

**Table 2.1** Pugh modification of Child's classification of liver disease severity

Assessment parameters	Assigned score		
	1 point	2 points	3 points
Encephalopathy grade *	0	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, mg/dL	1-2	2-3	>3
Serum albumin, g/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin time (sec >control)	1-4	4-10	> 10

**Classification of clinical severity**

Clinical severity	Mild	Moderate	Severe
Total points	5-6	7-9	>9

**\* Encephalopathy grade**

Grade 0	normal consciousness, personality, neurological examination, electroencephalogram
Grade 1	restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2	lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3	somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4	unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

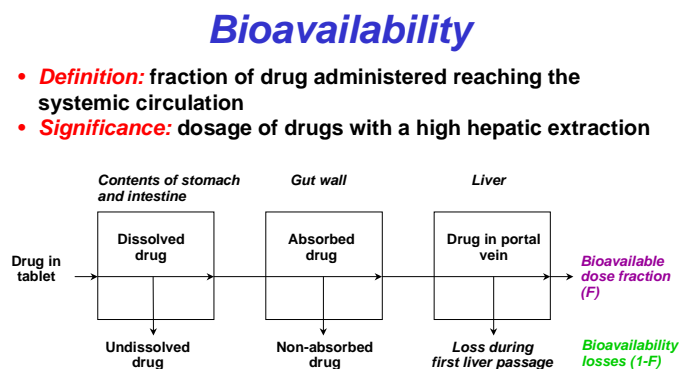


### 3 General Recommendation of Dosing in Liver Disease

#### 3.1 Drug metabolism and liver disease

##### Pharmacokinetics

A drug's portion reaching the systemic circulation denotes the bioavailable fraction of a dose. By definition, the bioavailability ( $F$ ) of an intravenously applied drug equals 1, thus 100%, its bioavailable fraction corresponding to the entire dose. If the same drug is administered orally, the value of 100% is rarely attained. Generally, the bioavailability of an orally administered drug varies between 0-1, thus between 0-100%. This is due to a set of obstacles an oral dose has to overcome before reaching the systemic circulation. Indeed, the liver is not the only obstacle, but represents the most dominant one, since dissolution and solubility are already optimized by appropriate galenics in most pharmaceutical preparations. The liver's influence on the bioavailability is called "first liver pass effect" or in short "first pass effect" (figure 3.1)



**Figure 3.1** 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 systemic circulation is either not absorbed or metabolized during the first passage across the liver. Patients with liver cirrhosis and/or portal hypertension can have intra- and extrahepatic porto-systemic shunts, preventing the drugs from reaching the hepatocytes and from being metabolized. Furthermore, important drug-metabolizing enzymes have a reduced activity in cirrhotic livers. These are the two main factors being responsible for an increase in the bioavailability of high extraction drugs in cirrhotics (Delco et al., 2005).

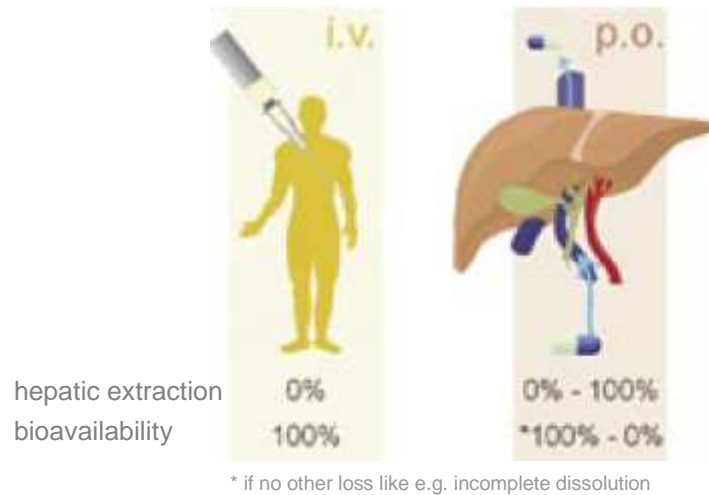
The extent of the effect depends on the characteristics of the drug. For our present purposes, those drugs with  $Q_0$  values  $< 0.5$  can be ignored in terms of liver metabolism, some exceptions of which will be discussed later. The  $Q_0$  value (the extrarenal dose fraction) represents the proportion of a dose *not* excreted unchanged in the urine, thus the proportion of the dose that is metabolized and/or biliary excreted. Otherwise, subtracting the  $Q_0$  value from 100% ( $1-Q_0$ ) gives the proportion of the dose which is excreted unchanged via the kidneys. Highly water-soluble drugs hold little  $Q_0$  values of  $< 0.5$ . They are predominantly excreted unchanged in the urine and the liver contributes less than 50% to the elimination of these drugs.

On the contrary, drugs owning  $Q_0$  values  $> 0.5$  are poorly water-soluble and have to be transformed into more water-soluble metabolites before their renal or biliar excretion. Therefore, the liver contributes more than 50% to the elimination of these drugs (25). These drugs thus possess one of the prerequisites for being processed during the first liver passage.

As regards the extent of the first liver pass effect, the drugs with  $Q_0$  values  $> 0.5$  can be further classified into two groups of drugs: those with high hepatic extraction ( $E_h$ ) and consequently low bioavailability and those drugs with low hepatic extraction associated with high bioavailability. In between these two groups lies the group of drugs with intermediate hepatic extraction and intermediate bioavailability (figure 3.2) (25). It is important to realize, that the problem with high extraction drugs (low bioavailability) does not consist primarily in the extensive reduction of the oral dose en route to the systemic circulation (this could be countersteered by applying higher doses), but in the intra- and interindividual highly variable extent of this reduction, resulting in poorly predictable blood levels.

As for the influence of liver disease on bioavailability, it is now easy to see, that all factors reducing the liver's capacity for hepatic extraction could dramatically and potentially toxically increase the bioavailability of normally highly extracted drugs. Therefore, the **initial dose** of **orally** applied high extraction drugs has to be reduced accordingly in the case of liver disease (25).





**Figure 3.2** Coherence between hepatic extraction and bioavailability (illustrated by PNN AG).

The appearance of the drug in the systemic circulation is immediately followed by the elimination process. Again, the influence of liver disease on drug elimination is relevant only for drugs with  $Q_0$  values  $> 0.5$ , since only these kind of drugs are predominantly (more than 50% of a dose) metabolized by the liver and/or biliary excreted.

The metabolic capacity of the liver is described by the intrinsic clearance ( $Cl_i$ ). The intrinsic hepatic clearance means the capacity of the liver to metabolize a certain drug without any limitations by the liver blood flow. It indicates the enzyme content of the liver. Together with the unbound fraction ( $f_u$ ) and the liver blood flow ( $Q$ ), the  $Cl_i$  determines the hepatic clearance ( $Cl_h$ ). The hepatic clearance, for its part, describes the blood plasma volume that is cleared per time from poorly water soluble drugs through formation of more water soluble metabolites.

In liver disease, the diminished exchange of materials between blood and hepatocytes as well as the reduced metabolic capacity may cause a decrease in hepatic clearance. This, in turn, will lead to prolonged elimination half-lives and potentially toxic accumulation of the drugs. Therefore, the **maintenance dose** of **intravenously** and **orally** applied drugs with  $Q_0$  values  $> 0.5$  has to be reduced accordingly in the case of liver disease (25).

## **Consequences of liver disease on drug kinetics**

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

### **Drug absorption**

Since patients with liver cirrhosis are frequently affected by gastritis and ulcers of the upper gastrointestinal tract (26, 27), absorption of orally administered drugs may be impaired. However, the amount of drug absorbed is generally not decreased in cirrhotic patients (28), but the absorption of orally administered drugs may be delayed in this group of patients. Delayed absorption, which is not explained by gastritis or ulcers, has for instance been shown for furosemide in cirrhotics (29, 30), but not for torasemide, another loop diuretic used in patients with ascites (29). The studies with furosemide suggested that impaired gastrointestinal motility may be the mechanism for delayed drug absorption in cirrhotic patients. Cirrhotic patients have indeed delayed gastric emptying (32, 33), possibly resulting from a decreased action of gastrointestinal hormones such as secretin, glucagon, cholecystokinin or motilin (30). In agreement with the proposed mechanism leading to this abnormality, prokinetic agents can speed up gastric emptying in cirrhotic patients (31, 32). Oral preparations coated with an acid resistant film, in particular those with delayed drug release, may therefore have a delayed and/or unpredictable onset of action in cirrhotic patients, and should be used with caution in this group of patients.

### **Drug distribution**

In patients with liver cirrhosis who have edema 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 beta-lactam antibiotics or for digoxin). Initial dosing of such drugs should therefore be performed according to body weight in cirrhotics with ascites. On the other hand, an increase in the volume of distribution is associated with an increase in the elimination half-life of such drugs (28). A slower elimination velocity in cirrhotics with ascites has indeed been demonstrated for furosemide (33, 34) and for beta-lactam antibiotics such as ceftazidime or cefprozil (37, 38). However, the

influence of edema and/or ascites on the elimination velocity of hydrophilic drugs used in this group of patients appears to be small and has therefore usually no practical consequences (33).

### **Drug metabolism**

Fibrosis impedes the flow of blood through the liver, consequently reducing the exchange of material between sinusoidal blood and hepatocytes. As a result, substances essential for synthesis are not provided adequately and xenobiotics, which are supposed to be detoxified by the liver, proceed into the systemic circulation. Drugs are likewise less exposed to the liver, which means a reduced drug metabolism. For drugs predominantly eliminated by the liver with  $Q_0$  values  $> 0.5$ , this may lead to a reduction of the hepatic clearance, followed by prolonged elimination half-lives and the danger of accumulation (2, 25).

The pathological formation of connective tissue in the space of Disse increases the flow resistance in the sinusoids. This may result in portal hypertension and provoke the generation of portasystemic shunts, which by-pass the obstructed sinusoids and lead the blood from the portal vein directly into the systemic circulation. In this way, oral drugs circumvent their metabolism during the first liver passage. For drugs with normally high hepatic extraction, this may manifest in an extensive reduction of hepatic extraction, which, in turn, may lead to a potentially toxic increase in bioavailability if the usual dose is administered (35).

With the loss of hepatocytes and reorganization of the connective tissue, the liver volume shrinks and the amount of well-functioning structures decreases. Such damage to the liver reduces the hepatic synthesis of proteins and enzymes. Diminished concentrations in metabolizing enzyme systems may reduce the intrinsic clearance of a certain drug. CYP P450-dependent systems are more often affected than conjugation reactions (36). For drugs with  $Q_0 > 0.5$  and a cytochrome-dependent metabolism, this may cause a decreased hepatic clearance, followed by prolonged elimination half-lives and the potential of accumulation.

Cirrhosis of the liver is often associated with reduced albumin synthesis (37). For drugs that are highly protein bound, the loss of albumin as a binding partner increases the free plasma fraction and possibly also the free plasma concentration. This allows a higher concentration of the unbound drug to be metabolized by the liver, which means that the hepatic clearance remains unchanged or even increases

a little, despite reduced intrinsic clearance. Only in the case of drugs with low hepatic extraction ( $Q_0 < 0.5$ ) and high albumin binding (>90%), however, might such a phenomenon prove clinically significant.

Liver cirrhosis may be accompanied by ascites (38). Ascites is caused by portal hypertension combined with reduced oncotic pressure due to hypalbuminemia. This results in an increased pressing out of fluid into the abdominal cavity. Cirrhotic changes of the liver may also impair bile excretion, leading to cholestasis. In the latter case, components of the bile enter the blood causing jaundice. The agonizing pruritus associated with this condition is probably caused by retained endorphins and/or bile salts. Decreased bile excretion into the intestine further causes fatty stools and malabsorption (e.g. vitamin K deficiency → increased risk of bleeding). In addition, cholestasis reduces the activity of drug metabolizing enzymes, hence reducing the clearance of predominantly hepatically eliminated and/or biliary excreted drugs (15-17).

Hypalbuminemia is a common consequence of the cirrhotic liver, which, together with portal hypotension enhances the formation of ascites, as discussed above. Ascites is accompanied by hypovolemia. On the other side, vasodilatoric endotoxins from the intestine reach the systemic circulation in default of clearance by the intact liver and cause a dilatation of the arteries. This is answered by an extensive activation of the renin-angiotensin axis and the sympathetic nervous system, finally resulting in renal vasoconstriction. The ascites-induced hypovolemia and the activated sympathetic nervous system manifest in reduced renal blood circulation and reduced glomerular filtration followed by renal insufficiency. For this reason cirrhotics are often afflicted, not only with hepatic insufficiency, but also with renal impairment, and show a prolonged renal clearance of predominantly renally excreted drugs (38).

## Conclusion

In conclusion, the decreased blood flow, the reduction in liver volume, the impaired exchange of materials between sinusoids and hepatocytes, and damaged metabolic enzyme systems are all responsible for the decreased hepatic clearance of predominantly hepatically eliminated drugs ( $Q_0 > 0.5$ ) (table 3.1). An adjustment in the maintenance dose is therefore required. Furthermore, in the special group of predominantly hepatically-eliminated drugs with additional high hepatic extraction, the portasystemic shunts cause a reduction of the liver first-pass effect and therefore a rise in bioavailability. In this case, not only the maintenance dose, but also the initial dose of orally administered drugs has to be adjusted accordingly.

Table 3.1: Effects of liver cirrhosis on pharmacokinetics

	Changes in cirrhosis	Effect on $Cl_h$	Effect on $E_h$
Hepatic blood flow (Q)	↓	↓	∅
Portasystemic shunts	↑	∅	↓
Liver volume	(↓) → $Cl_i$ ↓	↓	∅
Cytochrome P450	↓ → $Cl_i$ ↓	↓	∅ – (↓)
Albumin synthesis	↓ → $f_u$ ↑	(↑)	∅

$Cl_i$  = intrinsic clearance /  $Cl_h$  = hepatic clearance /  $E_h$  = hepatic extraction  
 ↓ = decreases / ↑ = increases / ∅ = unchanged

### 3.2 General recommendation of dosing in liver disease

While renal function can be determined by creatinine clearance (39), there is no satisfactory alternative available for the assessment of liver function and capacity. In cirrhotics, usually neither the liver blood flow nor the extent of the portasystemic shunting is known. While the hepatic blood flow could be estimated by Doppler sonography and the bile acid concentration in the serum might indicate the extent of the portasystemic shunts (40), it is not clear yet, if this could contribute to the dosing in liver cirrhosis. Furthermore, the complexity of the drug metabolizing enzyme systems, inter- and intraindividual fluctuations of the hepatic clearance and the diversity of affecting factors like genetics, gender, age and environmental factors has made impossible the clinical acceptance of a single test substance (table 3.2).

To date, the risk for clinical relevant drug accumulations has to be estimated for each drug individually. This estimation is based on the kinetic properties of the drug, in particular the  $Q_0$  value and the hepatic extraction  $E_h$  of a certain drug. Values for  $Q_0$  values and hepatic extraction rates can partly be looked up in acts like the “Arzneimittelkompendium der Schweiz”, the “Physicians Desk Reference” and “Grundlagen der Arzneimitteltherapie” (edition 2005). For new drugs, the regulatory authorities require the data of kinetic studies in liver insufficiency. Dosage recommendations – as far as available - can be found in “Arzneimittelkompendium der Schweiz” or “Physicians Desk Reference” or similar publications.

In order to use the hepatic extraction  $E_h$  for dosage recommendations of predominantly hepatically-eliminated drugs ( $Q_0 > 0.5$ ), the term “ $E_h$ ” has to be described mathematically first and pulled together with hepatic clearance  $Cl_h$  and liver blood flow  $Q$ . For this, equation (1) and (2) are useful:

$$E_h = \frac{f_u \times Cl_i}{(f_u \times Cl_i) + Q} \quad (1)$$

$Cl_i$ : intrinsic clearance

$f_u$ : fraction unbound

Q: liver blood flow

$E_h$ : hepatic extraction rate

By multiplication of equation (1) by the liver blood flow Q, the equation for hepatic clearance  $Cl_h$  results:

$$Cl_h = E_h \times Q = \frac{Q \times f_u \times Cl_i}{(f_u \times Cl_i) + Q} \quad (2)$$

Hepatic clearance  $Cl_h$  refers to the volume of blood that is cleared by the liver of the drug per time unit.

### High extraction drugs

High extraction drugs undergo a high extraction during the first passage across the liver ( $\geq 60\%$ ,  $E_h \geq 0.6$ ), and therefore have a low bioavailability of  $\leq 40\%$  (figure 3.2). Highly extracted drugs are characterized by a high intrinsic clearance  $Cl_i$ . This means, that more enzyme capacity for a certain drug is present than drug is arriving by blood flow Q per time. Thus, the value of  $[f_u \times Cl_i]$  greatly exceeds the value of Q. Therefore, the addition of Q in the denominator of equations (1) and (2) can be neglected. The equations are reduced to:

$$\text{Since } (f_u \times Cl_i) \gg Q, \rightarrow E_h \approx 1 \quad (3) \quad \text{and} \quad Cl_h \approx Q \quad (4)$$

As shown by equation (4), changes in the liver blood flow Q directly influence the hepatic clearance  $Cl_h$ , and the hepatic clearance  $Cl_h$  of high extraction drugs mainly depends on Q. These drugs are therefore called “flow-limited” or “high extraction”.

### Dose adaptation of “high extraction drugs”

Since the blood flow across the liver is typically decreased in patients with liver cirrhosis (41, 42), elimination of high extraction drugs is retarded in comparison to patients with normal liver function. In addition to a decreased blood flow across the liver, patients with liver cirrhosis frequently have porta-systemic shunts, preventing



the exposure of drugs to hepatocytes (28, 43). As a consequence, a variable amount of portal blood is not cleared by hepatocytes, potentially leading to a significant increase in bioavailability of orally administered high extraction drugs (figure 3.3).

For example, the bioavailability of clomethiazole is 10% in healthy persons and may increase to 100% in patients with liver cirrhosis (44). This increase in bioavailability is associated with a 10-fold higher drug exposure, eventually leading to adverse drug reactions.

As a consequence of increased bioavailability, the **initial dose** of orally administered “high extraction” drugs has to be reduced by 50% or more, depending on  $E_h$  and the therapeutic window of the drug (table 3.4) (25).

As demonstrated by equation (4), the hepatic clearance  $Cl_h$  depends on the blood flow  $Q$  across the liver. In liver cirrhosis, blood flow and exchange of materials between sinusoids and hepatocytes are impaired which decreases the hepatic clearance  $Cl_h$ . This reduction in hepatic clearance is associated with a prolongation of elimination half-life and a risk of accumulation, if no dose reduction or prolongation of the dosing interval is performed. In patients with liver cirrhosis, not only the initial dose, but also the **maintenance dose** of orally administered “high extraction” drugs has to be reduced by 50% or more, depending on  $E_h$  and the clinical sings (25).

In the case of **i.v. application**, the usual starting dose can be applied, but still the **maintenance dose** has to be adjusted according to hepatic clearance and should be reduced by about 50% depending on the drug and the clinical sings (tables 3.4 and 3.5) (25).

