Dose Adaptation of Drugs in Patients with Liver Disease

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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aus

Torricella-Taverne (TI)

Basel, 2004

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät

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Basel, den 08.06. 2004

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To my family

Abbreviations

ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
AUC	area under the curve
BW	body weight
Cl_{hep}	hepatic clearance
Cl_{in}	intrinsic hepatic clearance
Cl_{sys}	systemic clearance
C_{max}	maximum concentration
CYP450	cytochrome P450 isoenzyme
E	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
HPLC	high pressure liquid chromatography
IS	internal standard
i.v	intravenous
INR	international normalized ratio
Q	blood flow across the liver
Q_0	extrarenal dose fraction
min	minutes
MEGX	monoethylglycinexylidine
NSAID	non steroidal anti-inflammatory drug
PB	fraction bound to proteins (protein binding in %)
PD	pharmacodynamics
PK	pharmacokinetics
rpm	revolutions per minute
s	seconds
SD	standard deviation
TDM	therapeutic drug monitoring
T_{max}	time point of C_{max}
$t_{1/2}$	half life
ULN	upper limit of normal
V_d	volume of distribution

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I Summary

In my thesis I defined strategies for dosage adaptation of drugs in patients with liver disease. The major goal of the thesis was to classify antineoplastic drugs and central nervous agents according to pharmacokinetic principles (hepatic extraction and bioavailability) and to provide recommendations for their use in patients with liver disease. The antineoplastic drugs and central nervous agents available on the market in Switzerland were therefore studied. In a second time a clinical study was planned in patients with liver cirrhosis to define methods of dose adaptation for high-extraction drugs.

The dose adaptation of drugs in patients with liver disease is more difficult than in patients with renal disease. The dosage may have to be adjusted but the problem is to quantify the required changes.
Ideally, there should be a predictive liver function test that allows a more precise dosing in patients with liver disease analogous to the creatinine clearance for patients with renal dysfunction. Unfortunately, no such practical system is available as yet. Despite the absence of such a test, kinetic parameters and clinical studies can both help determining the kinetic behavior of a drug and providing dosage adjustments.

- **Project 1**

In **chapter 3.1**, the kinetic and dynamic changes in patients with liver disease of the most important drugs used in these patients were discussed.

- **Project 2**

In **chapter 3.2**, a guideline for dose reduction in patients with cholestasis for antineoplastic drugs with significant elimination via the bile was provided. 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 the drugs.
The antineoplastic drugs were classified 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 (identified by a structured, computer-based literature search) carried out with these drugs in patients with liver disease. It appears that obvious gaps about the kinetic behavior of drugs in patients with liver disease include data about hepatic extraction and kinetic studies of drugs with biliary elimination in patients with cholestasis.

- **Project 3**

Central nervous agents often need to be prescribed to patients with preexisting liver disease. In **chapter 3.3**, as for antineoplastic drugs, central nervous agents were classified according pharmakokinetic principles to provide recommendations for their use in patients with liver disease.

- **Project 4**

In a next step a clinical study was planned to define strategies of dose adaptation for high-extraction drugs (like propranolol) in patients with liver cirrhosis (**chapter IV**). It has been shown convincingly that the bile acid concentration in portal and peripheral venous blood is significantly correlated to the magnitude of portal-systemic shunts in patients with mild to moderate liver cirrhosis. Since bioavailability of high-extraction drugs is in part a function of the magnitude of portal-systemic shunts, it was hypothesized that the bioavailability of propranolol, a high-extraction drug, shows a linear correlation with serum bile acid concentrations in patients with liver cirrhosis. The relationships between the bioavailability of propranolol and serum bile acid concentration in patients with liver cirrhosis were therefore investigated.

In the current study we did not find a significant correlation between serum bile acids and bioavailability of propranolol in patients with liver cirrhosis. It is therefore possible that the serum bile acid concentration is not a reliable marker for porto-systemic shunts and can therefore not be used to predict bioavailability of high extraction drugs such as propranolol.
Individual bile acids provide more information about porto-systemic shunts and may therefore be able to predict bioavailability of propranolol. Individual bile acids will therefore be determined by GC-MS.

When the oral clearance of propranolol in patients with liver cirrhosis is correlated with the serum bile acid concentration, an inverse relationship between the two parameters was detectable. A small increase in the serum bile acid concentration (in cirrhotic patients a marker of liver function) can be associated with an important decrease in propranolol clearance. When only the data from cirrhotic patients with serum bile acids values under 50 μmol/l were considered, the clearance was negatively correlated.
In patients with liver cirrhosis, propranolol has a bioavailability of 60% and is therefore kinetically similar to drugs with medium extraction. In this situation, mainly intrinsic hepatic clearance predicts hepatic clearance of a drug. The serum bile acid concentration may therefore reflect not only porto-systemic shunting but also intrinsic hepatic clearance in patients with liver cirrhosis.

No significant correlation was found between serum bile acids and bioavailability of propranolol in patients with liver cirrhosis. The serum bile acid concentration seems not to be a reliable marker for porto-systemic shunts and can therefore not be used to predict bioavailability of high extraction drugs in patients with liver cirrhosis.
There are currently not enough data for safe use of cyctostatics and central nervous agents in patients with liver disease. Pharmaceutical companies should 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 advise for dose adaptation.

II General introduction

2.1 Anatomy and function of healthy liver

The liver is the largest gland in the human body and accounts for approximately 2.5% of total body weight. In the adult, the liver weighs almost 1500g. It receives a dual blood supply; approximately 20% of the blood flow is oxygen-rich blood from the hepatic artery, and 80% is nutrient-rich blood from the portal vein arising from the stomach, intestines and spleen (1).

The majority of cells in the liver are hepatocytes, which constitute about 80% of the mass of the liver. The remaining cells are Kupffer cells (members of the reticuloendothelial system), stellate (fat-storing) cells, endothelial cells and other cells of blood vessels, bile epithelial cells and supporting structures. The liver appears to be organized in lobules, with portal areas at the periphery and central veins in the center of each lobule (2). Blood flowing into the portal areas has therefore to flow through the sinusoids. The sinusoids are lined by unique endothelial cells that have prominent fenestrae, allowing the free flow of plasma but not cellular elements (3). The plasma is thus in direct contact with hepatocytes in the subendothelial space of Disse (figure 1.1).

The cell mass of the liver performs diverse metabolic and excretory functions with substrates being presented directly from the gut lumen (like nutritional substrates and also xenobiotics), from the gut-related endocrine organs (gut peptides) and pancreas (insulin, glucagon) and indirectly from the general circulation. The liver is exposed to a wide variety of potentially harmful influences (drugs, toxins, infectious agents and inflammatory substances) because of its strategic position in relation to the gut and its processing of 20 to 25% of the total circulation (4). A diverse range of disease processes in the liver derive from these noxious stimuli, resulting in loss of cell mass, circulatory disturbances, destruction of normal architecture and reduction in functional capacity.

Liver disease has general implications for health (nutritional and metabolic balance, maintenance of body fluid and electrolyte balance, coagulation control). However,

pharmacologists have taken particular interest in the influence of liver disease on drug dosage requirements and drug action.

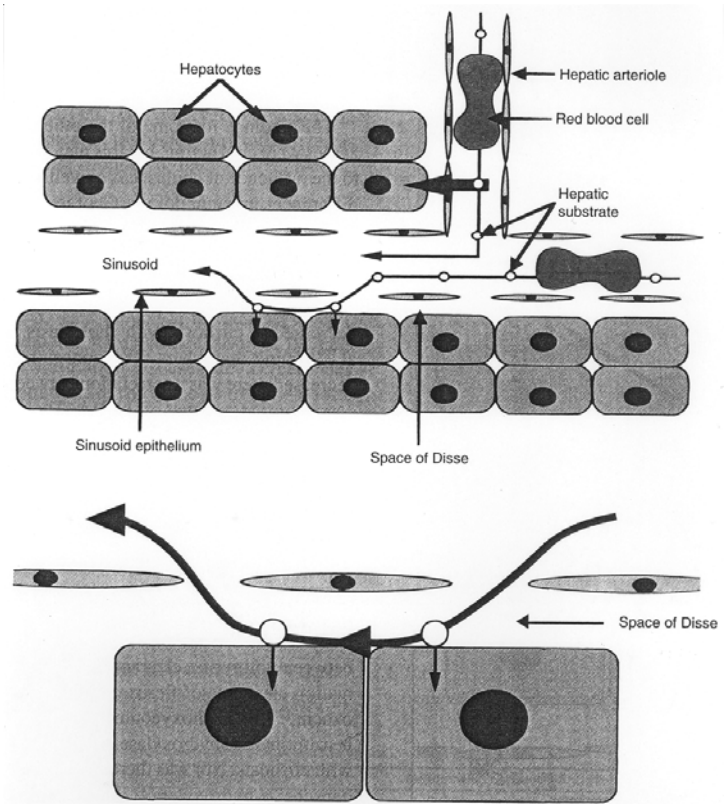

Figure 1.1 Schematic representation of the relationships between the hepatic sinusoid, the space of Disse and hepatocytes in the healthy liver. Top: the anatomy of the junction between a hepatic arteriole and the sinusoid in addition to the macroscopic relationships. Bottom: the free exchange of fluid and substrate(s) between the sinusoidal lumen and the space of Disse (5).

“Liver disease” is an umbrella term for a wide variety of syndromes resulting from infectious agents (viral, bacterial and parasitic), xenobiotics, alcoholism, circulatory disturbances (like cardiac failure) and autoimmune inflammation. Most noxes result in cell damage with cell death and/or pathological repair processes (4). Liver disease in humans can lead to a reduction in liver blood flow, extrahepatic or intrahepatic shunting of blood, hepatocyte dysfunction, quantitative and qualitative changes in serum proteins, and changes in bile flow. Different forms of hepatic disease may produce different alterations in drug absorption, disposition, and pharmacological

effect. The pharmacokinetic or pharmacodynamic consequences of a specific hepatic disease may differ between individuals or even within a single individual over time.

2.2 Liver disease relevant for drug metabolism

2.2.1 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. (6). 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 (2,7). 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 (8).

2.2.2 Alcoholic liver cirrhosis

Alcoholic cirrhosis is the most common type of cirrhosis encountered in many parts of Western Europe, North and South America. 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 (2).

2.2.3 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 inapparent 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 (9). Several informative studies about the effects of acute viral hepatitis on drug disposition were conducted (10-13). A small number of patients was studied during the time when they had acute viral hepatitis and subsequently after recovery. The drugs that were administered included phenytoin (10), tolbutamide (11), warfarin (13) 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 (14).

2.2.4 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. disturbed transport or hormones (15).

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. Drug metabolism in humans with cholestatic liver disease has also been predicted to be impaired based on studies of antipyrine clearance. An analysis of biopsy samples from 12 patients with intrahepatic cholestasis revealed a 30% decrease in microsomal cytochrome P450 (CYP) activity (16), other studies showed a impaired activity of CYP2E1 and CYP2C (17,18). In patients with cholestasis, drugs which are metabolized by CYP's can therefore have a diminished hepatic clearance, potentially needing adjustment of their dose.

2.3 Drug metabolism and liver disease

2.3.1 Introduction

Hepatic drug clearance depends on 3 major determinants: the extent of drug binding to the blood components, hepatic blood flow and hepatic metabolic activity. Drugs can be classified on the grounds of their hepatic extraction ratio: highly extracted drugs – the elimination of which is dependent mainly on the blood flow- and poorly extracted drugs, the elimination of which is sensitive only to changes in the intrinsic ability of the liver to eliminate the drug (intrinsic clearance). In liver disease, drug metabolism can be impaired because of hepatocyte dysfunction and portosystemic shunting. There are two types of hepatic metabolic processes. Phase I reactions, involve enzymes (mono-oxygenases) that belong to the CYP superfamily, and play a role in the hydrolysis, oxidation, dealkylation or reduction of lipophilic molecules reaching the

smooth endoplasmic reticulum. Phase II reactions involve conjugation of the parent compound or its hydrophilic metabolite with an endogenous molecule (such as glucuronic acid, sulphate, an amino acid, acetate or glutathione) rendering it more water soluble to assist excretion (8).