Another approach is to assume a 100% oral bioavailability of such drugs in cirrhotic patients. Accordingly, initial and first maintenance doses should be reduced taking into account the assumed increase in bioavailability:

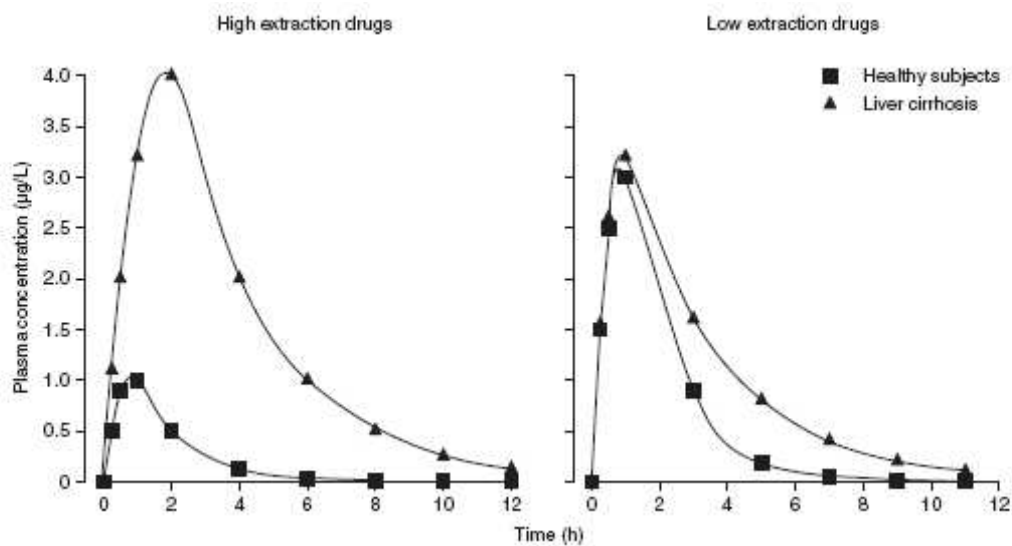
$$\text{Reduced dose} = \frac{\text{normal dose} \times \text{bioavailability}}{100} \quad (5)$$

“Normal dose” is the starting dose in a patient without liver disease and “bioavailability” the percentage of a drug ingested orally reaching 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 (25). Using

this approach, a possible reduction in drug clearance due to impaired hepatic blood flow is not considered, but may be neglectable compared to the assumed increase in bioavailability.

In conclusion, for high extraction drugs administered orally, both initial and maintenance doses have to be reduced in patients with liver cirrhosis. The extent of this reduction cannot be predicted accurately, however, since neither porta-systemic shunts nor hepatic blood flow are usually known in a given patient.

On the other hand, for high extraction drugs 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 (tables 3.4 and 3.5).



**Figure 3.3** *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 increase, and elimination is slowed. For drugs with a low hepatic extraction, only elimination is slowed. Accordingly, for drugs with a high hepatic extraction, both initial and maintenance dose have to be reduced, whereas for drugs with a low hepatic extraction, only the maintenance dose has to be adapted (Delco et al., 2005).

Table 3.2: *Substances investigated for quantification of liver function/liver metabolism*

Substance (application)	E (%)	Metabolism	Clinical use	Ref.
Serum bile acids (endogenous)	>90	Hydroxylation and conjugation, enterohepatic cycling	May be useful for estimation of portasystemic shunt	(43)
Indocyanine green (i.v.)	90	Biliary excretion	Estimation of hepatic blood flow	(45)
Galactose (i.v.)	95	Rate-limiting step is phosphorylation	First-order elimination reflects "functional hepatic capacity". Extrahepatic metabolism is problematic	(46)
Sorbitol (i.v.)	>80		Estimation of hepatic blood flow	(47)
Lidocaine (i.v.)	80	CYP3A		(48)
d-Propoxyphene (p.o.)	70	CYP3A	Ratio norpropoxyphene/d-propoxyphene may be useful to estimate portasystemic shunt	(49)
Erythromycin (i.v.)	30	CYP3A	CO <sub>2</sub> exhalation is used as a marker of CYP3A activity	(50)
Antipyrine (p.o.)	5	Different CYPs	Reflects activity of different CYPs	(51)
Aminopyrine (i.v.)	<30	Different CYPs	CO <sub>2</sub> exhalation is used as a marker of general CYP activity	(52)
Caffeine (p.o., i.v.)	<30	CYP1A2, N-acetyltransferase Type 2 (NAT2)	CO <sub>2</sub> exhalation measures mainly activity of CYP1A2	(53)

## Low extraction drugs

Predominantly hepatically eliminated drugs ( $Q_0 > 0.5$ ) which are only minimally extracted out of the blood during the first liver passage ( $\leq 30\%$ ;  $E_h < 0.3$ ) and have therefore a high bioavailability of  $\geq 70\%$ ). They are characterized by a low intrinsic clearance  $Cl_i$ . Only limited enzyme capacity is present for the metabolism of these drugs and the metabolic activity will not change, even if by a change in the liver blood flow more or less drug is delivered to the enzymes per time. Thus, the expression  $[f_u \times Cl_i]$  is much smaller than that of the blood flow  $Q$ . The addition of  $[f_u \times Cl_i]$  in the denominator of the equations (1) and (2) can therefore be neglected. As a consequence, the equations are reduced to:

$$\text{Since } (f_u \times Cl_i) \ll Q, \rightarrow E_h \approx \frac{f_u \times Cl_i}{Q} \quad (6) \quad \text{and} \quad Cl_h \approx f_u \times Cl_i \quad (7)$$

As shown by equation (7), the hepatic clearance  $Cl_h$  depends on the intrinsic metabolic capacity  $Cl_i$  of the liver and on the unbound fraction  $f_u$  of such drug, but is resistant to changes in the hepatic blood flow  $Q$ . These drugs are therefore called “enzyme-limited” or “low-extraction”.

### Dose adaptation of “low extraction drugs”

As shown by equation (7), hepatic clearance  $Cl_h$  does not depend on liver blood flow  $Q$ . Since the bioavailability of these drugs is already high (per definition  $\geq 70\%$ ), even in the presence of porta-systemic shunts, bioavailability of these drugs will not increase significantly. Therefore, therapy can be started with the usual **initial dose**. However, the hepatic clearance  $Cl_h$  of these drugs may be reduced. This reduction in hepatic clearance  $Cl_h$  is what high and low extraction drugs have in common (figure 2). Whereas in high extraction drugs this decrease in hepatic clearance  $Cl_h$  is explained by the changes in liver blood circulation ( $Q$  is reduced in equation (4)), the decreased hepatic clearance  $Cl_h$  of low extraction drugs has to be considered as a consequence of reduced enzyme activity ( $Cl_i$  is reduced in equation (7)).

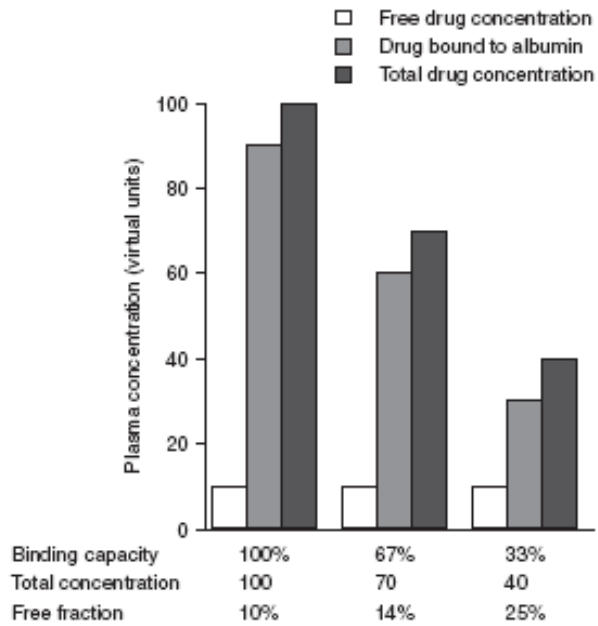
Therefore, depending on the drug and liver function, the **maintenance dose** of low extraction drugs should be reduced to about 50% of the normal dose. In the case of

**i.v. application**, a similar dose reduction of the maintenance dose is required as for orally administered drugs (tables 3.4 and 3.5) (25).

**“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 metabolizing enzymes ( $Cl_i$ ) (figure 3.4). In patients with reduced serum albumin concentrations, a frequent finding in patients with liver cirrhosis, the free fraction  $f_u$  (and also the free concentration) of such drugs is increased. Assuming a first order reaction (the reaction velocity is proportional to the free drug concentration), such drugs may be metabolized more rapidly in cirrhotic patients. According to equation 7,  $Cl_h$  of such drugs may therefore remain unchanged or may even be increased in cirrhotics.

Importantly, the total plasma concentration of such drugs is decreased when their free concentration is in the normal range. In order to avoid toxicity by overdosing, free drug levels should be determined and used to guide therapy of such drugs, e.g. for phenytoin or valproate.



**Figure 3.4.** *Effect of the serum albumin concentration 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 ( $\geq 90\%$  at a normal serum albumin concentration) is kept constant at 10. Under normal conditions (normal serum albumin, binding capacity 100%), 90% of the drug is albumin-bound and 10% is free. The total plasma concentration is 100. When the serum albumin concentration is lowered by one third (binding capacity 67%), the free concentration remains 10. The free fraction increases to 14% and the total serum concentration decreases to 70. After lowering the serum albumin concentration 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 (Delco et al., 2005).

## Intermediate extraction drugs

The hepatic clearance of drugs with a hepatic extraction  $E_h$  between 30% and 60% ("intermediate extraction drugs") is determined by both liver blood flow  $Q$  and intrinsic clearance  $Cl_i$ . The kinetic behavior of these drugs lies somewhere between that one of "high" and "low extraction drugs".

### Dose adaptation of "intermediate extraction drugs"

The hepatic clearance of these drugs is influenced by both liver blood flow  $Q$  and intrinsic clearance  $Cl_i$ , which are both decreased in patients with liver cirrhosis. However, since bioavailability of these drugs is 40% or more, the influence of porto-systemic shunts is less pronounced as compared to "high extraction" drugs. In general, the hepatic clearance  $Cl_h$  of these drugs is reduced, necessitating adjustment of their maintenance dose. Treatment should be started with an **oral initial dose** in the low range of normal. In the case of **i.v. application**, therapy can be started with the normal dose. In both applications, the **maintenance doses** should be reduced to about 50%, depending on the specific drug and liver function (tables 3.4 and 3.5) (25).

### Problems in classification of drugs according to hepatic extraction

Values for hepatic extraction  $E_h$  are published only for a minority of drugs.  $E_h$  has therefore to be estimated based on the bioavailability or by using the following equation (derived from equation 1 and from the definition of  $Q_0$ ):

$$E = \frac{Q_0 \times Cl_{sys}}{Q} \quad (8)$$

$Q_0$  is the fraction of a drug metabolized by the liver ( $Cl_{hep} = Q_0 \times Cl_{sys}$ ),  $Cl_{sys}$  the systemic clearance of this drug and  $Q$  liver blood flow. The values for  $Q_0$  and for  $Cl_{sys}$  can be obtained from different sources (54-56).

Both approaches, using oral bioavailability as a surrogate for hepatic extraction or calculation of hepatic extraction using equation (8), have their limitations. Oral bioavailability can be less than 100% not only due to a first liver pass effect but also

due to incomplete dissolution of tablets in the gut, incomplete absorption in the gut and/or degradation in the enterocytes (figure 3.2). Enterocytes contain CYP3A4, which can metabolize CYP3A4 substrates such as midazolam (57) or cyclosporine (58), before they reach the liver. They also contain P-glycoprotein, which can transport drugs from the enterocytes back to the lumen of the intestine, as shown for digoxin (59). 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 8 is that the systemic clearance of a drug is measured usually in plasma and not in blood. For substances with a different concentration in plasma and in erythrocytes (e.g. drugs which are trapped in erythrocytes such as ribavirin), the results of this approach will therefore be wrong. In our studies, we therefore used both approaches and detected an acceptable agreement between them (60).

### **Impact of liver disease on hepatic enzyme systems**

Studies assessing the protein content and/or the activity of important drug metabolizing enzymes (cytochrome P450 isoenzymes and conjugation reactions) in livers from cirrhotic patients show that enzyme activities and protein content are reduced with increasing disease severity as expressed by the Child score, but with a large interindividual variability (61-63).

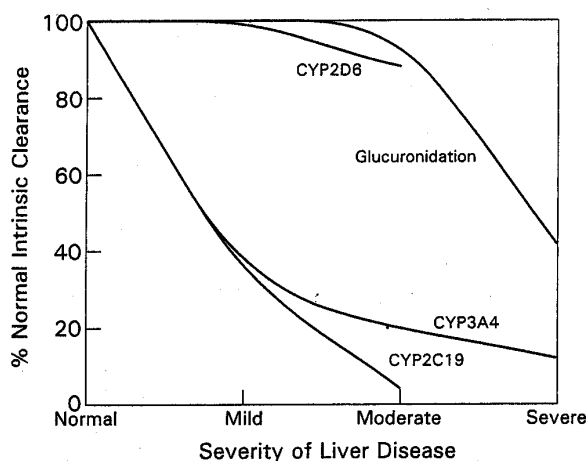
The reduction in  $Cl_i$  associated with liver cirrhosis appears not only to be a function of the Child score, but also of the metabolic reaction involved (figure 3.5). Conjugation reactions such as glycosylation and transfer of sulfate groups (phase II reactions) are considered to be affected to a lesser extent by liver cirrhosis than cytochrome P450 (CYP)-associated reactions (phase I reactions) (28). For instance, the clearance of oxazepam (64) or temazepam (65), two benzodiazepines which are only conjugated, are not reduced in patients with liver cirrhosis, whereas the clearance of diazepam (70, 71) or midazolam (66), both undergoing phase I and phase II reactions, is decreased. As discussed above, the decrease in CYP activity and/or protein content is highly variable in cirrhotic patients (61, 63, 67-70). This variability can be explained by the different mechanisms affecting CYP activity and/or protein content, such as impaired transcription for CYP 1A, 3A and 2C (73, 76), altered post-translational



modification for CYP 2E1 (67) or increased sensitivity to cholestasis as described for CYP 2E1 and 2C9 (61, 67).

Several studies have shown that also conjugation reactions can be impaired. Reduced glucuronidation has been demonstrated for zidovudine (71, 72), diflunisal (73), morphine (80, 81), mycophenolate (74), lormetazepam (75) and lamotrigin (76). The activity of sulfotransferases was also found to be reduced, whereas sulfatase activity appears to be spared (62).

Despite the finding that conjugation reactions are also impaired in cirrhotic patients, it appears to be justified to recommend preferentially drugs which 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 class A and of 25% in patients of Child class B and to adjust this dose according to the pharmacological effect and toxicity. For Child class C patients, it is recommended to use drugs whose kinetics is not affected by liver disease or for which therapeutic drug monitoring is available (25).



**Figure 3.5** Schematic diagram showing the effects of various stages of liver disease severity on the intrinsic clearance of drugs mediated by representative metabolic pathways. Estimates for glucuronidation (Hasselström et al., 1990), CYP2D6 (Adedoyin et al., 1998), CYP3A4 (Testa et al., 1997) and CYP2C19 (Adedoyin et al., 1998) pathways are based on the literature sources indicated in parentheses.

## **Dose adaptation in cholestasis**

As mentioned in a preceding section, cholestasis impairs the activity of several CYPs, for instance CYP2C (67) and 2E1 (61). In patients with cholestasis, drugs which are metabolized by CYPs can therefore have a diminished hepatic clearance, potentially needing adjustment of their dose.

While 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 few of such drugs. As discussed, kinetics and dynamics have been investigated in cholestatic patients particularly for antineoplastic agents, among them vinca alkaloids (77, 78), doxorubicin and derivatives (79-81) and dactinomycin (82). These studies resulted in recommendations for dose adjustment according to the serum bilirubin concentration and/or activity of alkaline phosphatase (82). It remains unclear, however, whether these two parameters are the best markers for dose adjustment in cholestasis or whether other enzyme activities and/or the serum bile acid concentration would be more accurate. Considering the impact of cholestasis on kinetics and dynamics of antineoplastic drugs (83), it is crucial that kinetic studies in cholestatic patients are performed also with other drugs exhibiting a predominant biliary excretion and/or enterohepatic cycling, e.g. phenprocoumon, mycophenolate and others.

## **Dose adaptation of predominantly renally excreted drugs**

It is well established that cirrhotics have reduced effective renal plasma flow and glomerular filtration rates, also in the absence of ascites (84-86). On the other hand, several studies have shown that patients with liver cirrhosis tend to have low serum creatinine concentrations (87-89), indicating that glomerular filtration rates cannot be estimated using the serum creatinine concentration. The low serum creatinine concentration in cirrhotics can be explained by impaired synthesis of creatine and a reduced skeletal muscle mass (89). For the same reasons, calculation of the creatinine clearance using the Cockcroft formula (90) may overestimate glomerular filtration (99-101). 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. While one study has

shown that the measured creatinine clearance reflects glomerular filtration in cirrhosis accurately (91), other studies indicate that glomerular filtration is overestimated, in particular in patients with reduced glomerular filtration rates (88, 92-94). This finding has been explained by an increased secretion of creatinine in cirrhotics (89, 95). The serum cystatin C concentration, another endogenous marker for renal function, may reflect glomerular filtration more accurately in cirrhotic patients (88).

Since the glomerular filtration rate is usually decreased in patients with liver cirrhosis, also drugs with mainly renal elimination and a narrow therapeutic range should be dosed with caution in this group of patients. A decreased renal elimination in cirrhotic patients has been shown for several drugs, among them cefpiramide (96), cilazapril (97), fluconazole (98), lithium (99, 100) and ofloxazin (101, 102).

Interestingly, in patients with renal failure, CYP-associated drug metabolism has been shown to decrease (103), in particular for CYP 2D6. Similar observations have been reported for rats, where several CYPs show a reduced expression (104). The clinical relevance of these findings has been demonstrated among others for metoclopramide, which reveals an over-proportional reduction in total body clearance in patients with renal failure (105).

### **Pharmacodynamic alterations in liver disease**

Patients with liver cirrhosis have been reported to be more sensitive to central adverse effects of morphine (106, 107) and benzodiazepines (108, 109), and to renal adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) (110), whereas the sensitivity to the natriuretic effect of loop diuretics was found to be reduced (28).

An early study described precipitation of hepatic encephalopathy after intravenous administration of morphine in patients with decompensated liver cirrhosis at low doses (8 mg i.v.) (106). In contrast, in a more recent study, none of 6 cirrhotics developed encephalopathy after i.v. administration of higher doses of morphine (111). Since several studies have shown that the oral bioavailability of morphine is increased and its elimination is impaired (112-114), morphine should be used with caution in cirrhotics, 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 (108, 109). In cirrhotics, benzodiazepines may induce encephalopathy which can be reversed by the administration of benzodiazepine antagonists (115). While impaired hepatic metabolism has been demonstrated in cirrhotics for midazolam (108) and diazepam (109, 116-118), no such changes were detected for oxazepam (64), temazepam (65) or triazolam (119), suggesting that increased sedation of benzodiazepines in cirrhotics is partially due to pharmacodynamic alterations.

Despite their disadvantages, benzodiazepines are difficult to replace as sedatives in cirrhotic patients. Neuroleptics undergo extensive hepatic metabolism and can also precipitate encephalopathy. Contrary to the benzodiazepines, they have the disadvantage that they cannot be antagonized. 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 cirrhotics (table 3.5).

As illustrated in the first section of this article, an unexpectedly high bioavailability can result in toxic drug levels 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 cirrhotics to excrete a given amount of sodium. This has been shown for the loop diuretics torasemide (125, 126), bumetanide (120) and furosemide (121-123). For torasemide, a diuretic metabolized by the liver, the kidney compensates for reduced hepatic metabolism in cirrhotics. A larger amount of drug is therefore eliminated by the kidney, leading to an apparently normal pharmacological effect in cirrhotics (124).

NSAIDs are known to precipitate renal failure in patients with cirrhosis and ascites (110). Patients with portal hypertension have a low peripheral resistance and hyperdynamic circulation due to increased production of vasodilating substances such as nitric oxide (125). In order to prevent a large drop in the arterial pressure, the renin angiotensin aldosterone and the sympathetic nervous system are activated, leading 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, eventually leading to renal failure in cirrhotics. Although no clinical data have been published for selective cyclooxygenase 2-inhibitors, it has to be assumed that they induce similar effects, as suggested by the impaired renal perfusion associated with the ingestion of celecoxib by salt-depleted normal subjects (126).