The oxidative metabolism of many drugs has been reported to be markedly impaired in patients with chronic liver disease, whereas glucuronide conjugation appears to be relatively unaffected (20). However this is not a general phenomenon; the elimination of certain drugs that are extensively glucuronidated in humans can be significantly impaired in patients with liver cirrhosis. For example, both phenolic and acyl glucuronidation pathways of diflunisal – a salicylic acid derivative that is almost entirely eliminated from the body by glucuronide and sulphate conjugation- are significantly impaired in cirrhosis (21). Furthermore, it has been reported that cirrhosis may exert differential effects on the various CYP isoforms (22,23).

2.3.2 Phase I biotransformations

Oxidative metabolism plays a fundamental role and it is largely catalyzed by enzymes belonging to the CYP family (24). Hepatic disease is associated with reduced metabolic capacity for most drugs that undergo oxidative biotransformation (25). There is direct evidence that there is a change in enzyme concentration and in the activity of drug metabolizing enzymes in cirrhosis (26,27), but this is not uniform among enzyme classes, since there are differences between the individual CYPs (28). As can be seen from the results of two *in vitro* studies, the CYP1A2 content is consistently reduced (by 53 to 71%) in cirrhosis (17,18,29,30). An *in vivo* study in patients with liver cirrhosis has indicated that the clearance of S-mephenytoin, a CYP2C19 substrate, was decreased by 63% in patients with mild cirrhosis and by 96% in patients with moderate cirrhosis, whereas administration of debrisoquine to these patients indicated normal function of CYP2D6 (19). Significant reductions in the expression and activity of CYP2E1 and CYP3A have also been found (17,18,29,30). In fact, the CYP3A4 pathway responsible for metabolizing lidocaine to its metabolite, monoethylglycinexylidine (MEGX) was well preserved in patients with mild and moderate chronic hepatitis. However, MEGX levels fell significantly in patients with cirrhosis and were well correlated with the clinical stage of cirrhosis (30).

These studies, in which the clearance of probe drugs has been examined in patients with different stages of liver disease, suggest the approximate relationships that are

shown in Figure 2.1. However, even when the metabolic pathway for a given drug is known, prediction of hepatic drug clearance in individual patients is complicated further by the effects of pharmacogenetic variation and drug interactions.

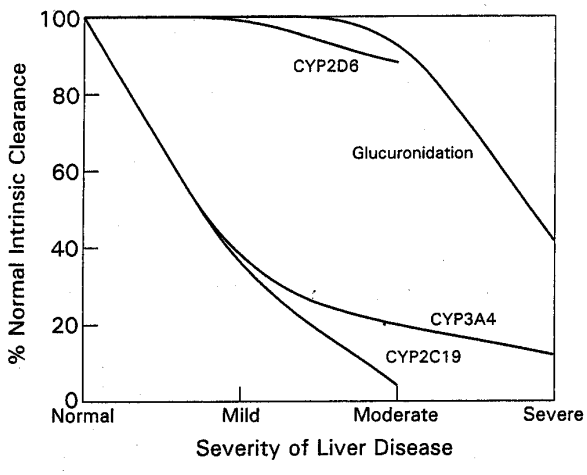

Figure 2.1 Schematic diagram showing the effects of various stages of liver disease severity on the intrinsic clearance of drugs mediated by representative metabolic pathways (31). Estimates for glucuronidation (32), CYP2D6 (19), CYP3A4 (30) and CYP2C19 (19) pathways are based on the literature sources indicated in parentheses .

2.3.3 Phase II biotransformations

Data in humans accumulated over many years indicate that, in cirrhosis, drug glucuronidation is relatively spared compared with drug oxidation (19,33). In the case of conjugation by glucuronidation, there is general agreement that for the majority of drugs studied there is minimal impairment. This has led to the hypothesis that glucuronidation is relatively unaffected in liver disease (34). In cirrhosis, there is no evidence of impairment of the metabolism of temazepam (35,36) and lorazepam (37), both substances which are metabolized to the ether glucuronide. Oxazepam (38; 39) and morphine (32,40,41) are also metabolized to the ether glucuronide and impairment of their metabolism is observed only in severe cirrhosis. However, other studies suggest that clearance of other drugs that are predominantly conjugated, to instance lamotrigine, can also be reduced in patients with liver cirrhosis (42). Thus,

conjugation reactions are less affected by liver cirrhosis than phase I reactions, but they are not completely spared.

2.4 Assessment of liver function

Although there are numerous causes of hepatic injury, it appears that the hepatic response to injury is a limited one and 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 proposed using endogenous marker substances, which are affected by liver such as bilirubin and albumin, or functional measures such as prothrombin time, or the ability of the liver to eliminate exogenous marker substrates such as antipyrine (43), indocyanine green (43), monoethylglycine-xylidide (MEGX) (28), and galactose (44). Despite extensive efforts, no single measure or group of measures has gained widespread clinical use to allow estimation in a given patient of the degree of hepatic impairment that will affect the pharmacokinetic and/or pharmacodynamic of a drug. The primary problem of all these test substrates is the considerable intersubject variability in their clearance, both in healthy individuals and in patients with liver disease, usualy leading to considerable overlap between these two groups (23,45,46). 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 (8).

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) (47). 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

	Assigned score		
Assessment parameters	**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 (characters per second) 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, delta activity

Even though clinically useful measures of hepatic function are not generally available to predict drug pharmacokinetics and pharmacodynamics, clinical studies in patients with hepatic impairment, usually performed during drug development, can provide information that may guide initial dosing in patients. However, because patients with only mild or moderately severe liver disease usually are enrolled in these studies, there is relatively little data from patients with severe liver disease, in whom both pharmacokinetic changes and altered pharmacologic response are expected to be most pronounced.

It would therefore be of importance to be able to predict pharmacokinetic and pharmacodynamic changes of high extraction drugs in the patients with liver disease using routine liver function tests.

2.5 Aims of the thesis

The major goal of the thesis was to define strategies for dose adaptation of drugs in patients with liver disease.

The dose adaptation of drugs in patients with liver disease is more difficult than in patients with renal disease. Ideally, there should be a predictive liver function test that allows a more precise dosing in patients with liver disease analogous to the creatinine clearance for patients with renal dysfunction. Unfortunately, no such practical system is available as yet.

In order to contribute to this field of research, the following points were elaborated during this project:

1. **Guidelines for dose reduction in patients with liver disease** (especially cholestasis) **for antineoplastic drugs** with significant elimination via the bile and **central nervous agents** were established. The antineoplastic drugs and central nervous agents available on the market in Switzerland were therefore studied in order to provide quantitative advise for dose adaptation in patients with liver disease (**project 1, 2,3**).

It has been shown convincingly that there is a linear relationship between the serum bile acid concentration and the hepatic shunt index (Ohkubo et al., 1984).

2. In order to determine, if the serum bile acid concentration may therefore be a suitable parameter to predict proper dosing of drugs with a high hepatic extraction in cirrhotic patients, a **clinical trial** was undertaken to study the relationship between the **serum bile acid concentration** and the

bioavailability of propranolol, a high extraction drug, in patients with liver cirrhosis (**project 4**).

III Dose adaptation in patients with liver disease

Project 1

3.1 General recommendation of dosing in patients with liver disease

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Introduction

Dose adaptation of drugs in patients with liver disease is more difficult than in patients with renal disease, since there is not yet an endogenous marker for hepatic clearance established, which could be used as a guide for dosing of drugs. In order to estimate the kinetic behavior of a given drug in patients with liver cirrhosis, drugs can be grouped according to hepatic extraction. For drugs with a high hepatic extraction (or low bioavailability) in subjects with normal hepatic function, bioavailability increases and hepatic clearance decreases in cirrhotic patients. Therefore, if such a drug is administered orally, the initial dose has to be reduced in cirrhotic patients according to hepatic extraction. Furthermore, the maintenance dose of such drugs has to be reduced irrespective of the way of administration, according to kinetic studies in patients with liver disease and taking into account effect and toxicity of such drugs. For drugs with a low hepatic extraction, bioavailability is not affacted by liver disease, but hepatic clearance may be reduced in cirrhotic patients. In this case, only the maintenance dose has to be reduced according to the estimated decrease in the activity of the enzymes metabolizing this drug in cirrhotic patients. Many drugs are between these two extremes and have an intermediate hepatic extraction. For these drugs, initial oral doses should be chosen in the low range of normal in cirrhotic patients, and maintenance doses should be reduced as described for high extraction drugs. In patients with cholestasis, the clearance of drugs with predominant biliary elimination is reduced, necessitating dose reduction according to the toxicity profile of the drug considered. Guidelines for dose reduction in patients with cholestasis exist for most antineoplastic drugs with significant elimination via the bile, but are mostly lacking for other drugs with predominant biliary elimination. For the clinicians it is important to realize that not only drugs eliminated primarily by the liver, but also those with renal elimination may have to be adapted in patients with liver disease. Patients with liver cirrhosis often have an impaired renal function, despite a normal serum creatinine concentration. In cirrhotic patients, creatinine clearance should therefore be measured or estimated routinely, in order to have a guideline for dosing of drugs with predominant renal elimination. Since the creatinine clearance tends to overestimate glomerular filtration in these patients due to increased secretion of creatinine, the dose of a given drug may still be too high after adaptation to creatinine clearance. The clinical monitoring for effects and toxicity of a drug is therefore important in patients with liver cirrhosis also for drugs with predominant renal elimination.

Besides the mentioned kinetic changes, the effect of some drugs is altered in cirrhotic patients also due to changes in their dynamics. Examples of such drugs include opiates, benzodiazepines, nonsteroidal antiinflammatory drugs and diuretics. Such drugs may exhibit unusual adverse effects which clinicians should be aware of, if they want to use these drugs safely in cirrhotic patients.

In this paper, we discuss the kinetic and dynamic changes in patients with liver disease of the most important drugs used in these patients. It is important to realize, however, that 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.

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

The present article deals with the kinetic and dynamic changes of drugs in patients with chronic liver disease and should help avoiding situations as described above.

Changes in pharmacokinetics

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 (1, 2), absorption of orally administered drugs may be impaired. However, the amount of drug absorbed is generally not decreased in cirrhotic patients (3), but the absorption of orally administered drugs may be delayed. Delayed absorption, which is not explained by gastritis or ulcers, has for instance been shown for furosemide in cirrhotics (4, 5), but not for torasemide, another loop diuretic used in patients with ascites (6). The studies with furosemide suggested that impaired gastrointestinal motility may be a mechanism for delayed drug absorption in cirrhotic patients. Cirrhotic patients have indeed delayed gastric emptying (7, 8), possibly resulting from a decreased action of gastrointestinal hormones such as secretin, glucagon, cholecystokinin or motilin (9). Prokinetic agents such as erythromycin or cisapride, which act differently as compared to the gastrointestinal hormones mentioned above, can speed up gastric emptying in cirrhotic patients (10, 11), indicating that the reasons for impaired gastric emptying are functional and not organic in nature. Impaired gastric emptying may be relevant for preparations with delayed drug release, since the action of these drugs may be delayed further in this group of patients and may therefore be unpredictable.

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). In cirrhotics with ascites, initial dosing of such drugs should therefore be performed according to body weight, if a rapid and complete effect of the drug is desired. On the other hand, an increase in the volume of distribution is associated with an increase in the elimination half-life of such drugs (3). A slower elimination velocity in cirrhotics with ascites has indeed been demonstrated for furosemide (4, 5) and for beta-lactam antibiotics such as ceftazidime or cefprozil (12, 13). 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 (5). Since many hydrophilic drugs are excreted non-metabolized primarily by the kidney, renal function has also to be taken into consideration for such drugs. This aspect is discussed below (see section “renal clearance”).

Hepatic clearance

While the creatinine clearance can be used for dose adjustments in case of impaired renal function (14), there is no naturally occurring substance which can be used to estimate the hepatic clearance of drugs (Cl_{hep}). The Child-Pugh classification is used widely for the assessment of the prognosis in patients with liver cirrhosis (15), but has not been shown to be useful to predict the kinetic and/or dynamic behaviour of drugs (16). Regarding the lack of endogenous markers for hepatic clearance of drugs, exogenous compounds might serve as an alternative. As shown in Table 1, the kinetics of several substances have been investigated, but none of them has gained wide acceptance in the prediction of drug kinetics in patients with liver disease. The most important reason for this observation may be the complexity of the hepatic metabolism of drugs. As discussed in the following sections, drugs can be metabolized by different enzymes (e.g. different cytochrome P450 isoenzymes [CYP] and different enzymes for drug conjugation) and can be excreted by the bile. One probe drug or exogenous substance is therefore most probably not sufficient to predict the kinetics of all drugs used in cirrhotic patients.

Table 1. *Substances investigated for quantification of liver function/liver metabolism*

Substance (application)	E (%)	Metabolism	Clinical use	Reference
Serum bile acids (endogenous)	>90	Hydroxylation and conjugation, enterohepatic cycling	May be useful for estimation of porto-systemic shunt	(20)
Indocyanine green (i.v.)	90	Biliary excretion	Estimation of hepatic blood flow	(108)
Galactose (i.v.)	95	Rate-limiting step is phosphorylation	First-order elimination reflects “functional hepatic capacity”. Extrahepatic metabolism is problematic	(109)
Sorbitol (i.v.)	>80		Estimation of hepatic blood flow	(110)
Lidocaine (i.v.)	80	CYP3A		(111)
d-Propoxyphene (p.o.)	70	CYP3A	Ratio norpropoxyphene/d-propoxyphene may be useful to estimate proto-systemic shunt	(112)
Erythromycin (i.v.)	30	CYP3A	CO_2 exhalation is used as a marker of CYP3A activity	(113)
Antipyrine (p.o.)	5	Different CYPs	Reflects activity of different CYPs	(114)
Aminopyrine (i.v.)	<30	Different CYPs	CO_2 exhalation is used as a marker of general CYP activity	(115)
Caffeine (p.o., i.v.)	<30	CYP1A2, N-acetyltransferase type 2 (NAT2)	CO_2 exhalation measures activity of CYP1A2	(116)

E: hepatic extraction

A cocktail of probe drugs could be used (16), but analysis of the substances applied would be time consuming and might therefore not be helpful in most clinical situations.

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

$$Cl_{hep} = Q \times E = Q \times \frac{C_{in} - C_{out}}{C_{in}} \qquad (1)$$

C_{in} is the concentration of a drug in the portal and C_{out} in the liver veins. According to the venous equilibrium model (the concentration of a substance in the liver is assumed to be uniform and equal to the hepatic outflow concentration), E can also be expressed as described in (3):

$$E = \frac{f_u \times Cl_i}{Q + (f_u \times Cl_i)} \qquad (2)$$

Cl_i is the intrinsic hepatic clearance and f_u the fraction of a drug not bound to serum proteins (free fraction). Cl_i reflects the capacity of the liver to metabolize a certain drug independently of the blood flow across the liver.
Using this expression for E, Cl_{hep} can be written as:

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

For drugs with a high hepatic extraction, (f_u x Cl_i) is >> Q and Cl_{hep} is approximating Q. These drugs are therefore called “flow-limited” or “high extraction”. Alternatively, for drugs with a low extraction, (f_u x Cl_i) is << Q and Cl_{hep} is

approximating (f_u x Cl_i). These drugs are called “enzyme-limited” or “low extraction”, and their Cl_{hep} is mainly determined by the capacity of the liver to metabolize such drugs. Many drugs are in between these two extremes, showing properties of both groups (Table 2).

High extraction drugs

High extraction drugs undergo a high extraction during the first passage across the liver (≥ 60%), and have therefore a bioavailability of ≤ 40% (see Figure 1).

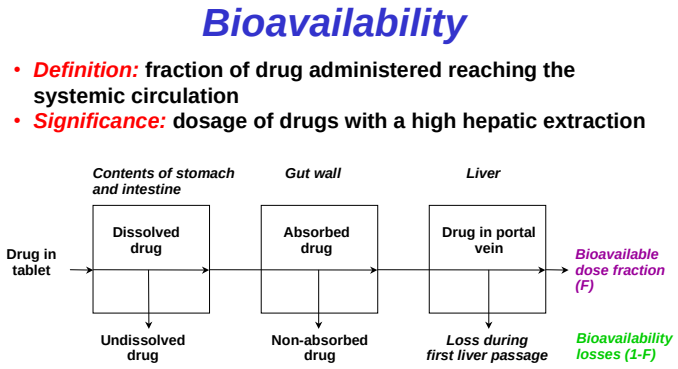

Figure 1. *Effect of liver cirrhosis on the bioavailability of high extraction drugs.* After oral administration, only a fraction of a drug reaches the systemic circulation. Most of the drug not reaching systemic circulation is either not absorbed or metabolized during the first passage across the liver. 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 (adapted from 17).

Since the blood flow across the liver is typically decreased in patients with liver cirrhosis (18, 19), the elimination of high extraction drugs is retarded in comparison to patients with normal liver function. In addition to decreased blood flow across the liver, patients with liver cirrhosis frequently have porto-systemic shunts, preventing the exposure of hepatocytes to drugs (3, 20). As a consequence, a variable amount of portal blood is not cleared by hepatocytes, potentially leading to a significant increase in the bioavailability of high extraction drugs administered orally (Figure 2).

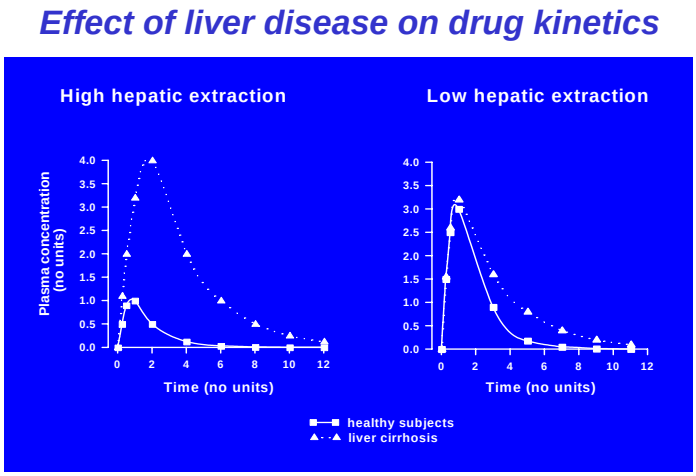

Figure 2. *Effect of liver cirrhosis on the kinetics of drugs with high or low hepatic extraction.* For drugs with a high hepatic extraction, the maximal plasma concentration and bioavailability increase, and elimination is slowed. For drugs with a low hepatic extraction, only elimination is slowed. 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 (21).

For example, the bioavailability of clomethiazole is 10% in healthy persons and may increase to 100% in patients with liver cirrhosis (22). This 90% increase in bioavailability is associated with a 10-fold higher drug exposure, eventually leading to adverse drug reactions. In Table 3, the observed increase in the bioavailability of some drugs in patients with liver cirrhosis as compared to healthy persons is listed. Therefore, for high extraction drugs administered orally, both the initial and the maintenance doses have to be reduced in patients with liver cirrhosis. The extent of this reduction cannot be predicted accurately, however, since neither the porto-systemic shunt nor the hepatic blood flow are usually known in a given patient. A conservative 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:

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

“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. 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. 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. Theoretically, assessment of the hepatic blood flow using Doppler sonography might be helpful in this situation, but to best of our knowledge, clinical studies supporting this hypothesis are so far lacking.

As shown in Fig. 3, a linear relationship has been described between the serum bile acid concentration and the extent of porto-systemic shunting in patients with liver cirrhosis (20). The serum bile acid concentration may therefore be helpful for initial dosing of high extraction drugs. However, to the best of our knowledge, currently no studies are available addressing this question.

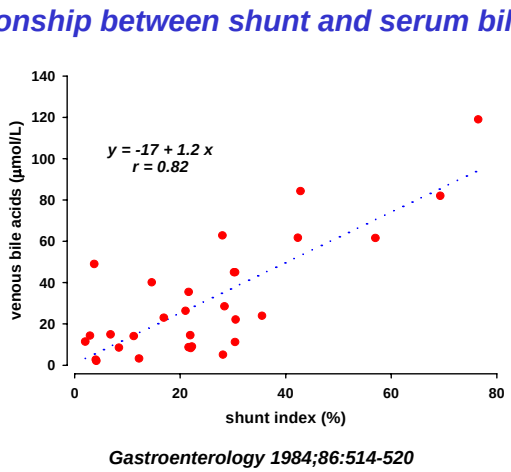

Figure 3. *Relationship between serum bile acid concentration and the hepatic shunt index*. As described by Ohkubo et al., there is a linear relationship between these two variables (Ohkubo). The determination of the serum bile acid concentration may therefore be suitable to predict proper dosing of drugs with a high hepatic extraction in cirrhotic patients.

Low extraction drugs

Low extraction drugs undergo a low extraction during the first passage across the liver (≤ 30%), and their Cl_{hep} is mainly determined by the product f_u x Cl_i. These drugs have a bioavailability which is ≥ 70% (unless dissolution in the gut and/or intestinal absorption are incomplete). Important examples of such drugs are listed in Table 2. As shown in Figure 2, their bioavailability is not affected grossly by liver cirrhosis but their clearance may be reduced, depending on their hepatic metabolism (reflecting Cl_i) and binding to albumin (f_u). Accordingly, the maintenance dose of these drugs should be reduced, whereas therapy can be started with a normal dose. Similar to high extraction drugs, it is impossible to predict precisely by how much the maintenance dose of such drugs has to be reduced. Studies assessing the protein content and/or the activity of important drug metabolizing enzymes (CYPs 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 (23-25).

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. Conjugation reactions such as glycosylation and transfer of sulfate groups (phase II reactions) are considered to be affected to a lesser extent by liver cirrhosis than CYP-associated reactions (phase I reactions) (3). For instance, the clearance of oxazepam (26) or temazepam (27), two benzodiazepines which are only conjugated, are not reduced in patients with liver cirrhosis, whereas the clearance of diazepam (28, 29) or midazolam (30), 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 (23, 25, 31-34). This variability can be explained at least to some extent by the different mechanisms affecting CYP activity and/or protein content, such as impaired transcription for CYP 1A, 3A and 2C (31, 34), altered post-translational modification for CYP 2E1 (31) or increased sensitivity to cholestasis as described for CYP 2E1 and 2C9 (23, 31).

Several studies have shown that also conjugation reactions can be impaired in patients with liver cirrhosis. Reduced glucuronidation has been demonstrated for zidovudine (35, 36), diflunisal (37), morphine (38, 39), mycophenolate (40), lormetazepam (41) and lamotrigin (42). The activity of sulfotransferases was also found to be reduced, whereas sulfatase activity appears to be spared (24).

Considering the large interindividual variability of the activity of drug metabolizing enzymes in cirrhotic patients, it is difficult to give general rules for dosing low extraction drugs in this group of patients. For drugs which are new on the market, kinetic studies in patients with impaired hepatic function due to liver cirrhosis are requested by the drug agencies for approval. Dosing recommendations for most of these drugs can therefore be found in the physician's desk reference or similar publications, but usually only for patients with Child class A or B, but not C (43). 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, we recommend the use of drugs whose safety has been demonstrated in clinical trials and/or whose kinetics is not affected by liver disease or for which therapeutic drug monitoring is available.

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). In patients with reduced serum albumin concentrations, a frequent finding in patients with liver cirrhosis, the free fraction (and possibly also the free concentration) of such drugs is increased. Such drugs may therefore be metabolized more rapidly in cirrhotic patients. According to equation 3, Cl_{hep} of such drugs may remain unchanged or may even be increased in cirrhotics. This argumentation is only valid, however, when the total drug concentration (free and bound to albumin in this case) is considered. For the free concentration only, f_u would equal 1 and Cl_{hep} for low extraction drugs would approach Cl_i.

Importantly, in patients with hypalbuminemia, the total plasma concentration of drugs with a high binding to albumin is decreased when their free concentration is in

the normal range (due to a decrease in drug concentration bound to albumin, see Fig. 4 for explanation). In order to avoid toxicity by overdosing, free drug levels should be determined and used to guide therapy of such drugs in cirrhotic patients, e.g. for phenytoin or valproate.