## **Liver disease and adverse effects of drugs**

Dose adaptation in patients with liver disease aims at reducing 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 often associated with dose-dependent, systemic adverse effects. For some of them, as discussed above, recommendations for dose adaptation in patients with liver disease have been established (82, 83).

Regarding adverse effects affecting the liver itself, most such events are type B reactions (127). Only few drugs reveal a dose-dependent hepatic toxicity, among them methotrexate (128), acetaminophen (134, 135) and isoniazid (136, 137). Patients with preexisting liver disease, in particular alcoholics, who are treated with one of these drugs may therefore be at a higher risk for hepatic toxicity. For methotrexate, the mechanism for increased toxicity in alcoholics is not completely clarified, but may be due to the presence of two different mechanisms associated with liver fibrosis and possibly cirrhosis (128). For acetaminophen, an important factor is induction of CYP2E1 by alcohol, increasing the generation of N-acetyl-p-benzoquinone imine, a toxic metabolite (134, 135). For isoniazid, both preexisting liver cirrhosis and ingestion of too much alcohol appear to be risk factors for hepatic toxicity (129, 130). Since isoniazid is metabolized also by CYP2E1, increased hepatic toxicity in alcoholics may be due to induction of CYP2E1 by alcohol.

The occurrence of hepatic microvesicular steatosis associated with the ingestion of drugs is a typical type B reaction. Microvesicular steatosis is a life-threatening condition caused by impaired  $\beta$ -oxidation of liver mitochondria (138, 139) and has been described in patients treated with valproic acid (131), analgetic doses of aspirin (131), certain opiates (132) or the uricosuricum benzbromarone (133). Since

microvesicular steatosis is considered to be more frequent in patients with a preexisting mitochondrial disorder, e.g. a defect in  $\beta$ -oxidation or in the urea cycle, or a mitochondrial cytopathy (134), certain preexisting liver diseases may also be risk factors for type B reactions.

## **Conclusion**

The most dangerous drugs in patients with liver cirrhosis are those with a low bioavailability and a narrow therapeutic range when administered orally. For these drugs, both initial and maintenance doses have to be reduced by 50% or more of the normal dose, depending on the severity of liver disease, hepatic extraction and metabolism, and toxicity of the drug. For most other drugs metabolized by the liver, only the maintenance dose has to be adjusted. It is important to realize that renal function can be impaired in cirrhotic patients despite normal serum creatinine. 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.

The predictions for dose adaptation remain general and cannot replace accurate clinical monitoring of patients with liver disease treated with drugs owing a narrow therapeutic range.

Table 3.4 *Adaptation of the drug dosage in patients with liver disease according to excretion, metabolism and hepatic extraction (if no studies available).*

	Application mode	Influenced parameter	Dosage recommendation
<b>low extraction drugs</b>	p.o.	<ul style="list-style-type: none"> <li>Hepatic extraction <math>E_h \rightarrow</math></li> <li>bioavailability <math>F \rightarrow</math></li> <li>hepatic clearance <math>Cl_h \downarrow</math></li> </ul>	<ul style="list-style-type: none"> <li>initial dose: normal</li> <li>maintenance dose: Dose reduction to about 50% of the normal dose depending on clinical signs; cautious up-titration.</li> </ul>
	i.v.	<ul style="list-style-type: none"> <li>hepatic clearance <math>Cl_h \downarrow</math></li> </ul>	<ul style="list-style-type: none"> <li>initial dose: normal</li> <li>maintenance dose: Dose reduction to about 50% of the normal dose depending on clinical signs; cautious up-titration.</li> </ul>
<b>intermediate extraction drugs</b>	p.o.	<ul style="list-style-type: none"> <li>hepatic extraction <math>E_h \downarrow \rightarrow</math></li> <li>bioavailability <math>F \uparrow</math></li> <li>hepatic clearance <math>Cl_h \downarrow</math></li> </ul>	<ul style="list-style-type: none"> <li>initial dose: Choose dosage in the lower range of normal</li> <li>maintenance dose: Dose reduction to about 50% of the normal dose depending on clinical signs; cautious up-titration.</li> </ul>
	i.v.	<ul style="list-style-type: none"> <li>hepatic clearance <math>Cl_h \downarrow</math></li> </ul>	<ul style="list-style-type: none"> <li>initial dose: normal</li> <li>maintenance dose: Dose reduction to about 50% of the normal dose depending on clinical signs; cautious up-titration.</li> </ul>
<b>high extraction drugs</b>	p.o.	<ul style="list-style-type: none"> <li>hepatic extraction <math>E_h \downarrow \rightarrow</math></li> <li>bioavailability <math>F \uparrow</math></li> <li>hepatic clearance <math>Cl_h \downarrow</math></li> </ul>	<ul style="list-style-type: none"> <li>initial dose: Dose reduction to about 50% or less of the normal dose depending on <math>E_h / F</math> and therapeutic range.</li> <li>Maintenance dose: Dose reduction to about 50% or less of the normal dose depending on clinical signs; cautious up-titration or further dose reduction.</li> </ul>
	i.v.	<ul style="list-style-type: none"> <li>hepatic clearance <math>Cl_h \downarrow</math></li> </ul>	<ul style="list-style-type: none"> <li>Initialdosis: normal</li> <li>maintenance dose: Dose reduction to about 50% of the normal dose depending on clinical signs; cautious up-titration or further dose reduction.</li> </ul>
<b>Drugs with significant biliar elimination (<math>\geq 5\%</math>)</b>	p.o.	In patients with cholestasis: $Cl_h \downarrow$ , $\rightarrow$ , or $\uparrow$	<ul style="list-style-type: none"> <li>Dose reduction according to serum bilirubin concentration and/or activity of alkaline phosphatase (quidelines exist only for some antineoplastic drugs)</li> </ul>
	i.v.	In patients with cholestasis: $Cl_h \downarrow$ , $\rightarrow$ , or $\uparrow$	<ul style="list-style-type: none"> <li>Dose reduction according to serum bilirubin concentration and/or activity of alkaline phosphatase (quidelines exist only for some antineoplastic drugs)</li> </ul>

Legend:  $\uparrow$  =increases /  $\downarrow$  = decreases /  $\rightarrow$  = unchanged

**Table 3.5** Classification of drugs metabolized by the liver according to pharmacokinetic characteristics

Hepatic extraction (E)	Effect of porto-systemic shunts on bioavailability	<b>Examples of drugs</b>
<b>Low extraction/low protein binding(&lt;90%)</b>		
<0.30	not relevant	<p><i>Benzodiazepines:</i> alprazolam, bromazepam, clobazam, flunitrazepam, flurazepam, nitrazepam, triazolam; <i>Other hypnotics and sedatives:</i> methaqualone, zopiclone; <i>Antidepressants:</i> citalopram, fluoxetine, fluvoxamine, moclobemide; <i>Antipsychotics:</i> risperidone; <i>Antiepileptics:</i> carbamazepine, ethosuximide, lamotrigine, levetiracetam, phenobarbital, primidone, topiramate; <i>Anti-Parkinson drugs:</i> pramipexole; <i>Antineoplastic and immunosuppressive agents:</i> cyclophosphamide, hydroxycarbamide, letrozol, melphalane, temozolomide; <i>Antibacterial drugs:</i> doxycycline, metronidazole; <i>Tuberculostatic drugs:</i> isoniazid; <i>Corticosteroids:</i> methylprednisone, prednisone; <i>Analgesics:</i> paracetamol; <i>Bronchodilators:</i> theophylline; <i>Antihistamines:</i> diphenhydramine; <i>Antiemetics:</i> metoclopramide</p>
<b>Low extraction/high protein binding(&gt;90%)</b>		
<0.30	not relevant	<p><i>Benzodiazepines:</i> chlordiazepoxide, diazepam, lorazepam, oxazepam, temazepam; <i>Other hypnotics and sedatives:</i> zolpidem; <i>Antidepressants:</i> maprotiline, trazodone; <i>Antipsychotics:</i> sertindole; <i>Antiepileptics:</i> phenytoin, tiagabine, valproate; <i>Anti-Parkinson drugs:</i> tolcapone; <i>Analgesics:</i> methadone; <i>Antineoplastic and immunosuppressive agents:</i> chlorambucil, mycophenolate; <i>Antibacterial drugs:</i> ceftriaxone, clarithromycin, clindamycin; <i>Tuberculostatic drugs:</i> rifampicin; <i>Corticosteroids:</i> prednisolone; <i>Antidiabetic drugs:</i> glipizide, tolbutamide; <i>Antihyperlipidemic drugs:</i> clofibrate, gemfibrozil; <i>Antiulcer drugs:</i> lansoprazole; <i>Anticoagulants:</i> phenprocoumon; <i>Antiestrogens:</i> tamoxifen, toremifen; <i>Antiandrogens:</i> Cyproterone</p>



Hepatic extraction (E)	Effect of porto-systemic shunts on bioavailability	<b>Examples of drugs</b>
<b>Intermediate extraction</b>		
0.30 - 0.60	may be clinically relevant	<p><i>Benzodiazepines:</i> midazolam (0.31); <i>Antidepressants:</i> amitriptyline (0.6), clomipramine (0.5), mirtazapin (0.43), nortriptyline (0.34), paroxetine (0.38); <i>Antipsychotics:</i> amisulpride (0.52), clozapine (0.45), fluphenazine (0.47), haloperidol (0.55), olanzapine (0.4), zuclopenthixol (0.51); <i>Psychostimulants:</i> methylphenidate (0.54); <i>Anti-Parkinson drugs:</i> entacapone (0.48); <i>Analgesics:</i> codeine (0.52); <i>Antineoplastic and immunosuppressive agents:</i> azathioprin (0.4), etoposide (0.48); <i>Antibacterial drugs:</i> ciprofloxacin (0.4), erythromycin (0.38); <i>Antifungal agents:</i> itraconazole (0.4); <i>Antiarrhythmics and anesthetic agents:</i> Amiodarone (0.54), lidocaine (0.4); <i>Beta-adrenergic blockers:</i> carvedilol (0.41); <i>Calcium channel blockers:</i> diltiazem (0.55), felodipine (0.56), nifedipine (0.33); <i>Antihyperlipidemic drugs:</i> atorvastatin (0.55), pravastatin (0.32), simvastatin (0.35); ); <i>Antiulcer drugs:</i> omeprazole (0.35), ranitidine (0.48); <i>Progestogens:</i> medroxyprogesterone (0.55); <i>Prolactine inhibitors:</i> lisuride (0.53);</p>
<b>High extraction</b>		
>0.60	clinically relevant	<p><i>Hypnosedatives, antianxiety drugs:</i> buspirone (0.96), clomethiazol (0.9), zaleplon (0.73); <i>Antidepressants:</i> dibenzepine (0.75), doxepin (0.72), imipramine (0.61), mianserine (0.67), sertraline (1), trimipramine (0.67), venlafaxine (0.73); <i>Antipsychotics:</i> chlorpromazine (0.68), chlorprothixen (n/a), flupenthixol (n/a), quetiapin (0.91), perphenazine (0.8), sulpiride (n/a); <i>Anticholinesterases:</i> tacrine (n/a); <i>Anti-Parkinson drugs:</i> bromocriptine (0.60), levodopa (n/a), selegiline (1), biperiden (n/a); <i>Analgesics:</i> morphine (0.76), pentazocine (0.8), propoxyphene (n/a); <i>Antineoplastic and immunosuppressive agents:</i> ciclosporine (0.72), fluorouracil (0.71), idarubicin (1), mercaptopurine (0.80), sirolimus (n/a), tacrolimus (0.75), vinorelbine (n/a); <i>Beta-adrenergic blockers:</i> labetalol (n/a), metoprolol (0.67), propranolol (0.75); <i>Calcium channel blockers:</i> nifedipine (0.33), verapamil (0.70); <i>Antianginal agents:</i> isosorbide dinitrate (0.78), nitroglycerine (1); <i>Antihyperlipidemic drugs:</i> fluvastatin (0.71), lovastatin (0.95); <i>Prokinetic drugs:</i> cisapride (0.65); <i>Antimigraine agents:</i> sumatriptan (0.82); <i>Antihelmintics:</i> praziquantel (n/a); <i>Antihistamines:</i> promethazine (0.76); <i>Phosphodiesterase inhibitors:</i> sildenafil (0.62)</p>

In brackets are the values for hepatic extraction (E), calculated as described in equation (5), or as estimated from bioavailability; n/a: value not available.



## **4 Online course for the Swiss Virtual Campus**

In collaboration with PNN AG (Nicolas Furrer, business data processing specialist, Karin Lattmann, webmaster), a German-language online course named “Dose Adaptation in Liver Insufficiency” was developed for the Swiss Virtual Campus ([www.virtualcampus.ch](http://www.virtualcampus.ch)). The course included topics such as anatomy and function of the liver, drug metabolism in liver disease, dose adaptation in liver disease and altered pharmacokinetics in liver disease.

This interactive online course was richly illustrated by graphics, tables, pictures and stereoscopic structures of drugs. The student’s learning success was verified by 23 multiple-choice questions. For each true or false answer an explanatory commentary was provided.

The PDF file of this online course is enclosed in the electronical appendix on CD-ROM.



## 5 Aim of the Thesis

In renal dysfunction, the creatinine clearance provides an excellent tool for the estimation of renal function upon which dosage recommendations in renal insufficiency can be based. Unfortunately, no such marker or clinically useful test system exists so far for dosage recommendations in liver disease. The major goal of this project was to define strategies for dosage adaptation of drugs in patients with liver disease.

In order to contribute to this field of research, the following was to be elaborated during this thesis:

To provide

**Guidelines for dose reduction in patients with liver disease** (especially cirrhosis) for

- **antineoplastic drugs**
- **psychotropic drugs**

with significant hepatic metabolism and / or biliar excretion available on the market in Switzerland.

Where available, the dosage recommendation should be based on kinetic studies in these patients. Where such studies are missing, the recommendation should be based on the handling of the drug by the liver, which would be predicted by the hepatic extraction rate (or bioavailability if missing) of the drug. At the same time, these predictions based on hepatic extraction rates or bioavailability should be compared with the results from kinetic studies in liver patients.

By this means, a considerable list of drugs including their pharmacokinetic data, both dose dependent and liver specific adverse reactions, summarized results of kinetic studies in liver patients and individual dosage recommendations in liver disease would be generated. These data could be further proceeded to a reference book or electronic database as a tool for dosage recommendations in liver disease.



## **6 Dose Adaptation in Patients with Liver Disease**

### ***6.1 Dose Adaptation of Antineoplastic Drugs in Patients with Liver Disease***

The paper has been published in: Drug Safety 2006; 29 (6): 509-522 (see below).

A complete list of the investigated antineoplastic drugs can be found in the electronic appendix on CD-ROM.

## **Dose Adaptation of Antineoplastic Drugs in Patients with Liver Disease**

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### **Summary**

Dose adaptation for liver disease is important in patients treated with antineoplastic drugs due to the high prevalence of impaired liver function in this population and the dose-dependent, frequently serious adverse effects of these drugs. We classified the antineoplastic drugs marketed in Switzerland by the end of the year 2004 according to their bioavailability/hepatic extraction in order to predict their kinetic behavior in patients with decreased liver function. This prediction was compared with kinetic studies carried out with these drugs in patients with liver disease. The studies were identified by a structured, computer-based literature search.

Of the 69 drugs identified, 52 had a predominant extrarenal (in most cases hepatic) metabolism and/or excretion. For 49 drugs, hepatic extraction could be calculated and/or bioavailability was available, allowing classification according to hepatic extraction. For 18 drugs, kinetic studies have been reported in patients with impaired liver function, with the findings generally resulting in quantitative recommendations for adaptation of the dosage. In particular, recommendations are precise for 13 drugs excreted by the bile (e.g. doxorubicin and derivatives, and vinca alkaloids). Validation studies comparing such recommendations with kinetics and/or dynamics of antineoplastic drugs in patients with decreased liver function have not been published.

We conclude that there are currently not enough data for safe use of cytostatics in patients with liver disease. Pharmaceutical companies should be urged to provide kinetic data (especially hepatic extraction) used for classification of such drugs and to conduct kinetic studies for drugs with primarily hepatic metabolism in patients with impaired liver function allowing to give quantitative advice for dose adaptation.

**Introduction**

Dose adaptation for patients with liver disease is more difficult to perform than for patients with impaired renal function. The main reason for this statement is the fact that, unlike the creatinine clearance for the kidney, there is no *in vivo* surrogate to predict hepatic drug clearance. Due to the lack of such *in vivo* markers, predictions concerning dose adaptation in patients with liver disease can only be made based on the kinetic properties of the drugs to be administered and on kinetic studies of such drugs in patients with liver disease (Delco 2005).

Several reviews have covered this subject during the last years (135-139) (Delco 2005). In these reviews, drugs are listed according hepatic extraction (E), which is an important determinant of hepatic clearance of drugs. The hepatic clearance ( $Cl_{\text{hep}}$ ) of a drug can be expressed as:

$$Cl_{\text{hep}} = E \times Q = \frac{(f_u \times Cl_i) \times Q}{(f_u \times Cl_i) + Q} \quad (1)$$

where Q is the blood flow across the liver, and  $f_u$  the unbound fraction and  $Cl_i$  the intrinsic clearance of a drug.  $Cl_i$  represents the maximal capacity of the liver to metabolize a given drug, not taking into account limitations by liver perfusion (140).  $Cl_i$  can therefore reach values which are larger than Q.

The basis of the classifications used can best be understood by considering the extremes of equation (1), namely  $(f_u \times Cl_i) \gg Q$  or  $Q \gg (f_u \times Cl_i)$ . When  $(f_u \times Cl_i) \gg Q$ , the denominator in equation (1) simplifies to  $(f_u \times Cl_i)$ , and  $Cl_{\text{hep}}$  equals:

$$Cl_{\text{hep}} = Q \quad (2)$$

For such drugs, the liver has a very large metabolic capacity, hepatic extraction (E) is approaching 1 and the blood flow across the liver becomes rate-limiting for hepatic clearance. Such drugs are therefore called “flow-limited”, “high capacity”, “high clearance” or “high extraction”. Due to the high hepatic extraction, they have a low bioavailability. Since portal blood flow can be decreased in patients with liver cirrhosis or patients with multiple metastases (141, 142), hepatic clearance of such drugs is decreased in these situations, possibly necessitating a reduction of the maintenance dose. A second potential problem of such drugs is an increase in their bioavailability in patients with porto-systemic shunts. Porto-systemic shunts are usually present in patients with portal hypertension due to liver cirrhosis or fibrosis or, of importance in patients with cancer, in patients with multiple metastases (143, 144). Therefore, when such drugs are administered orally in patients with portal hypertension, the initial and the maintenance doses have to be reduced according to the expected increase in bioavailability and to the decrease in hepatic blood flow. For intravenous administration, only the maintenance dose has to be reduced according to hepatic blood flow. A list of such drugs is given in a recent publication (Delco 2005).

For the second type of drugs,  $Q \gg (f_u \times Cl_i)$ , the metabolic capacity of the liver is much lower than blood flow across the liver. Equation (1) therefore simplifies to:

$$Cl_{\text{hep}} = (f_u \times Cl_i) \quad (3)$$

These drugs are therefore called “low extraction”, “low clearance” or “capacity-limited”. They only have a low extraction during the first passage across the liver and have therefore a high bioavailability, if bioavailability is not limited by other processes than first pass hepatic metabolism. Since  $Cl_i$  decreases for most drugs in patients

with liver cirrhosis due to a decrease in the activity of cytochrome P450 isozymes (CYP) (61, 67) and/or glucuronyl transferases (73, 76, 145), the maintenance dose of such drugs has generally to be decreased in such patients. For drugs with a high binding to albumin (>90%), the situation may be more complex. The free fraction ( $f_u$ ) and the free concentration of such drugs can increase in patients with a low serum albumin concentration, e.g. patients liver cirrhosis or malnourished patients such as patients with cancer. An increase in the free concentration and/or  $f_u$  of such drugs may be associated with increased toxicity, and, as shown in equation 3, also with an increased hepatic clearance (146, 147). The actual hepatic clearance of such drugs is therefore difficult to predict in patients with chronic liver disease.