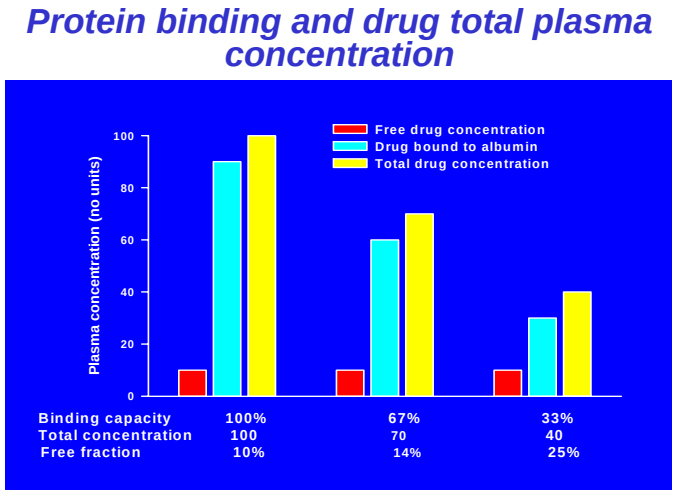

Figure 4. *Effect of the serum albumin concentration on the total serum concentration and free fraction of drugs with high albumin binding*. The free concentration of a drug with high binding to albumin (≥90% at a normal serum albumin concentration) is kept constant at 10. Under normal conditions (normal 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 (21).

Intermediate extraction drugs

The hepatic clearance of drugs with a hepatic extraction between 30% and 60% (”intermediate extraction drugs”) is determined by both Q and (fu x Cli). Since the bioavailability of these drugs is 40% or more, the influence of porto-systemic shunts is less pronounced as compared to “high extraction” drugs (compare Table 3). In general, Clhep of these drugs is reduced, necessitating adjustment of their maintenance dose. Treatment should be started with an initial dose in the low range of normal and maintenance doses should be adjusted as described above for low extraction drugs (Compate Table 4). Examples of such drugs are also listed in Table 2.

Table 2. *Classification of drugs metabolized by the liver according to pharmacokinetic characteristics*

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

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

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.

Problems in the classification of drugs according to hepatic extraction

In order to compare the prediction of the kinetic behavior as estimated using hepatic extraction with kinetic studies performed in patients with liver cirrhosis, we recently studied the antineoplastic agents on the market in Switzerland (44). Of the 64 antineoplastic drugs identified, the available kinetic data of only 49 were sufficient to allow a classification according to hepatic extraction. Values for hepatic extraction (E) are published only for a minority of them, however. E had 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):

$$E = \frac{Q_0 \times Cl_{sys}}{Q} \qquad (5)$$

Q_0 is the fraction of a drug metabolized by the liver (Cl_{hep} = Q_0 x 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 (43, 45, 46).

Both approaches, using oral bioavailabilitay as a surrogate for hepatic extraction or calculation of hepatic extraction using equation 5, 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 (compare Fig. 1). Enterocytes contain CYP3A4, which can metabolize CYP3A4 substrates such as midazolam (47) or cyclosporine (48), before they reach the liver. They also contain P-glycoprotein, which can transport drugs from the enterocytes back to the intestine, as shown for digoxin (49). On the other hand, oral bioavailability can be measured directly in humans, which is difficult for hepatic extraction. A weakness of the calculation of hepatic extraction using equation 5 is that the systemic clearance of a drug is 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 study concerning antineoplastic drugs (44), we therefore used both approaches and detected an acceptable agreement between them.

For 17 of the 64 antineoplastic drugs studied, kinetic studies had been reported in patients with impaired liver function, most of them in patients with cholestasis due to hepatic metastases. Kinetic studies in patients with impaired hepatic function due to liver cirrhosis have been published for only 4 of the 64 antineoplastic drugs identified.

Our study reveals that there are currently not enough data for safe use of antineoplastic drugs in patients with liver disease. While the kinetics of drugs with biliary excretion has been studied quite well in patients with cholestasis, there are many antineoplastic drugs for which hepatic extraction and/or metabolism are not known to a satisfactory extent. This is surprising, since most of these drugs exhibit dose-dependent, systemic toxicity which may be accentuated in patients with preexisting liver disease. Similar studies for other drug classes are so far lacking.

Renal clearance

It is well established that cirrhotics have reduced effective renal plasma flow and glomerular filtration rates, also in the absence of ascites (50-52). On the other hand, several studies have shown that patients with liver cirrhosis tend to have low serum creatinine concentrations (53-55), 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 creatin and a reduced skeletal muscle mass (55). For the same reasons, calculation of the creatinine clearance using the Cockcroft formula (54) may overestimate glomerular filtration (57-59). Theoretically, the determination of the creatinine clearance based on urinary excretion of creatinine should yield accurate results, even in patients with impaired creatin synthesis and/or reduced muscular mass. While one study has shown that the measured creatinine clearance reflects glomerular filtration in cirrhosis accurately (57), other studies indicate that glomerular filtration is overestimated, in particular in patients with reduced glomerular filtration rates (54, 59-61). This finding has been explained by an increased secretion of creatinine in cirrhotics (55, 62). The serum cystatin C concentration, another endogenous marker for renal function, may reflect glomerular filtration more accurately in cirrhotic patients (54).

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 (63), cilazapril (64), fluconazole (65), lithium (66, 67) and ofloxazin (68, 69).

Interestingly, in patients with renal failure, CYP-associated drug metabolism has been shown to decrease (70), in particular for CYP 2D6. Similar observations have been reported for rats, where several CYPs show a reduced expression (71). 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 (72).

Cholestasis

As mentioned in a preceding section, cholestasis impairs the activity of several CYPs, for instance CYP2C (31) and 2E1 (23). 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 (73, 74), doxorubicin and derivatives (75-77) and dactinomycin (78). These studies resulted in recommendations for dose adjustment according to the serum bilirubin concentration and/or activity of alkaline phosphatase (78). 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 (44), 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.

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 (44, 78).

Regarding adverse effects affecting the liver itself, most such events are type B reactions (79). Only few drugs reveal a “dose-dependent hepatic toxicity”, among them methotrexate (80), acetaminophen (81, 82) and isoniazid (83, 84). Patients with preexisting liver disease, in particular alcoholics, who are treated with on 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 (80). For acetaminophen, an important factor is induction of CYP2E1 by alcohol, increasing the generation of N-acetyl-p-benzoquinone imine, a toxic metabolite (81, 82). For isoniazid, both preexisting liver cirrhosis and ingestion of too much alcohol appear to be risk factors for hepatic toxicity (83, 84). 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 β-oxidation of liver mitochondria (85, 86) and has been described in patients treated with valproic acid (87), analgetic doses of aspirin (87), certain opiates (88) or the uricosuricum benzbromarone (89). Since microvesicular steatosis is considered to be more frequent in patients with a preexisting mitochondrial disorder, e.g. a defect in β-oxidation or in the urea cycle, or a mitochondrial cytopathy (90), certain preexisting liver diseases may also be risk factors for type B reactions.

Pharmacodynamics

Patients with liver cirrhosis have been reported to be more sensitive to central adverse effects of morphine (38, 91) and benzodiazepines (92, 93), and to renal adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) (92), whereas the sensitivity to the natriuretic effect of loop diuretics was found to be reduced (3).

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.) (91). In contrast, in a more recent study, none of 6 cirrhotics developed encephalopathy after i.v. administration of higher doses of morphine (95). Since several studies have shown that the oral bioavailability of morphine is increased and its elimination is impaired (39, 96, 97), 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 (92, 93). In cirrhotics, benzodiazepines may induce encephalopathy which can be reversed by the administration of benzodiazepine antagonists (98). While impaired hepatic metabolism has been demonstrated in cirrhotics for midazolam (92) and diazepam (28, 29, 93, 99), no such changes were detected for oxazepam (26), temazepam (27) or triazolam (100), 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 (compare Table 3). 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 (101, 102), bumetanide (103) and furosemide (102, 104, 105). 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 (101).

NSAIDs are known to precipitate renal failure in patients with cirrhosis and ascites (94). Patients with portal hypertension have a low peripheral resistance and hyperdynamic circulation due to increased production of vasodilating substances such as nitric oxide (106). 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 prostglandins 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 (107).

Table 3 *Comparison of the oral bioavailability of selected drugs in control subjects and patients with liver cirrhosis*

Drug	Bioavailability			Reference
	Control subjects	Cirrhotic patients	Increase (factor)	
Clomethiazole	0.10±0.07	1.16±0.25	11.6	(22)
Encainide	0.26±0.20	0.76±0.42	2.92	(117)
Flumazenil	0.28±0.06	0.65±0.26	2.32	(118)
Labetalol	0.33±0.09	0.63±0.19	1.91	(119)
Meperidine	0.48±0.13	0.87±0.27	1.81	(120)
Midazolam	0.38±0.16	0.76±0.37	2.00	(30)
Morphine	0.47±0.14	1.01±0.43	2.15	(97)
Nifedipine	0.51±0.17	0.91±0.26	1.78	(121)
Nisoldipine	0.04±0.02	0.15±0.10	3.75	(122)
Pentazocine	0.18±0.05	0.68±0.21	3.78	(120)
Propranolol	0.36±0.02	0.60±0.10	1.67	(123)
Verapamil	0.10±0.02	0.16±0.05	1.60	(124)

Table 4. *Adaptation of the drug dosage in patients with liver disease according to excretion, metabolism and hepatic extraction (if no studies available)*

Elimination pathway	***Expected changes in the kinetics***	***Recommended dosage adaptation***
Drugs with predominant renal elimination Q_o<0.5	• In cirrhotics with edema and/or ascites: $V_d\uparrow$ • $Cl_{ren}\downarrow$	In cirrhotics with edema and/or ascites: initial dose: adjustment according to body weight[2]. Dose reduction of maintenance therapy according to creatinine clearance, especially for drugs with a narrow therapeutic range.
Drugs with predominant hepatic elimination Q_o≥0.5	• High extraction drugs: $F\uparrow$, $Cl_{hep}\downarrow$	*Oral:* Initial dose: reduced dose = normal dose x F/100.Maintenance doses: adjustments according to clinical effect and drug toxicity. *Intravenously:* Initial dose: no dose adaptation necessary. Maintenance doses: dose reduction as for low extraction drugs, adjustments according to clinical effect and drug toxicity.
	• Intermediate extraction drugs: $F\uparrow$, $Cl_{hep}\downarrow$	*Oral*: Initial dose: in the low range of dosage for patients without liver disease. Maintenance doses: adjustments such as for low extraction drugs. *Intravenously*: Initial dose: no dose adaptation necessary. Maintenance doses: dose reduction as for low extraction drugs, adjustments according to clinical effect and drug toxicity.
	• Low extraction drugs: $F\rightarrow$, $Cl_{hep}\downarrow$ • Low extraction drugs with protein binding >90%: $Cl_{hep}\downarrow$, $\rightarrow$ or $\uparrow$, $f_u\uparrow$	*Oral or intravenously*: Initial dosage: no dose adaptation necessary Maintenance doses: if no studies available adjustment according to Child class: Child class A: 50% dose reduction; Child class B: 75% dose reduction; Child class C: choose drugs whose kinetics is not affected by liver disease and/or TDM is available. Use the free drug levels to guide the therapy of such drugs in the case of TDM.
Drugs with significant biliar elimination(≥5%)	• In patients with cholestasis: $Cl_{hep}\downarrow$, $\rightarrow$ or $\uparrow$	Dose reduction according to serum bilirubin concentration and/or activity of alkaline phosphatase (guidelines exist only for some antineoplastic drugs).

Conclusions

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. Obvious gaps in our knowledge about the kinetic behavior of drugs in patients with liver disease include data about hepatic extraction and kinetic studies of drugs with biliary elimination in patients with cholestasis.

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Project 2

3.2 Dose adaptation of antineoplastic drugs in patients with liver disease

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Drug Safety 2004; in press

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 2001 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. The studies were identified by a structured, computer-based literature search.

Of the 64 drugs identified, 49 had a predominant extrarenal (in most cases hepatic) metabolism and/or excretion. For 47 drugs, hepatic extraction could be calculated and/or bioavailability was available, allowing classification according to hepatic extraction. For 16 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. doxorubicine 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 cyctostatics 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 advise for dose adaptation.

Introduction

Dose adaptation for patients with liver disease is more difficult than for patients with impaired renal function. The main reason for this statement is the fact that, unlike the creatinine clearance for the kidney, for the liver there is no *in vivo* surrogate to predict 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.

Several reviews have covered this subject during the last years (1-5). In these reviews, drugs are listed according to pharmacokinetic variables which are derived from the hepatic clearance of drugs. The hepatic clearance (Cl_{hep}) of a drug is given by:

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

where f_u is the unbound fraction and Cl_i the intrinsic clearance of a drug, respectively, and Q the blood flow across the liver. Cl_i represents the maximal capacity of the liver to metabolize a given drug, not taking into account limitations by liver perfusion (6). Cl_i can therefore reach values which are larger than Q, which is important for understanding the special situations discussed below.