In between these two extremes, there are drugs with an “intermediate extraction”, showing characteristics of both groups. The dosage advice for such drugs in patients with liver cirrhosis is to start with a low dose and to up-titrate carefully in order to find the correct maintenance dose.

Regarding dose adaptation in patients with cancer, it has to be recognized, however, that the dosing guidelines discussed above focus on patients with liver cirrhosis or fibrosis, but not on patients with increased transaminases and/or cholestasis which are found frequently among patients treated with antineoplastic drugs. Since the majority of antineoplastic drugs is metabolized by the liver (see Table 2) and is associated with severe dose-dependent toxicity, the question whether the dose has to be adapted in a patient with increased transaminases and/or cholestasis is important. The most prevalent liver disease in this group of patients is the presence of liver metastases, possibly resulting in cholestasis and/or portal hypertension (144, 148, 149). Since many antineoplastic drugs are potentially hepatotoxic themselves (see Table 2), drug-induced liver disease may also be problematic in patients undergoing repetitive cycles of chemotherapy.

The aims of the current study were therefore 1) to categorize the antineoplastic drugs used according to pharmacokinetic criteria as discussed above 2) to compare this categorization with the dose recommendations in patients with liver disease given in the standard literature 3) to formulate dose recommendations for dose adaptation, and 4) to localize gaps in the current recommendations.

### **Methods**

We screened Medline and Embase for studies dealing with dose adaptation and hepatic adverse effects for all antineoplastic drugs which were on the market in Switzerland by the end of the year 2004. The data bases were screened using the following MESH terms: antineoplastic agents, drug toxicity, pharmacokinetics, liver diseases. The references detected by the search in the databases were screened for other references dealing with the subjects. In addition to databases, the standard literature was screened for dose adaptation recommendations and adverse effects on the liver, including the “Swiss Compendium of Drugs” (150) (similar to the “Physicians’ Desk Reference” (55)), “Therapeutic drugs” of Dollery et al. (151) and “Hepatotoxicity” of H. J. Zimmerman (127).

The antineoplastic drugs were categorized according to pharmacokinetic principles as outlined in the introduction and based on the reviews of Huet and Villeneuve (146) and Delco et al. (Delco 2005). The categorization system used is based on the hepatic extraction or bioavailability, and protein binding of the specific drugs (see Table 1). Values for bioavailability and protein binding could be found either in the original articles (cited in Table 3) or in other sources (55, 56, 150, 151). For hepatic extraction, data in the literature are rare, making it necessary to estimate extraction from bioavailability (see Table 1) or by the following equation:

$$E = \frac{Q_0 \times Cl_{sys}}{Q} \quad (4)$$

where  $Q_0$  is the extrarenal dose fraction (the fraction of a drug which is not excreted unchanged by the kidney),  $Cl_{sys}$  the systemic clearance (determined in plasma) and  $Q$  the plasma flow across the liver. Most of the values for  $E$  in Table 3 are estimated using this equation. The values for  $Q_0$  and  $Cl_{sys}$  were obtained from the literature (54, 55, 150, 151), and  $Q$  was assumed to be 900 mL/min.

Dosage recommendations originate either from the original articles or from the manufacturer as published in the PDR (55) and/or the Swiss Compendium of Drugs (150).

Drug-induced liver disease was classified according to Benichou (152) and the severity of liver disease according to Donelli et al. (153) (see Table 2).

## **Results**

Informations about all antineoplastic drugs on the market in Switzerland by the end of the year 2004 were collected. Using our search strategy, we identified a total of 112 articles which were found to be relevant for our study. In 64 of them, kinetic data were reported and 48 contained hepatic adverse effects of antineoplastic agents.

The 69 antineoplastic drugs on the Swiss market by the end of the year 2004 are listed in Table 3. From these 69 drugs, 15 fell into category 1, 9 into category 2 and 25 into category 3. Twenty drugs could not be classified (category 4), demonstrating a lack of data about hepatic extraction and/or bioavailability.

Fifty-two out of the 69 drugs have a  $Q_0$  value (extrarenal dose fraction, compare Table 3)  $>0.4$ , indicating that most antineoplastic drugs are heavily metabolized and/or excreted by the bile. Seven drugs have a  $Q_0$  value  $\leq 0.4$  and for 10 drugs, the

Q0 value could not be identified. For 25 drugs, metabolism by the cytochrome P450 system (CYP) is important, and 18 drugs are excreted to a significant extent (> 5%) by the bile (vinca alkaloids, doxorubicin and derivatives, amsacrine, bicalutamide, dactinomycin, estramustine, exemestan, irinotecan, imitanib, mitoxantrone, paclitaxel and topotecan). For 13 of these drugs, dose adaptation recommendations are given according to the serum bilirubin concentration and/or activity of alkaline phosphatase. For bicalutamide, estramustine, exemestan and paclitaxel, there are general statements in the Swiss Compendium of Drugs and/or PDR that the dose should be adapted or stopped in patients with decreased liver function. For topotecan, there are no recommendations regarding dosage in patients with liver disease. For only 18 of the 69 drugs identified, recommendations for dose adaptation are based on published studies in patients with hepatic dysfunction.

For 44 of the 69 drugs, significant adverse effects on the liver have been reported. This is important to realize, rendering drug-induced liver disease an important differential diagnosis in patients with malignant tumors and impaired hepatic function.

### ***Discussion***

Our study demonstrates that for antineoplastic drugs, there is a discrepancy between the general recommendations of how drugs should be dosed in patients with liver disease and the available kinetic data for these drugs. The most important gaps are a lack of information regarding hepatic extraction and of kinetic studies for critical drugs in patients with impaired liver function.

As explained in the introduction, data about hepatic extraction are important for classification of a specific drug regarding hepatic elimination in patients with chronic liver disease, in particular liver cirrhosis. It is evident that such data are difficult to obtain, especially the determination of hepatic extraction of a drug, necessitating an

invasive procedure which is usually not performed before a drug is marketed. Bioavailability is only a surrogate for hepatic extraction, since a low bioavailability can originate from both a high hepatic extraction and/or a low intestinal absorption. For drugs with a low bioavailability (<40%), hepatic extraction should therefore be known, since, as explained above, this parameter is critical for rational drug dosing in patients with impaired liver function. In order to circumvent this invasive procedure in humans, a possibility would be to get such data using perfused livers from animals, e.g. pigs. To the best of our knowledge, no data have been published so far comparing hepatic extraction data for critical drugs between animals (such as pigs) and humans. Another possibility is to estimate hepatic extraction using  $Q_0$ , systemic drug clearance and hepatic plasma flow (equation 4 and Table 3). As shown in Table 3, the values obtained with this technique are in a satisfactory agreement with the bioavailability for most drugs, with some exceptions.

Regarding antineoplastic agents, many of these drugs are used intravenously only, partially explaining the lack of data considering oral bioavailability. Nonetheless, taking into account the high prevalence of patients with impaired hepatic function among those treated with this type of drugs (154), such data should be available for all substances on the market.

Kinetic studies have been conducted in particular in two conditions, namely in patients with cholestasis (as suggested by an increased serum bilirubin concentration) and in patients with hepatic metastases. Considering cholestasis, studies exist for most antineoplastic drugs with significant biliary elimination (see Table 3). These studies resulted in quantitative recommendations for dose adaptation, for example in jaundiced patients according to their serum bilirubin concentration. To the best of our knowledge, however, these recommendations have not been validated by kinetic and dynamic studies (including the incidence and



severity of dose-dependent adverse effects) in such patients. Considering cholestasis, it remains unclear, whether the serum bilirubin concentration is the best parameter for dose adaptation or whether the serum bile acid concentration and/or activity of alkaline phosphatase would be more suitable.

Considering hepatic metastases, only few studies exist and they have generally not resulted in clear dose adaptation recommendations. Since hepatic metastases can be associated with portal hypertension and possibly porto-caval shunts (144, 148), the situation can be similar to patients with liver cirrhosis. Oral administration of drugs with a high hepatic extraction should therefore be performed cautiously and kinetic data for such drugs should be available in this type of patients when such drugs are approved.

As shown in Table 3, treatment with antineoplastic agents can either lead itself to liver disease or, for drugs metabolized by the liver and/or excreted by the bile, to increased systemic toxicity in patients with liver disease. For such drugs, there is an additional type of toxicity which may be relevant. In several patients with chronic hepatitis B, the immunosuppressive effect of antineoplastic agents was associated with a flare up of their hepatitis due to increased replication of the hepatitis B virus (155-161). Since this condition is potentially fatal (161), but can be prevented by previous treatment or prophylaxis with antiviral agents, the immune status regarding hepatitis B should be known before treatment with antineoplastic drugs.

In conclusion, there are currently considerable gaps in the data needed for safe administration of antineoplastic drugs in patients with decreased hepatic function. Drug authorities should urge pharmaceutical companies to provide such data before such drugs are approved. Considering kinetics, in particular data about oral bioavailability and/or hepatic extraction should be known. For drugs with a predominant hepatic metabolism and/or excretion, the kinetics in patients with liver

metastases and/or cholestasis should be known before marketing authorization is provided.

***References***

See below

Table 1

*Categorization of antineoplastic drugs screened according to pharmacokinetic variables.*

**1. High hepatic extraction (category 1)**

- Hepatic extraction  $> 60\%$  → oral bioavailability  $< 40\%$  in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete)

**2. Intermediate hepatic extraction (category 2)**

- Hepatic extraction 30 - 60% → oral bioavailability 40 - 70% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete)

**3. Low hepatic extraction (category 3)**

- Hepatic extraction  $< 30\%$  → oral bioavailability  $> 70\%$  in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete)
- In this category, protein binding may be relevant: for drugs with high binding to albumin ( $>90\%$ ), hepatic clearance may increase

**4. Hepatic extraction is not known (category 4)**

Table 2*Classification of liver disease and severity of liver dysfunction*

<i>Parameter</i>	<i>Pathophysiological condition and clinical significance</i>	<i>Severity<sup>1</sup></i>
Alanine aminotransferase (ALT)	Breakdown (necrosis or apoptosis) of hepatocytes. Hepatocellular injury <sup>2</sup> if > 2 x ULN <sup>3</sup>	2-5 x ULN: moderate injury > 5 x ULN: severe injury
Alkaline phosphatase	Cholestasis <sup>4</sup> if > 2 x ULN	2-5 x ULN: moderate cholestasis > 5 x ULN: severe cholestasis
Serum bilirubin concentration	Cholestasis (exclude prehepatic causes)	25 – 50 µmol/L: moderate > 50 µmol/L: severe
Serum albumin concentration	Impaired hepatic protein synthesis	30 – 35 g/L: moderate < 30 g/L: severe
Prothrombin activity	Impaired hepatic protein synthesis	40 – 70%: moderate < 40%: severe

<sup>1</sup>The severity is classified according to Donelli et al. (153) with some modifications

<sup>2</sup>Hepatocellular injury is defined according to Benichou (152)

<sup>3</sup>ULN: upper limit of normal

<sup>4</sup>Cholestasis is defined according to Benichou (152)

Table 3

*Kinetic data, hepatic adverse effects and dose recommendations in patients with liver disease of the antineoplastic drugs on the market in Switzerland by the end of the year 2001*

Drug	Cat <sup>1</sup>	Kinetic parameters							Hepatic adverse effects <sup>9</sup>	Dose-dependent adverse reactions	Studies performed and dosage recommendations
		Q <sub>0</sub> <sup>2</sup> , metabolism	V <sub>d</sub> <sup>3</sup> (L/kg)	t <sub>1/2</sub> <sup>4</sup> (h)	PB <sup>5</sup> (%)	F <sup>6</sup> (%)	Cl <sub>sys</sub> <sup>7</sup> (mL/min)	E <sup>8</sup>			
Aldesleukin	4	Not known	0.18	1					<i>Frequent:</i> hepatocellular injury, cholestasis, hyperbilirubinemia (150)	Capillary leak syndrome, myelosuppression (162)	<i>Recommendations:</i> Monitor patients for adverse effects, dose may need to be adjusted patients with liver disease (150, 151). Contraindicated in patients with elevated serum bilirubin (150).
Alemtuzumab	4	Not known	0.15	8						Infusion reaction (fever, chills, hypotension, nausea, vomiting), myelosuppression (162)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Aminoglutethimide	3	0.50 N-acetylation, N-hydroxylation (CYP) (151)	1.0	12	25	95	75	0.04	<i>Sporadic:</i> cholestasis, hyperbilirubinemia (127)	Adrenocortical failure, dizziness (151)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Amsacrine	4	1 Glutathion conjugation, biliary excretion (150)	1.40	5	97				<i>Sporadic:</i> cholestasis, hyperbilirubinemia (127)	Myelosuppression, cardiotoxicity (arrhythmia), hypotonia, nausea and vomiting, alopecia, mucositis (163, 164)	<i>Recommendation:</i> 50% dose reduction if serum bilirubin > 34 μmol/l (82). Dose reduction (70% of normal dose) in patients with severe liver disease (150, 151).
Anastrozole	3	0.95 N-dealkylation, hydroxylation (CYP), glucuronidation (151)		50	45	80		0.2	<i>Sporadic:</i> cholestasis	Nausea and vomiting, hot flashes, headache, musculo-skeletal pain (162, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions

Antineoplastic Drugs

Drug	Cat <sup>1</sup>	Kinetic parameters							Hepatic adverse effects <sup>9</sup>	Dose-dependent adverse reactions	Studies performed and dosage recommendations
		Q <sub>0</sub> <sup>2</sup> , metabolism	V <sub>d</sub> <sup>3</sup> (L/kg)	t <sub>1/2</sub> <sup>4</sup> (h)	PB <sup>5</sup> (%)	F <sup>6</sup> (%)	Cl <sub>sys</sub> <sup>7</sup> (mL/min)	E <sup>8</sup>			
Bicalutamide	2	≈1 Oxidation (CYP), glucuronidation. Biliary elimination 40% (150)		139	98		500	0.56	One case of fulminant liver failure (165)	Blocked androgenic action (hot flushes, breast tenderness, gynecomastia, reduced libido and erectile function), diarrhea (162-164)	<i>Recommendations:</i> Stop treatment if transaminases > 3 x ULN or in patients with hyperbilirubinemia (150)
Bleomycin	3	0.70 Hydrolysis (151)	0.30	3			90	0.07	<i>Case reports:</i> steatosis (127, 166)	Pulmonary fibrosis, mucositis, hyperpigmentation, nausea and vomiting, hypotension (163, 164)	<i>Recommendations:</i> No dose adjustment in patients with liver disease (151). Adjust dose according to dose-dependent adverse reactions
Buserelin	4	Not known		1.6		3				Blocked androgenic action (hot flushes, breast tenderness, gynecomastia, reduced libido and erectile function) (163, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Busulfan	2	1 Oxidation, sulfation	1.0	2.5	30	70	315	0.35	<i>Sporadic:</i> hepatocellular injury, cholestasis (167, 168). <i>Rare:</i> venoocclusive disease (127).	Myelosuppression, nausea and vomiting, seizures (162, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Capecitabine	1	0.97 Carboxylesterase, Cytidine desaminase, phosphorylation		1.3	54	42	4000	≈1	<i>Frequent:</i> hyperbilirubinemia <i>Sporadic:</i> cholestasis <i>Rare:</i> Hepatocellular injury (169)	Myelosuppression, mucositis, nausea and vomiting, skin reactions (hand and foot syndrome) (162, 164)	<i>Studies:</i> Increased bioavailability by 20% in patients with moderate liver disease due to metastases (170). <i>Recommendations:</i> No dose adjustment in patients with moderate liver disease (170). Adjust dose according to dose-dependent adverse reactions
Carboplatin	3	0.25	0.24	3	20		75	0.02	<i>Rare:</i> hepatocellular injury, cholestasis	Myelosuppression, nausea and vomiting, nephrotoxicity,	<i>Recommendations:</i> No dose adjustment in patients with liver

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									(127)	neurotoxicity, ototoxicity (163, 164)	disease (150). Adjust dose according to dose-dependent adverse reactions
Cetuximab	4	Binding to EGFR in hepatocytes and skin (171)	0.05	120			0.5		Frequent: mild elevation of transaminases and alkaline phosphatase (172)	Infusion reaction (bronchospasm, urticaria, hypotension), acneiform skin reactions (162, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Chlorambucil	3	1 β-oxidation (151)	1.0	1.5	99	87	175	0.19	Rare: hepatocellular injury (127) Case report: liver failure (173).	Myelosuppression, nausea and vomiting, seizures, pulmonary fibrosis (162, 163)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Chlormethine (Mechlorethamine)	4	1 ethyleneimmonium ion (151)								Myelosuppression, nausea and vomiting, alopecia, ototoxicity (164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Cisplatin	3	0.65 non-enzymatic degradation (174)	0.3-1	0.5	90	-	5.0	0.01	Rare: hepatocellular injury (127)	Myelosuppression, nausea and vomiting, visual disturbances, nephrotoxicity, neurotoxicity, ototoxicity (163, 164)	<i>Recommendations:</i> No dose adjustment in patients with liver disease (150, 151). Adjust dose according to dose-dependent adverse reactions
Cladribine	2	Not known	0.4	6	25	55	1000			Myelosuppression, neurotoxicity, nephrotoxicity (162, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Cyclophosphamide	3	0.9 Hydroxylation by CYP2B6, 2C19, 2C9, 3A4 (175)	0.80	7	15	75	75	0.08	Rare: Hepatocellular injury, cholestasis, hyperbilirubinemia (127). Case reports: venoocclusive	Myelosuppression, nausea and vomiting, alopecia, hemorrhagic cystitis, pulmonary fibrosis, venoocclusive disease VOD (163, 164)	<i>Studies:</i> Decreased clearance of active drug and decreased production of active metabolites in patients with liver metastases (179), severe liver disease in the presence of Hodgkin's disease (180) or liver

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									disease (176-178)		cirrhosis (82). <i>Recommendations:</i> Monitor patients with liver disease for adverse effects. Dose reduction by 25% in patients with serum bilirubin > 50 μmol/L (150)
Cyproterone	3	1 hydrolysis, hydroxylation, conjugation (151)	19	38	95	88			<i>Sporadic:</i> hepatocellular injury, cholestasis, hyperbilirubinemia <i>Rare:</i> liver failure (181-185)	decreased of libido and potency, gynecomastia, depression, diminished vitality, hepatotoxicity (163, 164)	<i>Recommendations:</i> Monitor liver function. Stop treatment in patients with liver injury (150, 151)
Cytarabine	1	0.90 cytidine deaminase (151)	3.0	2.3	13	<20	900	0.90	<i>Sporadic to frequent:</i> dose-dependent hepatocellular injury, cholestasis, hyperbilirubinemia (127)	Myelosuppression, arachnoiditis (nausea, fever, headache), nephrotoxicity, hepatotoxicity, mucositis, conjunctivitis, neurotoxicity, pulmonary toxicity (162, 164)	<i>Recommendations:</i> 50% dose reduction if serum bilirubin > 34 μmol/L, gradual increase while monitoring systemic toxicity (82)
Dacarbazine	3	0.30	1.5	0.7	5		200	0.07	<i>Case reports:</i> venoocclusive disease (186, 187), hepatic vein thrombosis (187)	Myelosuppression, nausea and vomiting, flu-like symptoms, flush, hepatotoxicity, renal impairment (162)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Dactinomycin	4	0.70 Biliary excretion 50%-90% (151)	12	36					<i>Rare:</i> hepatocellular injury, steatosis, venoocclusive disease (127)	Myelosuppression, nausea and vomiting, diarrhea, mucositis, alopecia (162, 163)	<i>Recommendation:</i> 50% dose reduction in patients with hyperbilirubinemia. Increase gradually while monitoring dose-dependent toxicity (82).
Daunorubicin	4	0.90 Reduction, biliary excretion 40% (151)	40	27					<i>Rare:</i> Venoocclusive disease when combined with radiation (127)	Myelosuppression, nausea and vomiting, mucositis, alopecia, cardiotoxicity, diarrhea (162, 163)	<i>Recommendation:</i> If serum bilirubin 20 - 50 μmol/L 25% dose reduction, if serum bilirubin > 50 μmol/L 50% dose reduction (150, 151)
Docetaxel	1	1	1.6	0.6	95		650	0.72		Myelosuppression, nausea	<i>Studies:</i> Population kinetic studies



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		Q <sub>0</sub> <sup>2</sup> , metabolism	V <sub>d</sub> <sup>3</sup> (L/kg)	t <sub>1/2</sub> <sup>4</sup> (h)	PB <sup>5</sup> (%)	F <sup>6</sup> (%)	Cl <sub>sys</sub> <sup>7</sup> (mL/min)	E <sup>8</sup>			
		Oxidation by CYP3A4 (151). Biliary excretion 75%, 10% as intact drug (150, 151)		(β) 11 (γ)						and vomiting, diarrhea, sensory neuropathy, mucositis, alopecia, fluid retention syndrome (162, 163)	show a 25% reduction of clearance in patients with transaminases > 1.5 x ULN and alkaline phosphatase > 2.5. In patients with moderate liver injury/cholestasis clearance was reduced by 27% (150, 151). <i>Recommendation:</i> If transaminases > 1.5 x ULN or alkaline phosphatase > 2.5 x ULN 25% dose reduction. If serum bilirubin is increased or transaminases > 3.5 x ULN or alkaline phosphatase > 6 x ULN docetaxel should not be administered (150, 151)
Doxorubicin	1	0.95 Reduction to doxorubicinol, sulfation, glucuronidation, biliary excretion 50% (151, 153)	17	26	80	5	1150	≈1	Rare: in combination with etoposide, cyclophosphamide and cisplatin cholestasis and venoocclusive disease (127)	Myelosuppression, nausea and vomiting, mucositis, alopecia, cardiotoxicity (162, 163)	<i>Studies:</i> In 5 patients with disseminated sarcoma, myelotoxicity and doxorubicin serum levels correlated with hyperbilirubinemia (188). In patients with hepatocellular carcinoma, myelotoxicity and serum doxorubicin/doxorubicinol levels correlated with hyperbilirubinemia (79, 189). In 17 patients with liver metastases and moderate liver disease, kinetics of doxorubicin were not changed but the half-life of doxorubicinol increased (190). In 4 patients with moderate liver disease the half-life of doxorubicin was doubled (191). In patients with liver metastases and mild increase in transaminases or alkaline phosphatase, kinetics and toxicity of doxorubicin were not changed (79, 189, 192, 193).

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											<i>Recommendation:</i> If serum bilirubin 20 - 50 µmol/l: 50% dose reduction. If serum bilirubin > 50 µmol/l: 75% dose reduction (82, 150, 151, 194). Donelli et al. advise dose reduction only if serum bilirubin is > 50 µmol/L (153).
Epirubicin	1	0.90 Reduction Biliary excretion 40% (195)	20	39	85		1500	≈1		Myelosuppression, nausea and vomiting, mucositis, alopecia, cardiotoxicity (162, 163)	<i>Studies:</i> In patients with liver metastases and increased serum bilirubin, the half-life of epirubicin/epirubicinol was increased (196-198). In patients with hepatocellular carcinoma, epirubicin kinetics correlates with liver function and serum bilirubin (199). In patients with liver metastases, epirubicin kinetics correlates better with transaminases than with serum bilirubin (80, 200, 201). <i>Recommendation:</i> If serum bilirubin 20 - 50 µmol/l: 50% dose reduction. If serum bilirubin > 50 µmol/l: 75% dose reduction (82, 150, 151)
Estramustine	2	0.90 Oxidation, partial biliary excretion (202)	0.04	1.3	99	44			<i>Sporadic.</i> Hepatocellular injury, cholestasis (150)	Nausea and vomiting, diarrhea, edema, cardiac ischemia (164, 203)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Etoposide	3	0.65 Esterases, glucuronidation. Biliary excretion <10%.	0.30	8.1	95	50	48	0.04	<i>Frequent.</i> Hepatocellular injury (127). <i>Case reports:</i> Reactivation of hepatitis B virus	Myelosuppression, nausea and vomiting, alopecia, mucositis, hypotension, hepatotoxicity (163, 164)	<i>Studies:</i> In patients with mild to moderate liver disease, etoposide kinetics was not altered (81, 205, 206). In patients with severe liver disease elimination and AUC were highly variable and tended to be

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									(156), liver failure (204)		increased in the case of impaired hepatic protein synthesis or hyperbilirubinemia (81, 205-207). <i>Recommendations:</i> Monitor patients with mild to moderate liver disease. If bilirubin 25 – 50 μmol/L or AST > 180 U/L 50% dose reduction (82). Contraindicated in patients with decompensated liver disease (150, 151).
Exemestane	1	1 CYP3A, biliary excretion 40% (208)	19	24	90	42	10000	≈1	<i>Sporadic:</i> hepatocellular injury, cholestasis (150)	Hot flushes, increased sweating, nausea, fatigue, edema (162, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions. Be cautious in patients with cholestasis.
Fludarabine	3	0.35	2.4	10-30		70	258	0.10		Myelosuppression, neurotoxicity (visual disturbances, seizures, coma, death), nausea and vomiting, mucositis, edema, hemorrhagic cystitis (162, 164)	<i>Recommendations:</i> No dose adjustment recommended in patients with liver disease (150, 151).
Fluorouracil	1	0.95 Dihydropyrimidine dihydrogenase	0.3	0.25	94	28	11202	≈1	<i>Sporadic:</i> hepatocellular injury when administered i.v. (127)	Myelosuppression, nausea, vomiting, alopecia, palmar-plantar erythrodysesthesia, neurotoxicity (cerebellar) (163, 164)	<i>Studies:</i> In patients with liver metastases, a weak correlation with cholestasis was present (209), but no dose adjustment was recommended. <i>Recommendations:</i> Start with 50% of normal dose in patients with liver cirrhosis. Increase gradually while monitoring systemic toxicity (82, 153).
Flutamide	4	1 Hydroxylation (210)		8	95				<i>Sporadic:</i> hepatocellular injury, hyperbilirubinemia	Gynecomastia, nausea and vomiting, decreased libido, hepatotoxicity (163, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose

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									(150). Case reports: liver failure (211-218).		according to dose-dependent adverse reactions
Formestane	1	Not known		120	93	25				Hot flushes, alopecia, edema, nausea and vomiting, constipation, arthralgia (151)	No dose adjustment recommendations available. Recommendations: Adjust dose according to dose-dependent adverse reactions
Fosfestrol	3	1		0.5		80					No dose adjustment recommendations available. Recommendations: Adjust dose according to dose-dependent adverse reactions
Gefitinib	2	CYP3A4, CYP2D6 (164)	20	27	90	50			Frequent: hepatocellular injury, cholestasis (55)	Diarrhea, dry skin, nausea and vomiting, interstitial lung disease (162, 164)	Recommendations: Reduce dosage by 50% or avoid in patients with liver disease (164)
Gemcitabine	1	0.9 Deamination, phosphorylation (150)	25	1 – 12 (?)	10		1500	≈1	Frequent: hepatocellular injury (self-limiting) (150, 151)	Myelosuppression, flue-like symptoms, nausea and vomiting, diarrhea, hepatotoxicity (162, 163)	No dose adjustment recommendations available. Recommendations: Adjust dose according to dose-dependent adverse reactions
Goserelin	3	0.4		4.0	25		135	0.06		Hot flushes, decreased libido, depression, edema (162, 164)	Recommendations: Dose adjustment not recommended in patients with liver disease (150).
Hydroxycarbamide	3	0.4	0.5	5.0	80	80			Case report: fulminant liver failure (219)	Myelosuppression, mucositis, skin reactions, alopecia, nausea and vomiting, nephrotoxicity, neurological disturbances (163, 164)	No dose adjustment recommendations available. Recommendations: Adjust dose according to dose-dependent adverse reactions
Idarubicin	1	≈1 Oxidation, biliary excretion 8 – 17% (220, 221)		15.2	96	28	2000	≈1	Frequent: hepatocellular injury, hyperbilirubinemia (150)	Myelosuppression, mucositis, alopecia, nausea and vomiting, diarrhea, elevated liver enzymes, cardiotoxicity (162, 222)	Studies: In patients with metastases, kinetics of idarubicin is not changed (223, 224). Recommendation: If serum bilirubin 20 - 34 μmol/l: 50% dose reduction.

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											If serum bilirubin > 34 μmol/l: contraindicated (150)
Ifosfamide	3	0.5 CYP3A (activation) (175)	0.5	6.5		100	60	0.03	Sporadic: hepatocellular injury, hyperbilirubinemia (127)	Myelosuppression, hemorrhagic cystitis, alopecia, nausea and vomiting (164, 222)	Recommendation: Monitor patients with preexisting liver disease closely (150). Contraindicated in patients with decompensated liver disease (151).
Imatinib	3	0.95 N-demethylation (CYP 3A), 20% biliary elimination (150)	4.9	18	95	98			Sporadic: hyperbilirubinemia, hepatocellular injury (150).	Myelosuppression, edema, myalgia, fatigue (164)	Recommendations: Stop treatment if serum bilirubin > 3 x ULN or transaminases > 5 x ULN (150)
Irinotecan	2	0.75 Esterases, glucuronidation, CYP3A4. Biliary excretion 25% (150, 225)	75	10	65		430	0.36		Myelosuppression, cholinergic syndrome (diarrhea), alopecia, nausea and vomiting, mucositis, pulmonary toxicity (162, 164)	Study: In patients with gastrointestinal cancer and cholestasis the AUC for SN-38 (active metabolite) was 50% increased (serum bilirubin 1.1-1.5 x ULN) or 100% increased (>1.5 ULN) (226). Recommendation: If serum bilirubin > 1.5 x ULN/transaminases > 5 x ULN dose reduction according to dose-dependent toxicity. Contraindicated if serum bilirubin >5 x ULN (150). According to (226) 350 mg <sup>2</sup> in patients with serum bilirubin 1.1-1.5 ULN and 200 mg/m <sup>2</sup> when serum bilirubin >1.5 ULN.
Letrozol	3	0.95 CYP3A4, 2D6 (150)	1.9	45	60	100	40	0.04		Hot flushes, fatigue, nausea, vomiting, diarrhea, hypertonia, edema, depression (162, 164)	No dose adjustment recommendations available. Recommendations: Adjust dose according to dose-dependent adverse reactions
Leuprorelin	3	Not known	0.5	3	46		140	0.05		Hot flushes, decreased libido,	No dose adjustment

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										nausea, gynecomastia, edema (162, 164)	recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Lomustine	3	1 Cis- and trans-4-hydroxylation (227)	1.70	10	-	100			<i>Sporadic:</i> hepatocellular injury (150)	Myelosuppression, nausea and vomiting, alopecia, mucositis, elevated liver enzymes, neurological disturbances, pulmonary fibrosis (164, 203)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Medroxy-progesteron	1	1 CYP3A4	0.6	36	94	<10	1270	≈1	<i>Rare:</i> cholestasis, peliosis hepatic (150)	Weight gain, edema, Cushing's syndrome, pulmonary and cerebral thromboembolism (164, 222)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Megestrol	4	1 Glucuronidation (151)		18					<i>Rare:</i> hepatocellular injury, hyperbilirubinemia (150)	Weight gain, edema, Cushing's syndrome, pulmonary and cerebral thromboembolism (164, 222)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Melphalan	2	0.9 Hydroxylation (151)	0.6	1.5	80	70	515	0.52	<i>Case reports:</i> veno-occlusive disease (VOD) (150)	Myelosuppression, nausea and vomiting, diarrhea, mucositis, alopecia, amenorrhea, pulmonary fibrosis, hepatotoxicity (VOD) (164, 222)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Mercapto-purine	1	0.9 Xanthine oxidase (thiouric acid), thiopurine methyltransferase (151)	0.6	0.9	19	12	765	0.77	<i>Frequent:</i> hepatocellular injury, cholestasis, hyperbilirubinemia in 6 – 40% (127). <i>Case reports:</i> liver failure (228-231), venoocclusive disease (127).	Myelosuppression, nausea and vomiting, diarrhea, hyperuricemia and/or hyperuricosuria, hepatocellular injury, mucositis, pancreatitis, nephrotoxicity, interstitial pneumonitis, alopecia, oligospermia (162, 222)	<i>Recommendations:</i> Monitor liver function. Contraindicated in patients with decompensated liver disease (150)

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									Risk may be higher in patients with reduced activity of thiopurine methyltransferase		
Methotrexate	3	0.05	0.70	7.2	50	70	145	0.01	<i>Sporadic:</i> Fatty liver, fibrosis, cirrhosis during long-term treatment with immunosuppressive doses (128, 232-237). <i>Case reports:</i> hepatocellular injury, acute liver failure when used as an antineoplastic agent (156, 238-241)	Myelosuppression, mucositis, nausea and vomiting, diarrhea, hepatotoxicity, nephrotoxicity, neurological disturbances (164, 222)	<i>Studies:</i> No correlation between liver function and methotrexate serum levels (242). <i>Recommendation:</i> Close monitoring in patients with decompensated liver disease. Reduce dose in the presence of ascites and/or decreased renal function (150, 151)
Mitomycine	4	0.9	0.3	0.5					<i>Rare:</i> steatosis <i>Case reports:</i> venoocclusive disease (127)	Myelosuppression, nausea and vomiting, nephrotoxicity, hemolytic uremic syndrome, hepatotoxicity (VOD) (164, 222)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Mitoxantrone	1	0.95 mono- or dicarboxylation (inactive), biliary excretion 25% (150)	10 - 15	57	76	-	750	0.79	<i>Frequent:</i> hepatocellular injury (127)	Myelosuppression, mucositis, nausea and vomiting, diarrhea, menstrual disorders, neurological disorders, cardiotoxicity, alopecia, hepatotoxicity, nephrotoxicity (162, 164, 222)	<i>Studies:</i> Clearance reduced by 50% in patients with moderate liver disease (243). Patients with serum bilirubin < 60 μmol/L tolerate 14 mg/m <sup>2</sup> , patients with serum bilirubin > 60 μmol/L and bad performance status have higher mortality with this dosage (244). In patients with liver metastases, half-life of mitoxantrone correlated with serum bilirubin and cholestasis

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											(245). <i>Recommendation:</i> Dose adjustment (8 mg/m <sup>2</sup> ) or contraindicated (bad performance status) in patients with serum bilirubin > 60 μmol/L (244)
Nimustine	4	1		0.6	34						No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to adverse reactions
Oxaliplatin	4	≈0.5, Reduction (non-enzymatic), biliary excretion 5% (246)		260	75					Myelosuppression, nausea and vomiting, mucositis, renal failure, neurotoxicity, visual disturbances, thromboembolism (162, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Paclitaxel	2	0.95 CYP 3A, 2C8. Biliary excretion >5% (247)	2.0	3	95		380	0.41	<i>Sporadic:</i> hepatocellular injury, cholestasis <i>Rare:</i> hyperbilirubinemia, liver failure (150)	Myelosuppression, peripheral neuropathy, arthralgia, myalgia, hypotension, nausea and vomiting, diarrhea, mucositis, cardiotoxicity (arrhythmias, bradycardia) (164, 222)	<i>Studies:</i> Liver disease/liver cirrhosis appears to be a risk factor liver for systemic toxicity (248, 249). Increased risk for myelosuppression in patients with increased transaminases and/or serum bilirubin > 25 μmol/L (250). In patients with increased transaminases (3-10 x ULN) and hyperbilirubinemia (1.3 – 2 x ULN) clearance was decreased by ≈ 40% (251) <i>Recommendation:</i> Monitor patients with liver disease well for adverse effects. Do not administer in patients with decompensated liver disease (150, 251)
Raltitrexed	4	0.5 Polyglutamate derivative (252)	7.0	2	93				<i>Frequent:</i> hepatocellular injury <i>Sporadic:</i>	Myelosuppression, nausea and vomiting, diarrhea, mucositis, rash, conjunctivitis,	<i>Recommendations.</i> No dose adjustment in patients with mild to moderate liver disease.



Antineoplastic Drugs

Drug	Cat <sup>1</sup>	Kinetic parameters							Hepatic adverse effects <sup>9</sup>	Dose-dependent adverse reactions	Studies performed and dosage recommendations
		Q <sub>0</sub> <sup>2</sup> , metabolism	V <sub>d</sub> <sup>3</sup> (L/kg)	t <sub>1/2</sub> <sup>4</sup> (h)	PB <sup>5</sup> (%)	F <sup>6</sup> (%)	Cl <sub>sys</sub> <sup>7</sup> (mL/min)	E <sup>8</sup>			
									cholestasis, hyperbilirubinemia <i>Case report:</i> liver failure (253)	alopecia, arthralgia, hepatotoxicity, hyperbilirubinemia, edema, flue-like symptoms, (164)	Contraindicated in patients with decompensated liver disease (150).
Rituximab	4	Not known		68						Infusion related reactions, B-cell depletion, myelosuppression, mucositis, tumor lysis syndrome (162, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Tamoxifen	4	1 Hydroxylation, N-dealkylation (CYP 2C9, 2D6, 3A4, 2C8) (151)	60	4 – 11 days	99				<i>Sporadic:</i> hepatocellular injury, cholestasis, fatty liver (127) <i>Rare:</i> liver failure (254-256)	Hot flushes, nausea, edema, vaginal bleeding, glaucoma, thromboembolism, hepatotoxicity, hypercalcemia (164, 222)	<i>Studies:</i> In a patient with liver metastases liver function deteriorated one year after start of tamoxifen (257). In a randomized trial in patients with hepatocellular carcinoma, liver function was not affected (258). <i>Recommendation:</i> Monitor liver function and systemic toxicity in patients with preexisting liver disease.
Temozolomide	3	0.9 non-enzymatic		1.8	15	100				Myelosuppression, nausea and vomiting, fatigue, headache, diarrhea (162, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Thiotepa	3	0.5 CYP 2B1, 2C11 (259)		2.4	99		315	0.18	<i>Case report:</i> liver failure (260)	Myelosuppression, gonadal dysfunction, nausea and vomiting, neurotoxicity, mucositis (203, 261)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Tioguanine	4	>0.9, Thiopurine methyltransferase (?)		5 - 9					<i>Rare:</i> hepatocellular injury, cholestasis (127). <i>Case reports:</i> Venocclusive disease	Myelosuppression, tumor lysis syndrome, nausea and vomiting, mucositis, hepatotoxicity (162, 164)	<i>Recommendation:</i> Monitor liver function after administration of high doses. Contraindicated in patients with decompensated liver disease (150).