Equation (1) can be simplified for the two extremes (f_u x Cl_i) >> Q or Q >> (f_u x Cl_i). For the first case, (f_u x Cl_i) >> Q, the denominator in equation (1) simplifies to (f_u x Cl_i), and Cl_{hep} equals:

$$Cl_{hep} = Q \qquad (2)$$

For such drugs, the liver has a very large metabolic capacity, and the blood flow across the liver becomes rate-limiting for hepatic clearance. These drugs are therefore called “flow-limited” or “high capacity” and are usually cleared by the liver to a substantial degree already during the first hepatic passage. Therefore, they have a high hepatic extraction or a low bioavailability. Since portal blood is impaired in patients with liver cirrhosis (7, 8), hepatic clearance of such drugs is decreased, necessitating a reduction of the maintenance dose in this group of patients. A second

potential problem of such drugs is an increase in bioavailability when they are administered orally. Since these drugs have a low bioavailability by definition, an increase in bioavailability could lead to toxic blood levels. This can be expected to happen in patients with porto-systemic shunts, which result from portal hypertension due to liver cirrhosis or fibrosis or, of importance in patients with cancer, due to multiple metastases (9, 10). Therefore, when such drugs are administered orally, 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 the impairment in hepatic blood flow. A list of such drugs is given in a previous publication (1).

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

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

These drugs are therefore called “low extraction” or “capacity-limited”. They have not a high 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 and/or biliary excretion. Since Cl_i decreases for most drugs in patients with liver cirrhosis due to a decrease in the activity of cytochrome P450 isoenzymes (CYP) (11, 12) and/or glucuronyl transferases (13-15), the maintenance dose of such drugs has generally to be decreased. 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 (16, 17). The actual hepatic clearance of such drugs is therefore difficult to predict in patients with chronic liver disease.

In between of 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 appears to be an important one. The most prevalent liver disease in this group of patients is the presence of liver metastases, possibly resulting in cholestasis and/or portal hypertension (10, 18, 19). Since many antineoplastic drugs are potentially hepatotoxic themselves (see Table 2), drug-induced liver disease may also be common in patients undergoing repetitive cycles of chemotherapy. On the other hand, with the exception of hepatocellular carcinoma, liver cirrhosis is probably not more prevalent in patients with cancer as compared to an age-matched population without cancer, but no exact data are available.

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 create a table with the current recommendations for dose adaptation 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 2001. 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” (20) (similar to the “Physicians’ Desk Reference” (21)), “Therapeutic drugs” of Dollery et al. (22) and “Hepatotoxicity” of H. J. Zimmerman (23).

The antineoplastic drugs were categorized according to pharmacokinetic principles as outlined in the introduction and based on the reviews of Huet and Villeneuve (16) and Krähenbühl and Reichen (1). 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 (20-22, 24). 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:

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

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 and Q the blood 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 (20-22, 25), and Q was assumed to be 1.5 L/min.

Dosage recommendations originate either from the original articles or from the manufacturer as published in the PDR (21) and/or the Swiss Compendium of Drugs (20).

Drug-induced liver disease was classified according to Benichou (26) and the severity of liver disease according to Donelli et al. (27) (see Table 2).

Results

Informations about all antineoplastic drugs on the market in Switzerland by the end of the year 2001 were collected. Using our search strategy, we identified a total of 109 articles which were found to be relevant for our study. In 61 one of them, kinetic data were reported and 48 contained hepatic adverse effects of antineoplastic agents.

The 64 antineoplastic drugs on the Swiss market by the end of the year 2001 are listed in Table 3. From these 64 drugs, 10 fell into category 1, 10 into category 2 and 27 in category 3. Seventeen drugs could not be classified (category 4), demonstrating a lack of data about hepatic extraction and/or bioavailability.

Fourtynine out of the 64 drugs had 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 had a Q_0 value ≤0.4 and for 8 drugs, the Q_0 value could not be identified. For 23 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, biculatamide, 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 biculatamide, estramustine, exemestan and paclitaxel, there is a general statement that the dose should be adapted or stopped in patients with decreased liver function. For topotecan, no dose reduction is recommended in patients with liver disease. For 16 of the 64 drugs studied, recommendations for dose adaptation are based studies in patients with hepatic dysfunction.

For 39 of the 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 be explained by 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 blood 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 (28), such data should be available for all substances on the market.

Kinetic studies have been conducted in particular in two conditions, namely 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 biliar elimination (see Table 3). These studies resulted in quantitative recommendations for dose adaptation 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 a large series of patients with cholestasis. It remains also unclear, whether the serum bilirubin concentration is the best parameter for dose adaptation in cholestatic patients or whether, for instance, 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 (10, 18), the situation resembles 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 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. There is a third 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 (29-35). Since this condition can be treated but is potentially fatal (35), 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 the drugs are approved. Considering kinetics, in particular oral bioavailability and hepatic extraction should be investigated. For drugs with a predominant hepatic metabolism and/or excretion, the kinetics in patients with liver metastases and/or cholestasis should have been studied before marketing authorisation is provided.

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

Parameter	*Pathophysiological condition and clinical significance*	*Severity*[1]
Alanine aminotransferase (ALT)	Breakdown (necrosis or apoptosis) of hepatocytes. Hepatocellular injury[2] if > 2 x ULN[3]	2-5 x ULN: moderate injury > 5 x ULN: severe injury
Alkaline phosphatase	Cholestasis[4] 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

[1]The severity is classified according to Donelli et al. (27) with some modifications
[2]Hepatocellular injury is defined according to Benichou (26)
[3]ULN: upper limit of normal
[4]Cholestasis is defined according to Benichou (26)

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[1]**	**Kinetic parameters**							**Hepatic adverse effects[9]**	**Studies performed and dosage recommendations**
		Q_0[2], metabolism	**V_d[3] (L/kg)**	**$t½$[4] (h)**	**PB[5] (%)**	**F[6] (%)**	**Cl_{sys}[7] (L/h)**	**E[8]**		
Aldesleukin	4	Not known	0.18	1	-	-			*Frequent*: hepatocellular injury, cholestasis, or hyperbilirubinemia (20).	*Recommendation*: Monitor patients for adverse effects, dose may need to be adjusted patients with liver disease (20, 22). Contraindicated in patients with elevated serum bilirubin (20).
Amino-glutethi-mide	3	0.50 N-acetylation, N-hydroxylation (CYP) (22)	1.00	12	25	95	4.5	0.03	*Sporadic*: cholestasis, hyperbilirubinemia (23).	No dose adjustment recommendations available for patients with liver disease.
Amsacrine	4	1 Glutathion conjugation, Biliar excretion (20)	1.40	5	97	-			*Sporadic*: cholestasis, hyperbilirubinemia (23).	*Recommendation*: 50% dose reduction if serum bilirubin > 34 µmol/l (36). Dose reduction (70% of normal dose) in patients with severe liver disease (20, 22).
Anastrozole	4	0.95 N-dealkylation, hydroxylation (CYP), glucuroni-dation (22)	-	50	45	80			*Sporadic*: cholestasis.	No dose adjustment recommendations available for patients with liver disease.
Bicaluta-mide	2	≈1 Oxidation (CYP), glucuronidation. Biliar elimination 40% (20)	-	139	98	-	30	0.34	One case of fulminant liver failure (37)	*Recommendation*: Stop treatment if transaminases > 3 x ULN or in patients with hyperbilirubinemia (20)
Bleomycin	3	0.70	0.30	3	-	-	5.2	0.04	*Case reports*:	*Recommendation*: No dose adjustment in patients

Drug	***Cat*[1]**	***Kinetic parameters***							***Hepatic adverse effects*[9]**	***Studies performed and dosage recommendations***
		***Q_0*[2], metabolism**	***V_d*[3] (L/kg)**	***t½*[4] (h)**	***PB*[5] (%)**	***F*[6] (%)**	***Cl_{sys}*[7] (L/h)**	***E*[8]**		
		Hydrolysis (22)							steatosis (23, 38)	with liver disease (22).
Buserelin	3	Not known	-	1.6	-	3				No dose adjustment recommendations available for patients with liver disease.
Busulfan	3	1 Oxidation, sulfation	1.0	2.5	30	70	18.9	0.21	*Sporadic*: hepatocellular injury, cholestasis (39, 40). *Rare*: venoocclusive disease (23).	No dose adjustment recommendations available for patients with liver disease.
Capecita-bine	1	0.97 Carboxylesterase, Cytidine desaminase, phosphorylation	-	1.3	54	42	251	>1	*Frequent*: hyperbilirubinemia *Sporadic*: cholestasis *Rare*: Hepatocellular injury (41)	*Studies*: Increased bioavailability by 20% in patients with moderate liver disease due to metastases (42). *Recommendation*: No dose adjustment in patients with moderate liver disease (42)
Carboplatin	3	0.25	0.24	3	20	-	4.5	0.01	*Rare*: hepatocellular injury, cholestasis (23)	*Recommendation*: No dose adjustment in patients with liver disease (20)
Chloram-bucil	3	1 β-oxidation (22)	1.0	1.5	99	87	11	0.12	*Rare*: hepatocellular injury (23) *Case report*: liver failure (43).	*Recommendation*: Monitor patients for adverse effects, dose may need to be adjusted patients with liver disease (20)
Chlorme-thine (Mechlore-thamine)	4	1 ethyleneimmonium ion (22)	-	-	-	-				No dose adjustment recommendations available for patients with liver disease.
Cisplatin	3	0.65 non-enzymatic degradation (44)	0.3-1	0.5	90	-	0.3	0.01	*Rare*: hepatocellular injury (23)	*Recommendation*: No dose adjustment in patients with liver disease (20, 22)
Cladribine	2	Not known	0.4	6	25	55	60			No dose adjustment recommendations available for patients with liver disease.
Cyclo-phospha-mide	3	0.9 Hydroxylation by CYPs 2B6, 2C19, 2C9, 3A4 (45)	0.80	7	15	75	4.4	0.04	*Rare*: Hepatocellular injury, cholestasis, hyperbilirubinemia (23).	*Studies*: Decreased clearance of active drug and decreased production of active metabolites in patients with liver metastases (49), severe liver disease in the presence of Hodgkin's disease (50) or liver cirrhosis

Drug	***Cat*[1]**	***Kinetic parameters***							***Hepatic adverse effects*[9]**	***Studies performed and dosage recommendations***
		***Q_0*[2], metabolism**	***V_d*[3] (L/kg)**	***t½*[4] (h)**	***PB*[5] (%)**	***F*[6] (%)**	***Cl_{sys}*[7] (L/h)**	***E*[8]**		
									Case reports: venoocclusive disease (46-48)	(36). *Recommendation*: Monitor patients with liver disease for adverse effects. Dose reduction by 25% in patients with serum bilirubin > 50 μmol/L (20)
Cyproterone	3	1 hydrolysis, hydroxylation, conjugation (22)	19	38	95	88			*Sporadic*: hepatocellular injury, cholestasis, hyperbilirubinemia *Rare*: liver failure (51-55)	*Recommendation*: Monitor liver function. Stop treatment in patients with liver injury (20, 22)
Cytarabine	2	0.90 cytidine deaminase (22)	3.0	2.3	13	<20	55	0.55	*Sporadic to frequent*: dose-dependent hepatocellular injury, cholestasis, hyperbilirubinemia (23)	*Recommendation*: 50% dose reduction if serum bilirubin > 34 μmol/L, gradual increase while monitoring systemic toxicity (36)
Dacarbazine	3	0.30	1.5	0.7	5	-	12	0.04	*Case reports*: venoocclusive disease (56, 57), hepatic vein thrombosis (57)	No dose adjustment recommendations available for patients with liver disease.
Dactinomycin	4	0.70 Biliar excretion 50%-90% (22)	12	36	-	-			*Rare*: hepatocellular injury, steatosis, venoocclusive disease (23)	*Recommendation*: 50% dose reduction in patients with hyperbilirubinemia. Increase gradually while monitoring systemic toxicity (36).
Daunorubicin	4	0.90 Reduction, biliar excretion 40% (22)	40	27	-	-			*Rare*: Venoocclusive disease when combined with radiation (23)	*Recommendation*: If serum bilirubin 20 - 50 μmol/L 25% dose reduction, if serum bilirubin > 50 μmol/L 50% dose reduction (20, 22)
Docetaxel	2	1 Oxidation by CYP3A4 (22). Biliar excretion	1.6	0.6 (□ 11 (γ)	95	-	39	0.43		*Studies*: Population kinetic studies 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