Antineoplastic Drugs

Drug	Cat <sup>1</sup>	Kinetic parameters							Hepatic adverse effects <sup>9</sup>	Dose-dependent adverse reactions	Studies performed and dosage recommendations
		Q <sub>0</sub> <sup>2</sup> , metabolism	V <sub>d</sub> <sup>3</sup> (L/kg)	t <sub>1/2</sub> <sup>4</sup> (h)	PB <sup>5</sup> (%)	F <sup>6</sup> (%)	Cl <sub>sys</sub> <sup>7</sup> (mL/min)	E <sup>8</sup>			
									(262, 263)		
Topotecan	2	0.6 Esterases. Biliary excretion 20% (264)	1.9	2.4	35	32	825	0.55		Myelosuppression, nausea and vomiting, alopecia, mucositis, diarrhea (162, 164)	<i>Studies:</i> 14 patients with increased transaminases and/or hyperbilirubinemia (some with cirrhosis) were treated with 1.5 mg/m <sup>2</sup> . Topotecan clearance correlated with ICG clearance but no more adverse effects were observed in patients with liver disease (265). On the other hand, two thirds of patients with hepatocellular carcinoma treated with topotecan developed grade IV neutropenia (266). <i>Recommendation:</i> No dose adjustment for patients with hepatic dysfunction but monitor patients well for systemic toxicity (265).
Toremifen	3	1 CYP3A4 (N-dealkylation, hydroxylation) Enterohepatic circulation (267)	12-15	148	99	100	75	0.08	<i>Sporadic:</i> hepatocellular injury, cholestasis, fatty liver (127)	Hot flushes, edema, vaginal bleeding, hepatotoxicity, thromboembolism, hypercalcemia (162, 164)	<i>Studies:</i> In 10 patients with liver cirrhosis or fibrosis the elimination half-life was increased by 75% and clearance decreased by 28% (267). <i>Recommendation:</i> Dose reduction in patients with liver cirrhosis by 50%, gradual increase while monitoring adverse effects (150).
Trastuzumab	4	Not known	0.04	140						Infusion related reactions, cardiotoxicity, hepatotoxicity, pulmonary infiltrates, exacerbation of chemotherapy-induced neutropenia (162, 164)	No dose adjustment recommendations available. <i>Recommendations:</i> Adjust dose according to dose-dependent adverse reactions
Tretinoin	4	CYP2C8, Isotretinoin, 4-oxo-retinoic acid (55)		1.25	95				<i>Frequent:</i> hepatocellular injury (164)	Capillary leak syndrome (weight gain, pulmonary infiltrates, pleural and/or	<i>Recommendation:</i> Need for dosage adjustments in patients with hepatic impairment has not been shown. A

Antineoplastic Drugs

Drug	Cat <sup>1</sup>	Kinetic parameters							Hepatic adverse effects <sup>9</sup>	Dose-dependent adverse reactions	Studies performed and dosage recommendations
		Q <sub>0</sub> <sup>2</sup> , metabolism	V <sub>d</sub> <sup>3</sup> (L/kg)	t <sub>1/2</sub> <sup>4</sup> (h)	PB <sup>5</sup> (%)	F <sup>6</sup> (%)	Cl <sub>sys</sub> <sup>7</sup> (mL/min)	E <sup>8</sup>			
										pericardial effusions), leukocytosis, neurological disturbances, dyslipidemia, hepatotoxicity, hypercalcemia (162, 164)	dose reduction to 25 mg/m <sup>2</sup> is recommended as a precautionary measure (55).
Triptorelin	3	0.52	0.5	3			85	0.05		Hot flushes, decreased libido, impotence, gynecomastia (162)	<i>Studies:</i> As compared to 6 healthy young males, 6 patients with normal renal function and hepatic impairment (Child A or B) had decreased total clearance (57 versus 210 mL/min) and prolonged elimination half-life (7.6 versus 2.8 hours) after a single intravenous bolus of 0.5 mg. Despite these differences after intravenous dosing, dose reduction of the sustained-release formulation used clinically is judged not necessary, because its release rate is much slower than its elimination rate (268). <i>Recommendation:</i> Dosage reduction of sustained-release triptorelin does not appear to be necessary in patients with liver disease (268).
Vinblastine	1	1 CYP3A4, biliary excretion >50% (151)	20	25	75		865	0.96		Myelosuppression, nausea and vomiting, alopecia, mucositis, neurotoxicity (peripheral and autonomic), inappropriate ADH secretion (SIADH) (164, 222)	<i>Recommendation:</i> If serum bilirubin > 50 μmol/L → 50% dose reduction (150).
Vincristine	3	0.9 CYP3A4, biliary excretion 70% (151)	8.0	23	75		140	0.14		Myelosuppression, nausea and vomiting, alopecia, mucositis, neurotoxicity (peripheral and autonomic), inappropriate ADH secretion	<i>Studies:</i> In the presence of cholestasis/hyperbilirubinemia β-half-life was prolonged (77). In patients with leukemia or lymphoma and cholestasis, AUC and toxicity

Antineoplastic Drugs

Drug	Cat <sup>1</sup>	Kinetic parameters							Hepatic adverse effects <sup>9</sup>	Dose-dependent adverse reactions	Studies performed and dosage recommendations
		Q <sub>0</sub> <sup>2</sup> , metabolism	V <sub>d</sub> <sup>3</sup> (L/kg)	t <sub>1/2</sub> <sup>4</sup> (h)	PB <sup>5</sup> (%)	F <sup>6</sup> (%)	Cl <sub>sys</sub> <sup>7</sup> (mL/min)	E <sup>8</sup>			
									(SIADH) (164, 222)	were increased (269). <i>Recommendation:</i> If serum bilirubin > 50 μmol/L → 50% dose reduction (150). Some authors advise 50% dose reduction also if alkaline phosphatase is increased (82).	
Vindesine	4	Not known CYP 3A, biliary excretion	8.8	24			17.5		Myelosuppression, nausea and vomiting, alopecia, mucositis, neurotoxicity (peripheral and autonomic), inappropriate ADH secretion (SIADH) (164, 222)	<i>Recommendation:</i> Monitor patients for dose-dependent adverse effects. Dose may need to be adjusted in patients with hyperbilirubinemia (see vincristine) (150).	
Vinorelbine	1	0.85 CYP 3A, biliary excretion 50% (78, 151)	75	30	15	≈40			Myelosuppression, neurotoxicity (peripheral and autonomic), mucositis, alopecia, pulmonary toxicity (162, 164)	<i>Studies:</i> In 19 patients with liver metastases, clearance was reduced by 50% in patients with >75% of the liver replaced by tumor (270). <i>Recommendation:</i> 50% dose reduction if more than 75% of liver replaced by tumor (270) or if serum bilirubin > 34 μmol/L (78).	

<sup>1</sup>Cat = drug category. Drugs were categorized as follows: Category 1: high hepatic extraction (E) (E > 60%, bioavailability < 40%), category 2: intermediate hepatic extraction (E = 30-60%, bioavailability 40-70%), category 3: low hepatic extraction (E < 30%, bioavailability >70%), category 4: hepatic extraction not known

<sup>2</sup>Q<sub>0</sub>: extrarenal dose fraction = fraction metabolized or excreted by bile (1 - Q<sub>0</sub>: fraction excreted unchanged by the kidney)

<sup>3</sup>V<sub>d</sub> = volume of distribution in L per kg. For calculation, body weight was assumed to be 70 kg.

<sup>4</sup>t<sub>1/2</sub>: dominant half-life

<sup>5</sup>PB: Fraction bound to proteins (protein binding in %)

<sup>6</sup>F: Bioavailability

<sup>7</sup>Cl<sub>sys</sub>: systemic clearance (L/min)

<sup>8</sup>E: hepatic extraction, calculated as described in equation 4

<sup>9</sup>Frequency of hepatic adverse effects: frequent > 10% of patients treated, sporadic: 1-10%, rare: < 1%

Abbreviations: CYP = cytochrome P450, ULN = upper limit of normal

Characterization of liver disease and severity of liver dysfunction: compare Table 2

## **6.2 Dose Adaptation of Psychotropic Drugs in Patients with Liver Disease**

This paper has been submitted to Drug Safety in April 2008 (see below).

A complete list of the investigated psychotropic drugs can be found in the electronic appendix on CD-ROM.

## **Dose Adaptation of Psychotropic Drugs in Patients with Liver Disease**

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**Abstract**

Dose adjustment of psychotropic drugs in patients with liver cirrhosis may be important as most of these drugs are predominantly eliminated by the liver and many of them have dose-dependent adverse reactions. Since no surrogate parameter is available to predict hepatic metabolism of drugs, dose adjustment according to pharmacokinetic properties of the drugs is proposed. Psychotropic drugs (antiepileptics, anti-parkinson drugs, psycholeptics such as antipsychotics, anxiolytics, sedatives and hypnotics, and psychoanaleptics such as antidepressants, psychostimulants and anti-dementia drugs) marketed in Switzerland in 2006 were therefore classified according to their hepatic extraction and/or bioavailability to predict their kinetic behaviour in cirrhotic patients. The expected changes in hepatic metabolism predicted by pharmacokinetic properties were compared with the results from kinetic studies carried out in patients with liver disease. These studies were identified using MEDLINE searches.

Of the 116 psychotropic drugs available on the Swiss market by the year 2006, only 12 were predominantly eliminated through the kidney. For 5 substances no  $Q_0$ -value could be determined because of lack of pharmacokinetic data. Of 106 drugs that could be classified according to their bioavailability and/or hepatic extraction, 27% were categorised as high, 25% as intermediate and 48% as low extraction drugs. Pharmacokinetic studies in patients with liver disease were available for 55 of 99 drugs eliminated predominantly by the liver ( $Q_0 \geq 0.5$ ). Only few kinetic studies in patients with liver disease were found for antipsychotics, anti-parkinson drugs and antidepressants, except for selective serotonin reuptake inhibitors and some newer antidepressants. The expected changes in pharmacokinetics were generally in good agreement with the changes reported in pharmacokinetic studies. For 12 drugs, the observed changes in pharmacokinetics from clinical studies were different from the changes expected based on their classification. However, for low extraction drugs metabolised by cytochrome P450 isozymes clearance may be reduced up to 50%.

In conclusion, the classification of drugs according to their hepatic extraction and/or bioavailability is a useful tool for dose adjustment, if information from clinical studies is lacking. There is a gap of information about pharmacokinetic changes in patients with liver cirrhosis for a large part of centrally acting drugs. Kinetic studies for centrally acting drugs with predominant hepatic metabolism should be carried out in

patients with liver disease to allow precise dose recommendations for enhancing patient safety.

### **Introduction**

The liver is involved in the clearance of many drugs through a variety of metabolic pathways and/or biliary excretion of unchanged drugs or metabolites. Alterations of these metabolic and/or excretory functions in patients with liver disease, most pronounced in patients with liver cirrhosis, can lead to drug accumulation or, less often, to failure to form an active metabolite.

The factors affecting drug disposition in patients with chronic liver disease have been discussed in numerous reviews.(1, 2, 7, 25, 271-274) In these reviews, drugs are classified according to their hepatic extraction (Eh), which determines mainly the hepatic clearance of drugs. Since, until now, no in vivo surrogate parameter exists to predict hepatic clearance of drugs, predictions concerning dose adjustment in patients with liver disease can only be made based on the pharmacokinetic properties of the drugs administered.(25) Dose recommendations made in this paper are based on the classification of the drugs according to their Eh. Only the basic principles underlying this classification will be reviewed in this article. For further information, refer to the publication of Delco et al.(25) or Tchambaz et al..(60)

Hepatic clearance (Cl<sub>hep</sub>) is defined as the volume of blood from which a drug is removed completely by the liver per unit time. Hepatic clearance can be expressed as (equation 1):

$$Cl_{hep} = \frac{(f_u \times Cl_i) \times Q}{(f_u \times Cl_i) + Q} \quad (\text{Eq. 1})$$

where Q is the blood flow across the liver, f<sub>u</sub> is the unbound fraction (free) and Cl<sub>i</sub> is the intrinsic clearance of the drug.

When (f<sub>u</sub> × Cl<sub>i</sub>) >> Q, equation 1 can be simplified to Cl<sub>hep</sub> ≈ Q. In this case, the blood flow across the liver becomes rate-limiting for hepatic clearance of a drug. Due to their high hepatic extraction, this class of drugs has a low bioavailability and is insensitive to changes in protein binding or activity of drug metabolising enzymes. Bioavailability of high extraction drugs may increase significantly in patients with liver cirrhosis due to porto-systemic shunts resulting from portal hypertension.(275) Also



altered hepatic blood flow will lead to changes in hepatic clearance of high extraction drugs.(272) Therefore, initial dose of orally administered high extraction drugs has to be reduced according to the expected increase in bioavailability and the maintenance dose according to bioavailability and impaired hepatic blood flow across the liver. For intravenous administration, the maintenance dose has to be reduced, since only the reduction in hepatic blood flow has to be considered.

In contrast, hepatic clearance of drugs for which  $(f_u \times Cl_i) \ll Q$  is mainly determined by the capacity of the liver to metabolise these substances. For such drugs, equation 1 can be simplified to  $Cl_{hep} \approx (f_u \times Cl_i)$ . Liver cirrhosis can alter  $Cl_i$  of these drugs by affecting the activity of cytochrome (CYP) P450 isozymes and/or glucuronyl transferases, whereby oxidation seems to be more sensitive than glucuronidation.(1, 273) Because of a low hepatic extraction during the first passage across the liver, such drugs have a high bioavailability, if bioavailability is not limited by processes different from first pass hepatic metabolism. Treatment can be started with normal initial doses, because no significant alteration in bioavailability is expected. Maintenance doses may be reduced due to impaired hepatic clearance, especially for drugs mainly metabolised by CYP 450 isozymes. Hepatic clearance of low extraction drugs highly bound to albumin may additionally be influenced by changes in plasma protein binding. In patients with liver cirrhosis protein binding may be diminished due to lower serum albumin resulting from impaired albumin synthesis (276) and/or due to accumulation of endogenous compounds (e.g. bilirubin), competing for plasma protein binding sites. As a consequence, the free (unbound) fraction of a drug may be increased and dose adjustment should be made according to the free plasma concentration of the drug (e.g. phenytoin, valproate) or according to pharmacodynamic parameters (e.g. phenprocoumon).

Drugs with an intermediate hepatic extraction show characteristics of both groups. The hepatic clearance of such drugs can be influenced by all the parameters included in equation 1. Initial doses should therefore be reduced according to the expected increase in bioavailability and maintenance dose should be further adjusted according to the expected decrease in intrinsic hepatic clearance.

Drugs acting on the central nervous system (e.g. anxiolytics, sedatives, antidepressants, antipsychotics, antiepileptics) are often prescribed to patients with liver cirrhosis due to a variety of psychiatric symptoms or illnesses associated with liver cirrhosis.(277) Benzodiazepines may be used for the management of alcohol

deprivation, for insomnia or as a pre-medication before upper gastrointestinal endoscopy. A study evaluating drug use in patients with liver cirrhosis showed that, beside the benzodiazepines, also antipsychotics, antidepressants and/or antiepileptics were frequently prescribed.(278) In fact, chronic depressive symptoms are not uncommon in cirrhotic patients.(279)

Most of the psychotropic drugs are lipophilic and are extensively metabolised through the liver, involving also biotransformation by CYP450 isozymes.(277) In cirrhotic patients, the decreases in hepatic clearance and hepatic extraction result in an increased risk for dose-related adverse drug reactions of psychotropic drugs. But not only pharmacokinetic changes should be considered when prescribing centrally acting drugs, also pharmacodynamic changes have been reported in patients with liver cirrhosis.(272)

Prescribing to patients with liver cirrhosis requires careful drug selection and dose adjustment based on the pharmacokinetic profile to prevent adverse effects. Classification according to pharmacokinetic properties and results from clinical trials in patients with liver cirrhosis and/or other liver diseases can therefore help to select and administer drugs more rationally in this group of patients. The aims of this work were therefore: (i) to collect pharmacokinetic data of psychotropic drugs (antiepileptics, anti-parkinson drugs, antipsychotics, anxiolytics, sedatives, hypnotics, antidepressants, psychostimulants and anti-dementia drugs) and to classify the drugs based on their pharmacokinetic profile; (ii) to compare the dose recommendations based on this classification with recommendations from the product information and from published clinical studies; (iii) to formulate recommendations for dose adjustment in patients with liver cirrhosis; and (iv) to localise gaps in the current databases and recommendations.

### **Methods**

We searched the database MEDLINE for studies dealing with pharmacokinetics, hepatic adverse effects and/or dose adjustment in patients with liver disease for all psychotropic drugs registered in Switzerland in 2006. To perform our literature search, the following medical subject heading (MeSH) terms were used: 'pharmacokinetics', 'metabolism', 'cytochromes', 'drug toxicity', 'liver diseases', 'central nervous system agents', and the specific generic name of each psychotropic drug. The references of the publications found were screened for additional relevant

studies. In addition to databases, the standard literature such as the Swiss Compendium of Drugs(280) containing product information of the drugs registered in Switzerland, the Physicians' Desk Reference,(281) as well as Therapeutic Drugs,(282) DRUGDEX<sup>®</sup> System from Thomson Healthcare(283), Avery's Drug Treatment(284), Goodman & Gilman's: The pharmacological basis of therapeutics(285) and Hepatotoxicity(286) were used to find data about pharmacokinetics, hepatic adverse effects, dose-dependent adverse effects, and dose recommendations of the psychotropic drugs investigated.

The psychotropic drugs were categorised as outlined in the previous section and according to a previous review of antineoplastic agents by Tchambaz et al..(60) The classification is based on the hepatic extraction and/or bioavailability of a given drug (table I). Because data for hepatic extraction is rare in the literature, hepatic extraction was estimated using the following equation (equation 2):

$$E = \frac{Cl_{\text{hep}}}{Q} = \frac{Q_0 \times Cl_{\text{sys}}}{Q} \quad (\text{Eq. 2})$$

where  $Q_0$  is the dose fraction metabolised or excreted extra-renally ( $1-Q_0$  is the dose fraction excreted non-metabolised by the kidney),  $Cl_{\text{sys}}$  is the systemic clearance (determined in plasma) and  $Q$  the plasma flow across the liver.  $Q$  was assumed to be 900 mL/min(60) and the values for  $Q_0$  and  $Cl_{\text{sys}}$  were obtained from the literature. If bioavailability and calculated hepatic extraction were not consistent, drugs were classified according to the measured value for absolute bioavailability except when bioavailability was lower than expected from hepatic extraction due to incomplete intestinal absorption.

Dose recommendations are based on the original articles from clinical studies, on the product information published in the Swiss Compendium of Drugs(280) or the Physicians' Desk Reference,(281) and based on the classification of the drugs according to their hepatic extraction. The available strengths and oral dosage forms of the drugs marketed in Switzerland were also taken into account for the dosage recommendations made.

Drug-induced liver disease was classified according to Benichou(287) if enough data was available for classification (see Table II). In addition to the hepatic adverse effects also the most important dose-dependent adverse effects of the psychotropic

drugs were retrieved from the standard literature and listed in Table IV.(280-283) Occurrence of such symptoms may serve as an indicator for drug accumulation in the case of insufficient dose adaptation to impaired liver function.

### **Results**

A total of 116 psychotropic drugs were available on the Swiss market by the year 2006. The complete list of these drugs (antiepileptics (n=18), anti-parkinson drugs (n=13), antipsychotics (n=22), anxiolytics, sedatives and hypnotics (n=29), antidepressants (n=24), psychostimulants (n=6) and anti-dementia drugs (n=4)) together with their pharmacokinetic properties and dose recommendations is available at <http://kpharm.unibas.ch>.

Data about pharmacokinetic properties of the drugs were either extracted from the standard literature(280-285, 288) or were based on published pharmacokinetic studies or reviews.(289-329) Only 12 of 116 psychotropic drugs (10%) are predominantly eliminated through the kidney ( $Q_0$ -value  $<0.5$ ): amantadine, lithium, phentermine, phenylpropanolamine, pramipexole, sulpiride, tiapride, and the newer antiepileptics gabapentin, levetiracetam, pregabalin, topiramate, and vigabatrin. For 5 substances, no  $Q_0$ -value could be determined because of lack of pharmacokinetic data. The remaining drugs are predominantly eliminated by the liver either through CYP-dependent metabolism and/or through conjugation. CYP isozymes involved in the phase I metabolism of antipsychotics are mainly CYP 2D6, 3A4 and to a lesser extent 1A2. CYP 2D6 plays a major role in the metabolism of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Whereas most of the benzodiazepines are metabolised through CYP 2C19 and/or 3A4, the major metabolic pathway of oxazepam, lorazepam and temazepam is glucuronidation.

Based on their bioavailability and/or hepatic extraction, 29 substances were classified as high extraction drugs, 26 as drugs with intermediate hepatic extraction, and 51 as low extraction drugs (Table III). Only 10 substances (8.6%) could not be classified because of lack of pharmacokinetic data. Most of the antiepileptic drugs were classified as low extraction drugs, except oxcarbazepine, the only high extraction drug in this therapeutic drug class. Also benzodiazepines were commonly classified as low extraction drugs, except flurazepam, midazolam and triazolam. In contrast, 8 of 13 anti-parkinson drugs available, namely biperiden, bromocriptine, cabergoline, dihydroergocryptine, entacapone, levodopa, pergolide, and selegiline were classified

as high extraction drugs. However, the maintenance dose of anti-parkinson drugs is commonly found by slow up-titration. Since treatments are therefore usually started at low doses, initial doses have not to be reduced additionally in patients with liver cirrhosis.

The expected dose-dependent adverse reactions in case of accumulation of a drug in patients with liver cirrhosis can usually be deduced from its pharmacological effect and receptor affinity.(280-283, 288, 289, 327, 330, 331) Since such adverse effects are important for guiding drug therapies, the most common dose-dependent adverse effects of selected therapeutic drug classes are summarised in Table IV.

Hepatic adverse drug effects have been reported for 88 of the 116 drugs studied (76%).(280-283, 286, 332-363) Phenothiazines may cause cholestatic liver injury, while some older antiepileptic drugs are associated with induction of acute intermittent porphyria in predisposed patients. The use of benzodiazepines may induce hepatic encephalopathy in cirrhotic patients. For other drug classes, no specific pattern of hepatic adverse reactions has been reported. Tricyclic antidepressants, for example, have been associated with hepatocellular as well as cholestatic liver injuries.

Pharmacokinetic studies, either published in Medline(9, 44, 295, 307, 311, 344, 351, 364-423) and/or in the respective product information(280, 281) or standard literature,(282, 283) evaluating the kinetic properties of drugs in patients with liver disease could be found for 56% of the drugs with known predominant hepatic elimination (55 of 99). Of the individual therapeutic groups assessed, for 3 of 4 anti-dementia drugs (75%) pharmacokinetic data in patients with liver cirrhosis was available. The only exception was memantine, for which 50% of the dose is eliminated unchanged through the kidney. Also for a high proportion of the anxiolytics, hypnotics and sedatives (20 of 28 drugs; 71%) as well as for antiepileptics (9 of 19 drugs; 64%), pharmacokinetic information in patients with liver disease was available. The drug class, for which only sparse information about pharmacokinetic changes in patients with liver disease was available, are the antipsychotics. For only 5 of 17 drugs (29%), clinical studies in patients with liver disease could be found (for aripiprazole, promazine, quetiapine, risperidone and sertindole). The best studied drug class are the selective serotonin reuptake inhibitors (SSRIs). For all of the 6 substances available in Switzerland (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) data about

pharmacokinetics in patients with liver cirrhosis could be found. In Table V, pharmacokinetic data and dosage recommendations are provided for drugs with a high hepatic extraction. For the drugs with intermediate or low hepatic extraction, the data are available on <http://kpharm.unibas.ch>.

### **Discussion**

Since no reliable surrogate parameter for hepatic drug metabolism is available, dose adjustment based on the hepatic extraction of drugs has been proposed in patients with liver diseases, provided that pharmacokinetic properties of a drug have been studied.(25) Of 116 psychotropic drugs studied, only 10 substances could not be classified according to their hepatic extraction. These drugs can be replaced in patients with liver cirrhosis by adequate alternatives without any problems. Because of the high proportion of centrally acting drugs eliminated predominantly through the liver, dosage has to be reduced for most of them in patients with liver cirrhosis in order to prevent dose-dependent adverse effects. When comparing the results from clinical pharmacokinetic studies in patients with liver cirrhosis and other liver diseases (available for 55 drugs) with the estimates based on measured or calculated hepatic extraction, only for 12 drugs the recommendations were not fully congruent. It must be pointed out, that for low extraction drugs, the observed reduction in drug clearance in patients with liver disease may be as high as 50% for drugs metabolised primarily by CYP 450 isozymes. For oxcarbazepine and cabergoline, both classified as high extraction drugs, higher changes would have been predicted based on their estimated hepatic extraction than observed in clinical studies. These differences between the expected and observed changes in cirrhotic patients may be explained mainly by the metabolic pathway of the substances. Oxcarbazepine for example undergoes 10-keto reduction by cytosolic arylketone reductases to the monohydroxy derivative(293) and is not metabolized by cytochrome P450 isozymes that are known to be affected by liver cirrhosis. Similarly, also for cabergoline, the contribution of CYP-mediated metabolism is minimal.(280)

Although pharmacokinetic data in patients with liver disease is available for 55 of the 116 drugs studied, there is an information gap for a larger part of centrally acting drugs. Only few studies in patients with liver cirrhosis are available for antipsychotics, anti-parkinson drugs and most of the antidepressants, except for SSRIs and some newer antidepressants. In general, information about pharmacokinetic properties in

patients with liver disease is lacking especially for older drugs, while for newer drugs results from pharmacokinetic studies are often included in the product information. There appears to be an effort by the pharmaceutical companies to provide information about the pharmacokinetics of drugs in vulnerable patient groups such as patients with liver disease. Information about pharmacokinetics in patients with renal or hepatic disease as well as for elderly patients should be included in the product information for every new drug released on the market.

Findings from clinical pharmacokinetic studies may sometimes be of limited value, as most of the studies were single dose trials, not reflecting exactly the situation in the every day practice. In contrast to single dose administration, a more accentuated accumulation of certain substances would be expected in patients with liver disease during long-term treatment.

Clinical studies as well as the product information did often not provide precise dose recommendations for patients with liver disease, suggesting only dose reduction of a specific drug without quantifying the reduction. The combination of the results from pharmacokinetic studies with the estimates based on hepatic extraction showed often to be helpful to formulate more precise dose recommendations. However, prospective clinical trials testing the appropriateness of such dose recommendations are mostly lacking.

For centrally acting drugs, not only dose adjustment based on pharmacokinetic properties is necessary, but also changes in pharmacodynamics should be considered. For example, cirrhotic patients have a greater cerebral sensitivity to a number of drugs acting on the central nervous system (CNS), e.g. benzodiazepines or antipsychotics.(7, 277) Although the mechanism underlying this hypersensitivity remains to be explained, there is evidence that it is not caused only by pharmacokinetic alterations. Patients with hepatic encephalopathy require special consideration, as benzodiazepines and/or drugs with anticholinergic properties may worsen cognitive function.(375, 396) Nevertheless, administration of benzodiazepines is indicated for treatment of alcohol withdrawal, anxiety or before endoscopic procedures or surgery in such patients. With the exception of flurazepam, midazolam and triazolam, benzodiazepines are all categorized as low extraction drugs. Since CYP-mediated metabolism is generally more affected by liver disease than glucuronidation,(1, 273) we consider lorazepam, oxazepam and temazepam as the benzodiazepines of choice for patients with liver cirrhosis.

### **Conclusion**

Dose recommendations which are based on the hepatic extraction and/or bioavailability of a drug are generally in a good agreement with the data from pharmacokinetic studies in patients with liver cirrhosis. Classification of drugs according to hepatic extraction is therefore a useful approach for dose adjustment in patients with liver cirrhosis, when appropriate clinical studies are lacking. For a larger part of centrally acting drugs, clinical pharmacokinetic studies and precise dose recommendations are not available. Pharmaceutical companies should be urged to provide precise dosage recommendations for new drugs and for critical drugs (e.g. drugs with a high hepatic extraction) already on the market.

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### **References**

See below



**Tables**

Table I. Categorisation of psychotropic drugs screened according to pharmacokinetic variables

Category	Level of hepatic extraction (%)	Resulting oral bioavailability
1	High (>60)	Oral bioavailability is <40% in the case of complete intestinal absorption (or lower, if intestinal absorption is not complete)
2	Intermediate (30-60)	Oral bioavailability is 40-70% in the case of complete intestinal absorption (or lower, if intestinal absorption is not complete)
3	Low (<30)	Oral bioavailability is >70% in the case of complete intestinal absorption (or lower, if intestinal absorption is not complete). In this category, protein binding may be relevant: for drugs with high binding to albumin (>90%), hepatic clearance may increase
4	Unknown	Not known

Table II. Classification of liver injury according to Bénichou C.(287)

Liver injury	Characterisation
Hepatocellular liver injury	Isolated elevation of transaminases of hepatic origin or $R^a \geq 5$ .
Cholestatic liver injury	Isolated elevation of alkaline phosphatase of hepatic origin or $R \leq 2$ .
Mixed liver injury	Concomitant elevation of transaminases and alkaline phosphatase and $2 < R < 5$ .

a 
$$R = \frac{\text{alanine aminotransferase (times upper limit of normal)}}{\text{alkaline phosphatase (times upper limit of normal)}}$$

Table III. Psychotropic drugs with  $Q_0 \geq 0.5$  listed by hepatic extraction category

Category	Drugs
	<b>Antiepileptics</b>
1	Oxcarbazepine
2	-
3	Barbexaclone, carbamazepine, clonazepam, ethosuximide, lamotrigine, phenobarbital, phenytoin, primidone, tiagabine, valproate
4	Methsuximide, sulthiame
	<b>Anti-parkinson drugs</b>
1	Biperiden, bromocriptine, cabergoline, dihydroergocryptine, entacapone, levodopa, pergolide, selegiline
2	Ropinirole
3	Procyclidine, tolcapone
	<b>Antipsychotics</b>
1	Chlorpromazine, chlorprothixene, fluphenazine, perphenazine, promazine, quetiapine
2	Amisulpride, clozapine, flupenthixol, haloperidol, levomepromazine, olanzapine, risperidone, zuclopenthixol
3	Aripiprazole, penfluridol, sertindole
4	Clothiapine, pipamperone
	<b>Anxiolytics, sedatives and hypnotics</b>
1	Buspirone, clomethiazole, flurazepam, hydroxyzine, promethazine, zaleplon
2	Diphenhydramine, midazolam, triazolam, zolpidem

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3	Alprazolam, bromazepam, chlordiazepoxide, clobazam, clorazepate, diazepam, flunitrazepam, lorazepam, lormetazepam, meprobamate, methaqualone, nitrazepam, oxazepam, prazepam, temazepam, zopiclone
4	Chloral hydrate, doxylamine, ketazolam
	<b>Antidepressants</b>
1	Bupropion, dibenzepin, doxepin, mianserin, sertraline
2	Amitriptyline, clomipramine, escitalopram, fluvoxamine, imipramine, maprotiline, mirtazapine, moclobemide, nortriptyline, oxitriptan, paroxetine, trimipramine, venlafaxine
3	Citalopram, fluoxetine, reboxetine, trazodone
4	Melitracen, opipramol
	<b>Psychostimulants</b>
1	Methylphenidate, sibutramine
2	-
3	Amfepramone, modafinil
	<b>Anti-dementia drugs</b>
1	Rivastigmine
2	-
3	Donepezil, galantamine, memantine

Table IV. Most common dose-dependent adverse reactions of selected psychotropic drug classes(280, 282)

<b>Anti-Parkinson drugs</b>	<p><b>Dopaminergic substances:</b> nausea, vomiting, orthostatic hypotension, hallucination, agitation, confusion, dyskinesia</p> <p><b>Anticholinergics:</b> dry mouth, blurred vision, constipation, tachycardia, urinary retention, hallucination, delirium</p>
<b>Antipsychotics</b>	<p>Adverse reaction profile depends on the specific receptor affinity:(330)</p> <p><b>Dopaminergic:</b> extrapyramidal symptoms (especially typical antipsychotics), hyperprolactinemia</p> <p><b>Adrenergic:</b> orthostatic hypotension</p> <p><b>Muscarinic:</b> anticholinergic effects</p> <p><b>Histaminergic:</b> sedation, weight gain</p> <p><b>Others:</b> QT prolongation</p>
<b>Anxiolytics, sedatives and hypontics</b>	<p><b>Benzodiazepines:</b> Somnolence, confusion, muscle weakness, ataxia, respiratory depression</p> <p><b>Benzodiazepine-like substances:</b> somnolence, drowsiness, asthenia</p> <p><b>Antihistamines:</b> anticholinergic effects, sedation</p>
<b>Antidepressants</b>	<p><b>Tricyclic antidepressants:</b> anticholinergic effects, sedation, ECG changes, hypotension, tachycardia</p> <p><b>SSRIs:(331)</b> nervousness, insomnia, diarrhea, nausea, tachycardia, serotonin syndrome</p>
<b>Psychostimulants</b>	<p>Restlessness, dizziness, insomnia, palpitation and/or tachycardia, hypertension, dry mouth, anorexia</p>
<b>Anti-dementia</b>	<p><b>Cholinesterase inhibitors:</b> nausea, vomiting, diarrhea,</p>

<b>drugs</b>	bradycardia, hypotension
<b>Antiepileptics</b>	<p><b>Barbiturates:</b> sedation, drowsiness, ataxia, nystagmus, respiratory depression</p> <p><b>Hydantoin derivatives (phenytoin):</b> <i>acute symptoms:</i> nystagmus, diplopia, ataxia, respiratory and circulatory depression</p> <p><b>Succinimide derivatives (ethosuximide, methsuximide):</b> nausea, vomiting, drowsiness, dizziness, photophobia, ataxia, hiccup</p> <p><b>Benzodiazepines:</b> see anxiolytics, sedatives and hypnotics</p> <p><b>Carboxamide derivatives (carbamazepine, oxcarbazepine):</b> diplopia, nystagmus, ataxia, dizziness, nausea, vomiting, hyponatremia</p> <p><b>Fatty acid derivatives (valproate):</b> somnolence, tremor, nausea, vomiting, hyperammonemia</p>

**Table V.** Kinetic data, hepatic adverse effects, and dose recommendations in patients with liver disease for antidepressants, antipsychotics, anxiolytics, sedatives and hypnotics with high hepatic extraction available in Switzerland in 2006.

Drug	Cat <sup>a</sup>	Kinetic parameters <sup>b, c, d</sup>	Hepatic adverse effects	Studies performed and dose recommendations
<b>Antidepressants</b>				
Bupropion	1	Metabolism: Hydroxylation (CYP 2B6), reduction.(281) Q <sub>0</sub> : >0.95 V <sub>d</sub> : 28 l/kg t <sub>1/2</sub> : 21 h PB: 84% Cl <sub>sys</sub> : 160 ml/min E: >0.9	Rare: abnormal liver tests, jaundice, hepatitis.(280, 362, 363)	<i>Studies:</i> Half-life of hydroxybupropion was prolonged (32 h vs 21 h; p>0.05) in patients with alcoholic liver disease compared to healthy volunteers.(420) <i>Product information:</i> No significant difference in the pharmacokinetics between patients with mild to moderate liver cirrhosis and healthy controls. C <sub>max</sub> increased by 70%, half-life by 40% and AUC by 200% in patients with severe liver cirrhosis compared to healthy controls. Half-life of metabolites prolonged about 2- to 4-fold. Contraindicated in patients with severe liver cirrhosis. Recommended daily dose for patients with mild to moderate liver disease 150mg. <i>Personal Recommendation:</i> According to pharmacokinetic data and clinical studies, start with lowest available dose (150mg/d). Adjust maintenance dose or dosage interval according to dose-dependent adverse effects. Because of expected massive increase in bioavailability, bupropion should better be avoided in patients with severe liver cirrhosis (Child C).
Dibenzepin	1	Metabolism: N-demethylation.(280) Q <sub>0</sub> : 1 V <sub>d</sub> : 4.2 l/kg t <sub>1/2</sub> : 5 h PB: 85% F: 25%		<i>Studies:</i> No clinical studies available in patients with liver disease. <i>Product information:</i> Caution in patients with liver insufficiency. <i>Personal Recommendation:</i> According to pharmacokinetic data, initial doses should not exceed 25% of normal in patients with liver cirrhosis. Maintenance doses should be adjusted according to clinical effect and dose-dependent adverse reactions.

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Doxepin	1	Metabolism: Demethylation, N-oxidation, hydroxylation, glucuronidation;(280, 282) Q <sub>0</sub> : 1 V <sub>d</sub> : 20 l/kg t <sub>1/2</sub> : 17 h PB: 95% F: 27% Cl <sub>sys</sub> : 65 ml/min E: >0.9	<i>Rare:</i> hyperbilirubinemia, (280) cholestatic and/or hepatocellular liver injury.(286)	<i>Studies:</i> No clinical studies available in patients with liver disease. <i>Product information:</i> Caution in patients with liver disease. Dose adjustment is recommended in patients with severe liver disease (no specification). <i>Personal Recommendation:</i> Based on the pharmacokinetic data, start with lowest possible dose (10mg/d). Adjust maintenance dose according to clinical effect and dose-dependent adverse reactions.
Mianserin	1	Metabolism: CYP 2D6,(323) N-oxidation, hydroxylation, N-demethylation(282) Q <sub>0</sub> : 0.95 V <sub>d</sub> : 15.7 l/kg t <sub>1/2</sub> : 33 h PB: 95% F: 25% Cl <sub>sys</sub> : 19.1 ml/min i.v. (higher Cl <sub>sys</sub> after p.o. administration observed) E: 0.34	<i>Cases:</i> mixed hepatic injury, cholestatic liver disease,(358) elevated liver enzymes.(280)	<i>Studies:</i> No clinical studies available in patients with liver disease. <i>Product information:</i> Mianserin is contraindicated in patients with severe liver disease. <i>Personal Recommendation:</i> According to pharmacokinetic data, start with lowest possible dose (15mg/d). Adjust maintenance dose according to dose-dependent adverse reactions.
Sertraline	1	Metabolism: N-demethylation (CYP 2D6, 2C9, 2B6, 2C19, 3A4), hydroxylation, oxidative deamination, N-carbamoyl glucuronidation.(320) Q <sub>0</sub> : 1 V <sub>d</sub> : 25 l/kg t <sub>1/2</sub> : 23 h PB: 98%	<i>Rare:</i> hepatocellular injury.(286) <i>Case reports:</i> liver failure.(280)	<i>Studies:</i> AUC increased 4 times, half-life 2.5 times and c <sub>max</sub> 1.7 times in patients with liver cirrhosis after intake of 100mg sertraline as a single oral dose.(414) It was recommended to start with 50mg sertraline per day and increase dosage only after 15 days, if necessary. <i>Product information:</i> Start treatment in patients with liver cirrhosis Child Pugh A and B with 50% of normal initial dose. Contraindicated in patients with liver cirrhosis Child Pugh C. <i>Personal Recommendation:</i> According to pharmacokinetic data and product information, it is recommended to start with 50% of normal



		Cl <sub>sys</sub> : 96 ml/min E: >0.9		dose (25mg/d). Adjust maintenance dose according to dose-dependent adverse reactions. Do not up-titrate the dose before 2 weeks after treatment beginning or dose adjustment.
<b>Antipsychotics</b>				
Chlorpromazine	1	Metabolism: Hydroxylation (CYP 2D6, 1A2), N-demethylation, N-oxidation, deamination, sulfoxidation,(282, 299) partial biliary excretion(280) Q <sub>0</sub> : 1 V <sub>d</sub> : 22 l/kg t <sub>1/2</sub> : 30 h PB: 95% F: 32% Cl <sub>sys</sub> : 36.1 ml/min E: 0.67	Risk of hepatic encephalopathy in patients with liver cirrhosis.(344) <i>Sporadic</i> : cholestatic liver injury.(286)	<i>Studies</i> : Changes in EEG associated with drowsiness and increased sensitivity in patients with liver cirrhosis, particularly in patients with previous history of encephalopathy.(344, 375) Should be avoided in patients with liver cirrhosis due to the risk of hepatic encephalopathy.(344) <i>Product information</i> : Contraindicated in patients with cholestatic liver injury. <i>Personal Recommendation</i> : According to pharmacokinetic data, start with 25-50% of normal initial dose. Adjust maintenance dose according to dose-dependent adverse effects.
Chlorprothixene	1	Metabolism: Sulfoxidation, N-demethylation, hydroxylation, N-oxidation(280) Q <sub>0</sub> : 0.95 V <sub>d</sub> : 15.5 l/kg t <sub>1/2</sub> : 12 h PB: 99% F: 12% Cl <sub>sys</sub> : 72 ml/min E: >0.9	<i>Sporadic</i> : cholestatic liver injury.(286)	<i>Studies</i> : No clinical studies available in patients with liver disease. <i>Product information</i> : Caution in patients with severe liver disease. Dose adjustment recommended (no specification). <i>Personal Recommendation</i> : According to pharmacokinetic data, start with lowest possible dose (5mg). Adjust maintenance dose according to dose-dependent adverse reactions.