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]***, metabolism***	***V_d***[3] ***(L/kg)***	***t½***[4] ***(h)***	***PB***[5] ***(%)***	***F***[6] ***(%)***	***Cl_{sys}***[7] ***(L/h)***	***E***[8]		
		75%, 10% as intact drug (20, 22)								clearance was reduced by 27% (20, 22). *Recommendation*: 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 adminstered (20, 22)
Doxorubicin	1	0.95 Reduction to doxorubicinol, sulfation, glucuronidation, biliar excretion 50% (22, 27)	17	26	80	5	69	0.73	*Rare*: in combination with cyclophosphamide, etoposide and cisplatin cholestasis and venoocclusive disease (23)	*Studies*: In 5 patients with disseminated sarcoma, bone marrow toxicity and doxorubicin serum levels correlated with hyperbilirubinemia (58). In patients with hepatocellular carcinoma, bone marrow toxicity and serum doxorubicin/doxorubicinol levels correlated with hyperbilirubinemia (59, 60). In 17 patients with liver metastases and moderate liver disease kinetics of doxorubicin was not changed but the half-life of doxorubicinol increased (61). In 4 patients with moderate liver disease the half-life of doxorubicin was doubled (62). In patients with liver metastases and mild increase in transaminases or alkaline phosphatase, kinetics and toxicity of doxorubicin was not changed (59, 60, 63, 64). *Recommendation*: If serum bilirubin 20 - 50 μmol/l: 50% dose reduction. If serum bilirubin > 50 μmol/l: 75% dose reduction (20, 22, 36, 65). Donelli et al. advise dose reduction only if serum bilirubin is > 50 μmol/L (27).
Epirubicin	1	0.90 Reduction Biliar excretion 40% (66)	20	39	85	-	89	0.89		*Studies*: In patients with liver metastases and increased serum bilirubin, the half-life of epirubicin/epirubicinol was increased (67-69). In patients with hepatocellular carcinoma, epirubicin kinetics correlates with liver function and serum bilirubin (70). In patients with liver metastases, epirubicin kinetics correlates better with transaminases than with serum bilirubin (71-73).

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]***, metabolism***	***V_d***[3] ***(L/kg)***	***t½***[4] ***(h)***	***PB***[5] ***(%)***	***F***[6] ***(%)***	***Cl_{sys}***[7] ***(L/h)***	***E***[8]		
										Recommendation: If serum bilirubin 20 - 50 μmol/l: 50% dose reduction. If serum bilirubin > 50 μmol/l: 75% dose reduction (20, 22, 36)
Estramusti-ne	2	0.90 Oxidation, partial biliar excretion (74)	0.04	1.3	99	44			*Sporadic.* Hepatocellular injury, cholestasis (20)	*Recommendation:* Monitor patients for adverse effects, dose may need to be adjusted patients with liver disease (20).
Etoposide	3	0.65 Esterases, glucuronidation. Biliar excretion <10%.	0.30	8.1	95	50	2.9	0.02	*Frequent.* Hepatocellular injury (23). *Case reports*: Reactivation of hepatitis B virus (30), liver failure (75)	*Studies*: In patients with mild to moderate liver disease, etoposide kinetics was not altered (76-78). In patients with severe liver disease elimination and AUC were highly variable and tended to be increased in the case or impaired hepatic protein synthesis or hyperbilirubinemia (76-79). *Recommendation*: Monitor patients with mild to moderate liver disease. If bilirubin 25 – 50 μmol/L or AST > 180 U/L 50% dose reduction (36). Contraindicated in patients with decompensated liver disease (20, 22).
Exemesta-ne	1	1 CYP3A, biliar excretion 40% (80)	19	24	90	42	609	>1	*Sporadic* hepatocellular injury, cholestasis (20)	*Recommendation*: Monitor patients for adverse effects, dose may need to be adjusted patients with liver disease (20).
Fludarabine	3	0.35	2.4	10-30	-	70	15.5	0.06		*Recommendation*: No dose adjustment recommended in patients with liver disease (20, 22).
Fluorouracil	1	0.95 Dihydropyrimidine dihydrogenase	0.3	0.25	94	28	67.2	0.71	*Sporadic*: hepatocellular injury when administered i.v. (23)	*Studies*: In patients with liver metastases, a weak correlation with cholestasis was present (81), but no dose adjustment was recommended. *Recommendation*: Start with 50% of normal dose in patients with liver cirrhosis. Increase gradually while monitoring systemic toxicity (27, 36).
Flutamide	4	1 Hydroxylation (82)	-	8	95	-			*Sporadic*: hepatocellular injury, hyperbilirubinemia (20).	*Recommendation*: Monitor liver function (20).

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]***, metabolism***	***V_d***[3] ***(L/kg)***	***t½***[4] ***(h)***	***PB***[5] ***(%)***	***F***[6] ***(%)***	***Cl_{sys}***[7] ***(L/h)***	***E***[8]		
									Case reports: liver failure (83-90).	
Formesta-ne	1	Not known	-	120	93	25				No dose adjustment recommendations available for patients with liver disease
Fosfestrol	3	1	-	0.5	-	80				*Recommendation*: Monitor liver function (20, 22).
Gemcitabi-ne	1	0.9 Deamination, phosphorylation (20)	25	1 – 12	10	-	90	0.9	*Frequent*: hepa-tocellular injury (self-limiting) (20, 22)	No dose adjustment recommendations available for patients with liver disease
Goserelin	3	0.4	-	4.0	25	-	8.2	0.04		*Recommendation*: Dose adjustment not recommended in patients with liver disease (20).
Hydroxy-carbamide	3	0.4	0.5	5.0	80	80			*Case report*: fulminant liver failure (91)	No dose adjustment recommendations available for patients with liver disease
Idarubicin	1	≈1 Oxidation, biliar excretion 8 – 17% (92, 93)	-	15.2	96	28	120	≈1	*Frequent*: hepatocellular injury, hyperbilirubinemia (20)	*Studies*: In patients with metastases, kinetics of idarubicin is not changed (94, 95). *Recommendation*: If serum bilirubin 20 - 34 μmol/l: 50% dose reduction. If serum bilirubin > 34 μmol/l: contraindicated (20)
Ifosfamide	3	0.5 CYP3A (activation) (45)	0.5	6.5	-	100	3.6	0.02	*Sporadic*: hepatocellular injury, hyperbilirubinemia (23)	*Recommendation*: Monitor patients with preexisting liver disease (20). Contraindicated in patients with decompensated liver disease (22).
Imatinib	3	0.95 N-demethylation (CYP 3A), 20% biliar elimination (20)	4.9	18	95	98			*Sporadic*: hyperbilirubinemia, hepatocellular injury (20).	*Recommendation:* Stop treatment if serum bilirubin > 3 x ULN or transaminases > 5 x ULN (20)
Irinotecan	3	0.75 Esterases, glucuronidation, CYP3A4 Biliar excretion	75	10	65	-	26	0.21		*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) (97). *Recommendation*: If serum bilirubin > 1.5 x

Drug	***Cat*[1]**	***Kinetic parameters***							***Hepatic adverse effects*[9]**	***Studies performed and dosage recommendations***
		***Q_0*[2], metabolism**	***V_d*[3] (L/kg)**	***t½*[4] (h)**	***PB*[5] (%)**	***F*[6] (%)**	***Cl_{sys}*[7] (L/h)**	***E*[8]**		
		25% (20, 96)								ULN/transaminases > 5 x ULN dose reduction according to adverse events. Contraindicated if serum bilirubin > 5 x ULN (20). According to (97) 350 mg/^{2} in patients with serum bilirubin 1.1-1.5 ULN and 200 mg/m^2 when serum bilirubin >1.5 ULN.
Letrozol	3	0.95 CYP3A4, 2D6 (20)	1.9	45	60	100	2.4	0.03		No dose adjustment recommendations for patients with liver disease available
Leuprorelin	3	Not known	0.5	3	46	-	8.3	0.05		No dose adjustment recommendations available for patients with liver disease
Lomustine	3	1 Cis- and trans-4-hxdroxylation (98)	1.70	10	-	≈100			*Sporadic*: hepatocellular injury (20)	No dose adjustment recommendations available for patients with liver disease
Medroxypro-gesteron	1	1 CYP3A4	0.6	36	94	<10	76	0.84	*Rare*: cholestasis, peliosis (20)	No dose adjustment recommendations available for patients with liver disease.
Megestrol	4	1 Glucuronidation (22)	-	18	-	-			*Rare*: hepatocellular injury, hyperbilirubinemia (20)	No dose adjustment recommendations available for patients with liver disease
Melphalan	2	0.9 Hydroxylation (22)	0.6	1.5	80	70	31	0.31		*Recommendation*: No adjustment recommended in patients with liver disease (22).
Mercapto-purine	2	0.9 Xanthine oxidase (thiouric acid), thiopurine methyltransferase (22)	0.6	0.9	19	12	46	0.46	*Frequent*: dose-dependent hepatocellular injury, cholestasis, hyperbilirubinemia in 6 – 40% (23). *Case reports*: liver failure (99-102), venoocclusive disease (23). Risk may be higher in patients with reduced activity of thiopurine	*Recommendation*: Monitor liver function. Contraindicated in patients with decompensated liver disease (20)

Drug	***Cat*[1]**	***Kinetic parameters***							***Hepatic adverse effects*[9]**	***Studies performed and dosage recommendations***
		***Q_0*[2], metabolism**	***V_d*[3] (L/kg)**	***t½*[4] (h)**	***PB*[5] (%)**	***F*[6] (%)**	***Cl_{sys}*[7] (L/h)**	***E*[8]**		
									methyltransferase	
Methotre-xate	3	0.05	0.70	7.2	50	70	8.8	0.01	*Sporadic*: Fatty liver, fibrosis, cirrhosis during long-term treatment with immunosuppressive doses (103-109). *Case reports*: hepatocellular injury, acute liver failure during use as an antineoplastic agent (30, 110-113)	*Studies*: No correlation between liver function and methotrexate serum levels (114). *Recommendation*: Close monitoring in patients with decompensated liver disease. Reduce dose in the presence of ascites and/or decreased renal function (20, 22)
Mitomycine	4	0.9	0.3	0.5	-	-			*Rare*: steatosis *Case reports*: venoocclusive disease (23)	No dose adjustment recommendations available for patients with liver disease
Mitoxantro-ne	2	0.95 mono- or dicarboxylation (inactive), biliar excretion 25% (20)	10 - 15	57	76	-	45	0.48	*Frequent:* hepatocellular injury (23)	*Studies*: Clearance reduced by 50% in patients with moderate liver disease (115). Patients with serum bilirubin < 60 µmol/L tolerate 14 mg/m^2, patients with serum bilirubin > 60 µmol/L and bad performance status have higher mortality with this dosage (116). In patients with liver metastases, half-life of mitoxantrone correlated with serum bilirubin and cholestasis (117). *Recommendation*: Dose adjustment (8 mg/m^2) or contraindicated (bad performance status) in patients with serum bilirubin > 60 µmol/L (116)
Nimustine	4	1	-	0.6	34	-				No dose adjustment recommendations available for patients with liver disease
Oxaliplatin	4	≈0.5, Reduction (non-	-	260	75	-				*Recommendation*: No dose adjustment in patients with liver disease (20).

Drug	***Cat*[1]**	***Kinetic parameters***							***Hepatic adverse effects*[9]**	***Studies performed and dosage recommendations***
		Q_0*[2], *metabolism	***V_d*[3] *(L/kg)***	***t½*[4] *(h)***	***PB*[5] *(%)***	***F*[6] *(%)***	***Cl_{sys}*[7] *(L/h)***	***E*[8]**		
		enzymatic), biliar excretion 5% (118)								
Paclitaxel	3	0.95 CYP 3A, 2C8. Biliar excretion > 5% (119)	2.0	3	95		23	0.24	*Sporadic*: hepatocellular injury, cholestasis *Rare*: hyperbilirubinemia, liver failure (20)	*Studies*: Liver disease/liver cirrhosis appears to be a risk factor liver for systemic toxicity (120, 121). Increased risk for myelosuppression in patients with increased transaminases and/or serum bilirubin > 25 μmol/L (122). In patients with increased transaminases (3-10 x ULN) and hyperbilirubinemia (1.3 – 2 x ULN) clearance was decreased by ≈ 40% (123) *Recommendation*: Monitor patients with liver disease well for adverse effects. Do not administer in patients with decompensated liver disease (20, 123)
Raltitrexed	4	0.5 Polyglutamate derivative (124)	7.0	2	93	-			*Frequent*: hepatocellular injury *Sporadic*: cholestasis, hyperbilirubinemia *Case report*: liver failure (125)	*Recommendation*. No dose adjustment in patients with mild to moderate liver disease. Contraindicated in patients with decompensated liver disease (20).
Rituximab	4	Not known	-	68	-	-				No dose adjustment recommendations available for patients with liver disease
Tamoxifen	4	1 Hydroxylation, N-dealkylation (CYP 2C9, 2D6, 3A4, 2C8) (22)	60	4 – 11 days	99	-			*Sporadic*: hepatocellular injury, cholestasis, fatty liver (23). *Rare*: liver failure (126-128).	*Studies*: In a patient with liver metastases liver function deteriorated one year after start of tamoxifen (129). In a randomized trial in patients with hepatocellular carcinoma, liver function was not affected (130). *Recommendation*: Monitor liver function in patients with preexisting liver disease.
Temozolo-mide	3	0.9 non-enzymatic	-	1.8	15	≈100				No dose adjustment recommendations available for patients with liver disease
Thiotepa	3	0.5 CYP 2B1, 2C11 (131)	-	2.4	99	-	19	0.11	*Case report*: liver failure (132)	No dose adjustment recommendations available for patients with liver disease

Drug	***Cat*[1]**	***Kinetic parameters***							***Hepatic adverse effects*[9]**	***Studies performed and dosage recommendations***
		***Q_0*[2], metabolism**	***V_d*[3] (L/kg)**	***t½*[4] (h)**	***PB*[5] (%)**	***F*[6] (%)**	***Cl_{sys}*[7] (L/h)**	***E*[8]**		
Tioguanine	4	>0.9, Thiopurine methyltransferase	-	5 - 9	-	-			*Rare*: hepatocellular injury, cholestasis (23). *Case reports*: Veno-occlusive disease (133, 134)	*Recommendation*: Monitor liver function after administration of high doses. Contraindicated in patients with decompensated liver disease (20).
Topotecan	2	0.6 Esterases Biliar excretion 20% (135)	1.9	2.4	35	32	49.5	0.33		*Studies*: 14 patients with increased transaminases and/or hyperbilirubinemia (some with cirrhosis) were treated with 1.5 mg/m^2. Topotecan clearance correlated with ICG clearance but no more adverse effects were observed in patients with liver disease (136). On the other hand, two thirds of patients with hepatocellular carcinoma treated with topotecan developed grade IV neutropenia (137). *Recommendation*: No dose adjustment for patients with hepatic dysfunction but monitor patients well for systemic toxicity (136).
Toremifen	3	1, CYP3A4 (N-demethylation, hydroxylation). Enterohepatic circulation (138)	12-15	148	99	≈100	4.5	0.05		*Studies*: In 10 patients with liver cirrhosis or fibrosis the elimination half-life was increased by 75% and clearance decreased by 28% (138). *Recommendation*: Dose reduction in patients with liver cirrhosis by 50%, gradual increase while monitoring adverse effects (20).
Trastuzu-mab	4	Not known	0.04	140	-	-				No dose adjustment recommendations available for patients with liver disease
Vinblastine	2	1 CYP3A4 biliar excretion >50% (22)	20	25	75	-	52	0.58		*Recommendation*: If serum bilirubin > 50 μmol/L → 50% dose reduction (20).
Vincristine	3	0.9 CYP3A4 biliar excretion 70% (22)	8.0	23	75	-	8.5	0.09		*Studies*: In the presence of cholestasis/hyperbilirubinemia □-half-life was prolonged (139). In patients with leukemia or lymphoma and cholestasis, AUC and toxicity were increased (140).

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]***, metabolism***	***V_d***[3] ***(L/kg)***	***t½***[4] ***(h)***	***PB***[5] ***(%)***	***F***[6] ***(%)***	***Cl_{sys}***[7] ***(L/h)***	***E***[8]		
										Recommendation: If serum bilirubin > 50 µmol/L → 50% dose reduction (20). Some authors advise 50% dose reduction also if alkaline phosphatase is increased (36).
Vindesine	4	Not known CYP 3A, biliar excretion	8.8	24	-	-	17.5			*Recommendation*: Monitor patients for adverse effects, dose may need to be adjusted patients with hyperbilirubinemia (20).
Vinorelbine	1	0.85 CYP 3A, biliar excretion 50% (22, 141)	75	30	15	≈40				*Studies*: In 19 patients with liver metastases, clearance was reduced by 50% in patients with >75% of the liver replaced by tumor (142). *Recommendation*: 50% dose reduction if more than 75% of liver replaced by tumor (142) or if serum bilirubin > 34 µmol/L (141).

[1]*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
[2]Q_0: extrarenal dose fraction = fraction metabolized or excreted by bile (1 - Q_0: fraction excreted unchanged by the kidney)
[3]V_d = volume of distribution in L per kg. For calculation, body weight was assumed to be 70 kg.
[4] *t½:* dominant half-life
[5]*PB*: Fraction bound to proteins (protein binding in %)
[6]*F*: Bioavailability
[7]Cl_{sys}: systemic clearance (L/min)
[8]*E*: hepatic extraction, calculated as described in equation 4
[9]*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

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Project 3

3.3 Dose adaptation of central nervous system agents in patients with liver disease

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 can lead to drug accumulation or, less often, to failure to form an active metabolite.

The most important factors affecting drug disposition in patients with chronic liver disease have been discussed in numerous reviews (1-9), where drugs are classified according to the way they are handled by the liver on the ground of their hepatic clearance.

Hepatic clearance (Cl_{hep}) is defined as the volume of blood from which drug is removed completely by the liver per unit time. Hepatic clearance can be expressed as:

$$Cl_{hep} = \frac{Q \times (f_u \times Cl_i)}{[Q + (f_u \times Cl_i)]} \qquad (1)$$

When (f_u x Cl_i) >> Q, equation (1) can be simplified to $Cl_{hep} \approx Q$. In this case, hepatic clearance is said to be blood *flow-limited* and is insensitive to changes in protein binding or enzyme activity (i.e. Cl_i). Patients with liver cirrhosis may have porto-systemic shunts, which may increase bioavailability of *flow-limited* drugs (10,11). Blood flow across the liver may be reduced in cirrhotic patients (12), leading to an impaired hepatic clearance of such drugs. This may be of particular importance for psychotropic drugs since many of them are metabolised primarily by the liver (13).

Drugs for which (fu x Cli) >> Q are called low-extraction drugs. For such drugs, equation (1) can be simplified to $Cl_{hep} \approx$ (fu x Cli). Cl_{hep} is mainly determined by the capacity of the liver to metabolise this drugs and is influenced by changes in the plasma protein binding of such drugs. Hepatic disease can alter the intrinsic clearance of this drugs (by affecting the activity of cytochrome p450 isoenzymes) and also their binding to plasma proteins (hypoalbuminemia in cirrhotics patients) (14).

Few drugs have an intermediate extraction ratio and cannot be assigned to either group. The hepatic clearance of these drugs can be influenced from all the parameters included in equation (1).

Psychooanaleptics, psycholeptics, anti-Parkinson agents and antiepileptics often need to be prescribed to patients with pre-existing hepatic disease. Sedatives, for example, are used in patients with liver cirrhosis as a premedication before upper

gastrointestinal endoscopy for the diagnostic assessment of gastrointestinal haemorrhage the presence of esophageal varices. Antidepressant drugs may also not infrequently be given to cirrhotic patients. In fact, depressive symptoms are not uncommon in patients with impaired liver function, since the mental slowing accompanying hepatic encephalopathy may be depression (15).

Most psychoactive medications, with the exception of lithium, are highly fat-soluble and require phase-I (hepatic) metabolism. Therefore, impairment of hepatic clearance can lead to drug accumulation and dose-related adverse drug reactions. Chronic usage of sedatives including phenothiazine, for example, may precipitate somnolence or coma (15-17). The increased cerebral sensitivity to many psychoactive drugs observed in patients with liver impairment may be due to changes in the pharmacokinetics (resulting in a greater concentration of free drug in the brain or to in pharmacodynamics (13). These effects may necessitate dosage modification or a change in the medication.

Classification according to pharmacokinetic properties and conducted clinical trials in patients with liver cirrhosis can help to select and administer drugs more rationally in patients with liver disease. The aims of this article were to classify psychoanaleptics (antidepressants, psychostimulants, anti-Alzheimer agents), psycholeptics (antipsychotics, anxiolytics, hypnotics and sedatives), antiepileptics and anti-Parkinson agents according to pharmacokinetic principles (hepatic extraction) and to provide recommendations for their use in patients with liver disease.

Methods

We used the databases Medline and Embase to detect the clinical studies that have been carried out in the topics of hepatic adverse effects, pharmacokinetics and pharmacodynamics as well as dose adaptation of psychoanaleptics, psycholeptics, antiepileptics and anti-Parkinson agents in patients with liver disease. We restricted our search for the drugs that had been registered in Switzerland by the end of the year 2002. To perform our literature search, the following MeSh (Medica Subject Headings) terms were used:

Central nervous system agents, liver disease, pharmacokinetics, drug effects, metabolism, drug toxicity.

We used the standard literature as well to review thoroughly dose adaptation recommendations, adverse effects and modified pharmacokinetics or pharmacodynamics in patients with liver impairment (18,19) (similar to the (20)), (21).
We categorized the drugs according to pharmacokinetic variables as mentioned in the introduction which is based on the hepatic extraction or bioavailability of a given drugs. Low-extraction drugs were additionally subdivided according to their protein binding in binding sensitive (protein binding to albumin >90% or f_u<10%) and binding-insensitive drugs (protein binding to albumin <90% or f_u>10%) (see Table 1).
The pharmacokinetic variables or data for liver toxicity were obtained either from the original literature (see Table 4) or from the standard literature (18-21). Hepatic extraction was either obtained from the literature or estimated using the following equation:

$$E = \frac{Cl_{hep}}{Q} \qquad (2)$$

Since Cl_{hep} can be expressed as Q_0 x Cl_{sys}, equation (2) can be rewritten as follows:

$$E = \frac{Cl_{sys} \times Q_0}{Q} \qquad (3)$$

where Cl_{sys} is the systemic clearance, Q_0 the extrarenal dose fraction, and Q the blood flow across the liver. The values for Q_0 and Cl_{sys} were found in the literature (18-20, 22-24).
Dose recommendations are based on the original articles found in our literature search or from the product information published in the PDR (20) or the Swiss Compendium of Drugs (22). Where no dose recommendations were available, we give concrete suggestions according to the pharmacokinetic variables of the specific drugs and the clinical experience of the authors (see Table 4).
Drug-induced liver disease was classified according to Benichou (25) (see Table 2).
Since impaired liver function can be associated with increased experience of drugs with hepatic metabolism, we have listed the important dose-related adverse reactions of central nervous agents found in the standard literature (see Table 3) (18, 24-26).

Results

With a computer-based literature research, data about psychoanaleptics, psycholeptics, anti-Parkinson drugs and antiepileptics marketed in Switzerland by the end of the year 2003 were collected. A total of 121 articles dealing with the topic of our study, dosing in patients with liver disease were found: 91 articles contained kinetic data and results of clinical studies whereas 30 articles reported hepatic adverse effects.

The 114 studied drugs were psychoanaleptics (including psychostimulants, antidepressants and anti-Alzheimer drugs), psycholeptics (antipsychotics, anxiolytics, hypnotics and sedatives), anti-Parkinson drugs and antiepileptics which are listed in Table 4. According to their bioavailability 25 drugs fell into category 1, 24 drugs into category 2 and 40 drugs in category 3 whereas 25 drugs fell into category 4 due to an absence of kinetic data (hepatic extraction or bioavailability not known). For 19 drugs neither the hepatic extraction nor the bioavailabilty was available. From this 114 drugs 89 had a Q_0 value (extrarenal dose fraction = fraction metabolized or excreted by bile) > 0.4, indicating that the majority of the studied central nervous system (CNS) drugs undergoes an extensive metabolism and/or biliary excretion. 10 drugs had a $Q_0 \leq 0.4$ whereas for 15 drugs the Q_0 was not available.