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Fluphenazine	1	<p>Metabolism: Hydroxylation, glucuronidation, sulfoxidation, demethylation,(288) biliary excretion, enterohepatic circulation.(280)  <math>Q_0</math>: 1  <math>V_d</math>: 25 l/kg  <math>t_{1/2}</math>: 16.4 h  PB: 90%  F: 2.7% (oral)  <math>Cl_{sys}</math>: 42 ml/min  E: 0.78</p>	<p><i>Rare</i>: cholestatic liver injury.(286)</p>	<p><i>Studies</i>: No clinical studies available in patients with liver disease.  <i>Product information</i>: In Switzerland only slow-release preparation for intramuscular injection available. Dose adjustment recommended in patients with impaired liver function. Contraindicated in patients with liver injury.  <i>Personal Recommendation</i>: Only a slow-release preparation for intramuscular injection is available in Switzerland. In patients with liver disease alternatives should be used, since there are no clinical studies.</p>
Perphenazine	1	<p>Metabolism: CYP 2D6.(283) Hydroxylation, demethylation, sulfoxidation, glucuronidation.(282) Enterohepatic circulation.(280)  <math>Q_0</math>: 1  <math>V_d</math>: 20 l/kg  <math>t_{1/2}</math>: 9.5 h  PB: 90%  F: 20%  <math>Cl_{sys}</math>: 107 ml/min  E: &gt;0.9</p>	<p><i>Sporadic</i>: cholestatic liver injury.(286)</p>	<p><i>Studies</i>: No clinical studies available in patients with liver disease.  <i>Product information</i>: No recommendations provided.  <i>Personal Recommendation</i>: According to pharmacokinetic data, start with the lowest possible dose (2mg) and adjust maintenance dose according to clinical effect and dose-dependent adverse reactions.</p>

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Promazine	1	<p>Metabolism: Hydroxylation, N-oxidation, N-demethylation (CYP 1A2, 2C19), sulfoxidation (CYP 1A2, 3A4).(282, 300)</p> <p>Q<sub>0</sub>: 1  t<sub>1/2</sub>: 15 h (variable)  PB: 92%  F: 16%</p>	<p>Phenothiazines may cause intrahepatic cholestasis.(282)</p>	<p><i>Studies:</i> In cirrhotic patients (Child A and B) total plasma clearance decreased by 76%, elimination half-life was 2 times, AUC 2.9 times higher compared to healthy subjects.(377) No change in pharmacokinetics during acute phase of viral hepatitis B, but more adverse effects observed (sedation, postural hypotension, dizziness).(376) Adjust dosage in cirrhotic patients (no specific dosage recommendation).(377)</p> <p><i>Product information:</i> Caution in patients with liver disease.(280) Use not recommended in patients with liver disease because phenothiazines may cause intrahepatic cholestasis.(282)</p> <p><i>Personal Recommendation:</i> According to the pharmacokinetic parameters, start with 25% of normal initial dose. Adjust dosage according to dose-dependent adverse reactions.</p>
Quetiapine	1	<p>Metabolism: Dealkylation, hydroxylation (CYP 3A4, 2D6 [minor]), sulfoxidation, glucuronidation.(303)</p> <p>Q<sub>0</sub>: 0.95  V<sub>d</sub>: 10 l/kg  t<sub>1/2</sub>: 6 h  PB: 83%  F: 9%  Cl<sub>sys</sub>: 79.8 ml/min  E: &gt;0.9</p>	<p><i>Rare:</i> jaundice, transient and reversible elevations in serum transaminase (primarily ALT).(280, 283)</p> <p><i>Case report:</i> subfulminant liver failure.(347)</p>	<p><i>Studies:</i> Compared to healthy controls clearance decreased by 25% in patients with liver cirrhosis, AUC and c<sub>max</sub> increased by 40% and elimination half-life prolonged by 77%.(379) The authors concluded that patients with hepatic liver cirrhosis may be given 25mg quetiapine as starting dose, and dose escalation should be conducted with caution.</p> <p><i>Product information:</i> Recommendations based on the study from Thyrum PT et al. (2000) conducted by Astra Zeneca. Start with 25mg quetiapine on the first day. Up-titrate carefully in increments of 25-50mg/d to an effective dose, depending on clinical response and dose-dependent adverse reactions.</p> <p><i>Personal Recommendation:</i> According to pharmacokinetic data and clinical study, start with 25mg and up-titrate carefully according to clinical effect and dose-dependent adverse reactions.</p>

Anxiolytics, hypnotics, sedatives				
Buspirone	1	Metabolism: CYP 3A,(280) oxidative dealkylation, hydroxylation, glucuronidation.(282) Q <sub>0</sub> : 1 V <sub>d</sub> : 5 l/kg t <sub>1/2</sub> : 2.4 h PB: 95% F: 4% Cl <sub>sys</sub> : 92.5 ml/min E: >0.9		<i>Studies:</i> C <sub>max</sub> about 16 times higher in patients with liver cirrhosis than in controls. Elimination half-life in cirrhotics about twice that of normal subjects.(392) Should be used with caution in patients with liver disease.(392) Due to the high intra- and inter-subject variability of the plasma buspirone concentration data in patients with liver cirrhosis, dosing recommendations cannot be made.(393) <i>Product information:</i> Contraindicated in patients with liver disease. <i>Personal Recommendation:</i> According to pharmacokinetic data start with lowest possible dose (5mg) due to variable bioavailability in patients with portosystemic shunts. Adjust maintenance dose according to dose-dependent adverse reactions. Dose interval may be reduced from 3 times to 1-2 times daily.
Clomethiazole	1	Metabolism: CYP 2A6, 3A4/5, 2B6, 1A1, 2C19.(280) Q <sub>0</sub> : 0.95 V <sub>d</sub> : 9 l/kg t <sub>1/2</sub> : 6 h PB: 65% F: 10% Cl <sub>sys</sub> : 100 ml/min E: >0.9	Elevation of transaminases. <i>Rare:</i> jaundice, cholestatic hepatitis.(280)	<i>Studies:</i> Clearance decreased by 30%, bioavailability 10 times higher in patients with advanced alcoholic liver cirrhosis compared to healthy subjects.(44) Dose reduction recommended (no specification).(44) After continuous infusion of clomethiazole systemic clearance decreased by 50% and half-life prolonged by 90% in patients with liver cirrhosis (Child B and C).(408) No statistically significant difference between subjects with mild liver impairment and healthy controls. <i>Product information:</i> Avoid in patients with severe liver disease. Clomethiazole should not be given to alcoholics with liver cirrhosis, because of fatal respiratory depression in combination with alcohol. <i>Personal Recommendation:</i> Oral administration should be avoided in patients with liver cirrhosis since bioavailability is unpredictable. Start intravenous therapy with 25-50% of normal dose and adjust dose according to dose-dependent adverse effects. Lorazepam, oxazepam and temazepam are better alternatives.
Flurazepam	1	Metabolism: N- desalkylation, hydroxylation(282)	<i>Rare:</i> cholestatic liver injury.(286)	<i>Studies:</i> No clinical studies available in patients with liver disease. <i>Product information:</i> Flurazepam should be used with caution in patients with impaired hepatic function.

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		<p>Q<sub>0</sub>: 1  V<sub>d</sub>: 3.4 l/kg  t<sub>1/2</sub>: 2 h  PB: 95%  F: 30%</p>		<p><i>Personal Recommendation:</i> Flurazepam is not an ideal hypnotic in patients with liver disease. Lorazepam, oxazepam, and temazepam are the benzodiazepines of choice for patients with liver disease.</p>
Hydroxyzine	1	<p>Metabolism: Hepatic metabolism to cetirizine (active),(307) 70% of the dose eliminated by biliary excretion.(280)  Q<sub>0</sub>: 1  V<sub>d</sub>: 16 l/kg  t<sub>1/2</sub>: 20 h  Cl<sub>sys</sub>: 41.1 ml/min  E: 0.76</p>	<p><i>Rare:</i> hepatic or cholestatic jaundice.(280)</p>	<p><i>Studies:</i> Prolonged elimination half-life (36.6h), decreased clearance (36.3 L/h), and increased volume of distribution (23 L/kg) in patients with primary biliary cirrhosis.(307) Increase normal dosage interval of 2-3 times daily to once per 24 hours or less.(307)  <i>Product information:</i> In patients with liver cirrhosis clearance was reduced by about 33%. Elimination half-life was increased to 37h and serum concentration of cetirizine were higher compared to healthy individuals. Reduce dosage in patients with moderate liver disease. Contraindicated in patients with severe liver insufficiency.  <i>Personal Recommendation:</i> According to the pharmacokinetic data, start with 50% of normal initial dose (12.5mg). Adjust maintenance dose according to dose-dependent adverse reactions.</p>
Promethazine	1	<p>Metabolism: Sulfoxidation, N-dealkylation (CYP 2D6), biliary excretion.(282)  Q<sub>0</sub>: 1  V<sub>d</sub>: 14 l/kg  t<sub>1/2</sub>: 12 h  PB: 85%  F: 25%  Cl<sub>sys</sub>: 68 ml/min  E: &gt;0.9</p>	<p>jaundice(283)</p>	<p><i>Studies:</i> No clinical studies available in patients with liver disease.  <i>Product information:</i> Caution in patients with liver impairment.(281)  <i>Personal Recommendation:</i> In Switzerland only a combination of promethazine with carbocisteine as expectorant is available. Promethazine is contained at lower dose compared to a monosubstance preparation available in the USA, therefore no recommendation for patients with liver disease are made.</p>

Zaleplon	1	Metabolism: Aldehyde oxidase, desalkylation (CYP 3A4), followed by glucuronidation.(280) Q <sub>0</sub> : 1 V <sub>d</sub> : 1.4 l/kg t <sub>1/2</sub> : 1 h PB: 60% F: 31% Cl <sub>sys</sub> : 70 ml/min E: >0.9	<p><i>Studies:</i> No clinical studies available in patients with liver disease.</p> <p><i>Product information:</i> Oral clearance reduced by 70% and 87% in compensated and decompensated cirrhotic patients, respectively, up to 4-fold increase in c<sub>max</sub> and up to 7-fold increase in AUC in comparison with healthy subjects.(281) Contraindicated in patients with liver insufficiency.(280)</p> <p><i>Personal Recommendation:</i> According to pharmacokinetic data and product information, start with lowest possible dose in patients with mild to moderate hepatic insufficiency (5mg). Adjust dosage according to dose-dependent adverse reactions. Zaleplon should be avoided in patients with severe hepatic impairment. Better alternatives are available: lorazepam, oxazepam and temazepam.</p>
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a *Cat* = drug category. Drugs were categorized as follows: Category 1: high hepatic extraction (E >60%, F <40%), category 2: intermediate hepatic extraction (E = 30-60%, F = 40-70%), category 3: low hepatic extraction (E <30%, F >70%), category 4: hepatic extraction not known.

b The fraction metabolised or excreted by bile (1-Q<sub>0</sub>: fraction excreted unchanged by the kidney).

c For calculation, bodyweight was assumed to be 70kg.

d Calculated as described in equation 2 of the main article.

**ALT** = alanine aminotransferase; **AP** = alkaline phosphatase; **AST** = aspartate aminotransferase; **AUC** = area under the concentration-time curve; **Cat** = drug category; **Cl<sub>sys</sub>** = systemic clearance; **c<sub>max</sub>** = maximum concentration; **CYP** = cytochrome P450; **E** = hepatic extraction; **F** = bioavailability; **γGT** = gamma-glutamyl transpeptidase; **PB** = fraction bound to proteins; **Q<sub>0</sub>** = extrarenal dose fraction; **t<sub>1/2</sub>** = dominant half-life; **V<sub>d</sub>** = volume of distribution







## 7 General Discussion and Outlook

Adaptation of the dosage of drugs in patients with liver disease is more difficult than in patients with renal disease, since there is no endogenous marker for hepatic clearance, which could be used as a guide for dosing of drugs.

In this thesis strategies for dosage adaptation of drugs in patients with liver disease were defined.

In **chapter 3** the kinetic and dynamic changes of drugs in patients with liver disease were discussed and general dosage recommendations given. However, these predictions for dose adaptation remain general and cannot replace accurate clinical monitoring of patients with liver disease treated with drugs owing a narrow therapeutic range.

In **chapter 4**, an interactive e-learning course about dose adaptation in liver disease was developed for the Swiss Virtual Campus.

In **chapter 6.1.** and **6.2.**, the antineoplastic drugs and psychotropic agents marketed in Switzerland were classified according to their bioavailability / hepatic extraction in order to predict their kinetic behaviour in patients with decreased liver function. This prediction was compared with kinetic studies carried out with these drugs in patients with liver disease.

Both studies showed that for most of the drugs studied, dosage recommendations are not available for patients with liver insufficiency. This is due to the absence of published data about hepatic extraction (E) (which is essential to help dosing in patients with liver disease) and the scarcity of performed clinical studies in patients with liver disease.

However, dose recommendations which are based on the hepatic extraction and / or bioavailability of a drug are generally in a good agreement with the data from pharmacokinetic studies in patients with liver cirrhosis. Classification of drugs according to hepatic extraction is therefore a useful approach for dose adjustment in patients with liver cirrhosis, when appropriate clinical studies are lacking.

Therefore, individual dosage recommendations were provided for each drug with relevant hepatic metabolism based on the results of the literature research and / or the general principles of dose adaptation in liver disease as discussed in chapter 3.

For a larger part of drugs, we consider that there are currently not enough data for the safe use in patients with liver disease. Pharmaceutical companies should be urged to provide kinetic data (especially hepatic extraction) needed for the classification of such drugs. For drugs with primarily hepatic metabolism, kinetic studies should be performed in patients with impaired liver function, thus allowing to give quantitative advice for dose adaptation.

The collected data and results for antineoplastic and psychotropic agents will be expanded by the antiinfective agents (about 160 drugs) and a further group of chosen therapeutic classes frequently applied to patients with liver disease (about 200 drugs).

The data content of this collected work including more than 540 drugs could be further proceeded to a reference book or electronic database as a useful tool for dosage in patients with liver disease.





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## Electronic appendix on CD-ROM

- Online course:  
Schlatter C, Krähenbühl S: Dosisanpassung bei Leberinsuffizienz. Bern: Swiss Virtual Campus, 2004.  
*„SVC - Dosisanpassung bei Leberinsuffizienz“ (PDF file)*
- Online course:  
Schlatter C, Krähenbühl S: Dosisanpassung von Arzneistoffen bei Patienten mit Leberinsuffizienz. In: Online Academy. Ausgabe Nr. 3.1. Zürich: PNN pharma nation network, 2004.  
*„Online Academy – Dosisanpassung bei Leberinsuffizienz“ (PDF file)*
- Schlatter C, Krähenbühl S: Dosisanpassung bei Leberkrankheiten. In: Grundlagen der Arzneimitteltherapie. Basel: Documed, 2005.  
*„Documed – Dosisanpassung bei Lebererkrankungen“ (PDF file)*
- Complete table of all studied antineoplastic agents:  
*„Psychotropic Drugs – Complete List“ (PDF file)*
- Complete table of all studied psychotropic drugs:  
*„Antineoplastic Drugs – Complete List“ (PDF file)*





## Curriculum Vitae



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### education

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**additional courses**


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2006	„PC-Skills in Word, Excel, PowerPoint“ course at the Pharmacenter Basel
2007	„Elocution lessons“ at the ZHAW (Zürcher Hochschule für angewandte Wissenschaften; 24 lessons)
2008	„Professional Writing“ compact course at the ZHAW (3 days)
2008	„Evidence based medicine“ course and workshop at the ZHAW (3 days)

**gainful employment**


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1994-1996	Kitchen help at Merkur Le Café Schanzenpost, Bern Several auxiliary incomes as waitress, a charwoman and by doing a paper route
1996-1997	Nanny at family P. Végh, Aesch, BL (6 children and my own firstborn)
1999-2002	Regular deputyships in different pharmacies (Engelmannsche Apotheke, Tell Apotheke)  Sporadic translations of civil marriages from German into Spanish at the Civil Registry Office, Basel
2002-2003	Pharmacy's head deputy (100%) at two different pharmacies who belonged to the same owner (Apotheke St. Jakob-Park, Basel and Gartenstadt Apotheke Münchestein)
2003-2007	Responsible person at Desitin Pharma GmbH, Liestal
2004	Pharmacist (40%) at a QMS certified pharmacy (Kapuziner-Apotheke, Rheinfelden), followed by sporadic deputyships
2004	Scientific officer at the Division of Clinical Pharmacology and Toxicology, University Hospital of Basel, University of Basel  Design of the online course named „Dosisanpassung bei Leberinsuffizienz“ for the Swiss Virtual Campus”

- 2004-today Author for "i.m@il®- Offizin" informational service of the Division of Clinical Pharmacology and Toxicology, University Hospital of Basel, by writing one of two monthly issued articles
- Creation of FPH certified continuing education for pharmacists issued at the "Online Academy" by Pnn AG:  
"Dose adaptation in liver insufficiency"  
"Nausea and vomiting in pregnancy"  
"Breast feeding"
- 2006 Lecture of the revision course in pharmacology at the institute for traditional chinese medicine, Basel (Institut für traditionelle chinesische Medizin)

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**language skills**

German	first language
English	excellent written and spoken
French	basic written and spoken
Spanish	excellent written and spoken

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**scientific publications**

**Schlatter C**, Krähenbühl S. Dosisanpassung bei Lebererkrankungen. In: Buclin T, Desmeules J, Fattinger K, Krähenbühl S, Kupferschmidt H: Grundlagen der Arzneimitteltherapie, Documed, Basel, 2005, P 6-13.

Tschambaz L, **Schlatter C**, Jakob M, Krähenbühl A, Wolf P, Krähenbühl S. Dose adaptation of antineoplastic drugs in patients with liver disease. Drug Safety ; 29: 509-522 (2006).

**Schlatter C**, Egger S, Tschambaz L, Krähenbühl S. Dose adaptation of psychotropic drugs in patients with liver disease. Submitted to Drug Safety in April 2008.

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**lectures**

During my studies I followed courses of the following lecturers:

Barass J.P., Bruppacher R., Drewe J., Erb P., Ernst B., Haefeli W., Hersberger K., Guentert, Krähenbühl S., Kress A., Leuenberger H., Oelhafen P., Schaffner W., Scholer A., Sequin U., Zuberbühler A.