51 of the 114 drugs undergoes a phase-I hepatic metabolism by the cytochrome P450 system and 18 drugs showed a biliar excretion. However for only one drug, hydroxyzine, a kinetic studies have been conducted in patients with biliary cirrhosis.

Quantified dosage recommendations based on clinical studies in patients with hepatic disease (most of them in patients with liver cirrhosis) could be found for 48 of the 114 drugs studied. For one of the 7 psychostimulants, 9 of the 23 antidepressants, 18 of the 30 anxiolytics and hypnosedatives, 7 of the 20 antipsychotics, 8 of the 16 antiepileptics, 2 of the 14 anti-Parkinson and 3 of the 4 anti-Alzheimer drugs, recommendations for dose adaptation based on studies in patients with liver disease could be found.

Hepatic adverse drug effects have been reported for 74 of the 114 drugs studied.

Table 1

Categorization of psycholeptics, psychoanaleptics, antiepileptics and anti-Parkinson agents 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 0 -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 binding sensitive drugs (with high protein binding >90%), hepatic clearance may increase

4. Hepatic extraction is not known (category 4)

Table 2

Classification of liver disease

Parameter	*Pathophysiological condition and clinical significance*
Alanine aminotransferase (ALT)	Breakdown (necrosis or apoptosis) of hepatocytes. Hepatocellular injury[1] if > 2 x ULN[2]
Alkaline phosphatase	Cholestasis[3] if > 2 x ULN
Serum bilirubin concentration	Cholestasis (exclude prehepatic causes)
Serum albumin concentration	Impaired hepatic protein synthesis
Prothrombin activity	Impaired hepatic protein synthesis

[1]Hepatocellular injury is defined according to Benichou (25)
[2]ULN: upper limit of normal
[3]Cholestasis is defined according to Benichou (25)

Table 3

Most important dose-related adverse reactions of psycholeptics, psychoanaleptics, antiepileptics and anti-Parkinson agents (18,24,26).

Drugs	***Dose-related adverse reactions***
Psychostimulants	
Amphetamines: *amfepramon, dexamfetamine, methylphenidate, phentermine, phenylpropanolamine* Other psychostimulants: *mazindol, modafinil*	Central effects (restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, tenseness, irritability, weakness, insomnia, fever, euphoria). Confusion, aggressiveness, changes in libido, anxiety, delirium, hallucinations, panic states, suicidal or homicidal tendencies. Fatigue, depression. Cardiovascular effects (headache, pallor or flushing, palpitation, arrhythmia, anginal pain, hypertension or hypotension, circulatory collapse). Excessive sweating. Gastrointestinal effects (dry mouth, metallic taste, anorexia, nausea, vomiting, diarrhea, abdominal cramps). Metabolic effects (glycogenolysis in liver and adipose tissues).
Antidepressants	
Tricyclic antidepressants: *amitriptyline, clomipramine, dibenzepin, doxepin, imipramine, lofepramine, melitracen, nortriptyline, opipramol, trimipramine*	Sedative effects, anticholinergic effects (dry mouth, sweating, confusion, constipation, blurred vision, urinary hesitancy). Weight gain. Cardiovascular effects (hypotension, alterations in heart rate, delayed conductivity and decreased myocardial contractility, sinus tachycardia, palpitations). Increased frequency of epileptic convulsions.
Tetracyclic antidepressants: *maprotiline, mianserin, mirtazapine*	*Maprotiline:* Lowered consciousness, convulsions, confusion, disorientation, visual hallucinations and EEG changes similar to tricyclic compounds. Skin rashes and seizures in overdose. *Mianserine:* Reduced anticholinergic and cardiotoxic effects, lower risk of convulsions. Relatively high risk of agranulocytosis. *Mirtazapine:* Weakness, fatigue.
SSRI: *citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*	Gastrointestinal disturbances (such as nausea, diarrhea or constipation), CNS-effects (including insomnia, somnolence, tremor, dizziness and headache), effects on the autonomic nervous system (such as dry

	mouth and sweating), sexual disturbances.
Serotonin precursor: *oxitriptan*	Frequent stools or frank diarrhea, nausea and drowsiness, agitation and restlessness, hyperventilation, hallucination, confusion.
MAO-A inhibitor: *moclobemide*	Insomnia, agitation, paresthesias, hypotension, autonomic disturbance such as dry mouth, sweating, constipation, weight gain. Toxic effects (hepatocellular damage).
Other antidepressants: *nefazodone, trazodone, venlafaxine*	*Nefazodone*: Somnolence, dizziness, asthenia, dry mouth, nausea, constipation, headache and amblyopia. *Trazodone*: Sedation, hypotension. Rarely priapism (due to antiadrenergic actions). *Venlafaxine*: Nausea, sexual dysfunction, cardiovascular effects with dose-dependent increase in blood pressure. Insomnia, nervousness, loss of body weight.
Anxiolytics, hypnotics and sedatives	
Benzodiazepines: *alprazolam, bromazepam, brotizolam, clobazam, cloxazolam, diazepam, flunitrazepam, flurazepam, ketazolam, lorazepam, lormetazepam, midazolam, nitrazepam, oxazepam, prazepam, temazepam, triazolam*	Drowsiness, ataxia, in-coordination, memory impairment, loss of insight, transient euphoria, irritability, aggressive behavior and excitement. Patients with liver cirrhosis may be sensitive to sedative effects of benzodiazepines (risk of encephalopathy).
Imidazopyridine/ cyclopyrrolone derivatives: *zolpidem, zopiclon*	*Imidazolpyridine, cyclopyrrolone derivatives:* Like benzodiazepines. Gastrointestinal disturbances and visual hallucinations. Zolpidem relatively toxic in overdose due to respiratory depression.
Pyrazolopyrimidine: *zaleplon*	Amnesia, depression, irritability, agitation, hallucinations.
Antihistamines: *diphenhydramine, doxylamin, hydroxyzine, promethazine*	Sedation, neuroleptic and anticholinergic side effects. Gastrointestinal side effects. Rarely blood dyscrasies. Cardiac arrhythmias.
Aldehyde: Chloral hydrate	By chronic use hepatic damage possible.
Barbiturates:	*see antiepileptics*
Carbamate: Meprobamate	Drowsiness and ataxia, impairment of learning and motor coordination, prolongation of time reaction, by overdose hypotension, respiratory depression, and death.
Other anxiolytics, hypnotics and sedatives: *buspirone, clomethiazole, methaqualone*	*Buspirone:* dose-related adverse effects similar to the SSRIs (nausea, headache, insomnia, dizziness, and sexual dysfunction). Less sedation and memory impairment than benzodiazepines.

	Clomethiazole: Sedation and memory impairment, nasal irritation. Hypotension, phlebitis, and respiratory depression possible after intravenous use. *Methaqualone:* Drowsiness, headache, nausea, dry mouth.
Antipsychotics	
Benzamides: *amisulpride, sulpiride, tiapride* Benzisoxazole: *risperidone* *Butyrophenones:* *haloperidol, pipamperone* Dibenzodiazepines: *clozapine, quetiapine* Indol derivative: *sertindole* Phenothiazines: *chlorpromazine, levomepromazine, promazine, fluphenazine, perphenazine, thioridazine* Piperidine: *penfluridol* Thienobenzodiazepine: *olanzapine* Thioxantenes: *chlorprothixen, flupentixol, zuclopenthixol*	Nervous system side effects like extrapyramidal reactions and sedation. Less frequently seizures, unwanted behavioral effects, tardive dyskinesia. Anticholinergic effects (dry mouth, blurred vision, constipation). Postural hypotension. Weight gain. Breast engorgement and galactorrhea. Amenorrhea, gynecomastia, hyperglycemia, hypoglycemia, elevation of growth hormone, inappropriate ADH secretion, disturbances of sex hormones possible.
Lithium	Hand tremor, nausea, vomiting, diarrhea, abdominal pain, sedation, ataxia, coma and convulsions. Cardiac side effects rare and reversible. Transient impairment of memory possible. Apathy, drowsiness, muscle weakness, unsteady gait, dysarthria by mild poisoning. Cerebral hemorrhage, increased muscle tone and seizures by severe intoxication.
Antiepileptic drugs	
Benzodiazepine: *clonazepam*	Drowsiness, ataxia, in-coordination, memory impairment, loss of insight, transient

	euphoria, irritability, aggressive behavior and excitement. Patients with liver cirrhosis may be sensitive to sedative effects of benzodiazepines (risk of encephalopathy).
Barbiturates: *barbexaclone, phenobarbital, primidone*	Sedation, fatigue, dizziness, cognitive dysfunction, ataxia, dysarthria, nystagmus, and headache, often dose-related. Exacerbation of seizures and psychiatric reactions not uncommon. Hepatotoxic reactions reported.
Carbamazepines and derivatives: *carbamazepine, oxcarbazepine*	Drowsiness, vertigo, ataxia, diplopia, and blurred vision. Increased frequency of seizures possible. Nausea, vomiting, serious hematological toxicity (aplastic anemia, agranulocytosis), and hypersensitivity reactions (dermatitis, eosinophilia, lymphadenopathy, splenomegaly). By acute intoxication, stupor or coma, hyperirritability, convulsions, and respiratory depression.
Succinimide derivatives: *ethosuximide, methsuximide*	Gastrointestinal effects (nausea, vomiting and anorexia) and CNS effects (drowsiness, lethargy, euphoria, dizziness, headache, and hic-cough). Parkinson-like symptoms and photophobia. Restlessness, agitation, anxiety, aggressiveness, inability to concentrate, and other behavioral effects. Urticaria and other skin reactions.
Hydantoin derivative: *phenytoin*	Dose-related cerebellar-vestibular effects, oculomotor, and cognitive dysfunction, behavioral changes, increased frequency of seizures, gastrointestinal symptoms, gingival hyperplasia, osteomalacia, and megaloblastic anemia. Hirsutism.
Fatty acid derivatives: tiagabin, valproic acid, vigabatrin	*Tiagabine:* Dizziness, somnolence, and tremor. *Valproic acid:* Weight gain, transient gastrointestinal symptoms including anorexia, nausea, vomiting. Sedation, ataxia, and tremor. Rash, alopecia. Effects on hepatic function. *Vigabatrin:* fatigue, somnolence, agitation, nervousness, nystagmus, ataxia, headache, tremor.
Other antiepileptics: *gabapentin, lamotrigine, levetiracetam, topiramate*	*Gabapentin:* Somnolence, dizziness, ataxia, and fatigue. *Lamotrigine:* Dizziness, ataxia, blurred or double vision, nausea, vomiting. *Levetiracetam*: Somnolence, asthenia, and dizziness.

	Topiramate: Somnolence, fatigue, weight loss, and nervousness.
Anti-Parkinson agents	
Anticholinergic agents: *biperiden, procyclidine, trihexphenidyl*	*Biperiden*: Anticholinergic side effects. *Procyclidine:* Anticholinergic side effects, involuntary movements like chewing and sucking. Sedation. *Trihexphenidyl:* Anticholinergic side effects, excitement, combined with levodopa acute toxic confusional state. Impairment of memory, irreversible brain failure.
Levodopa	Severe gastrointestinal upsets, postural hypertension, dyskinesias, mental changes, hallucinations, confusion.
Amantadine	Nausea, psychotic episodes (mania, hallucinations, agitation, confusion), restless legs and convulsions. Livedo reticularis. Anticholinergic agents, e.g. blurred vision, dryness of the mouth, insomnia, lethargy and rash. Insomnia.
MAO-B inhibitor: *selegiline*	May accentuate the adverse effects of levodopa therapy. Anxiety, insomnia.
Dopamine agonists: *ergotamine derivatives (bromocriptine, lisuride, dihydroergocryptine, pergolide), pramipexole, apomorphine*	*Ergotamine derivatives*: Postural hypotension, nausea, vomiting, psychiatric changes, confusions, hallucinations. *Apomorphine:* Somnolence, nausea, vomiting. *Pramipexole:* Orthostatic hypotensive effects, syncope, tachycardia, chest pain. Drowsiness, dizziness, insomnia, increased dyskinesia. Hallucinations, restlessness. Gastrointestinal symptoms.
COMT inhibitors: *entacapone, tolcapone*	*Entacapone:* Fatigue, light-headedness or dizziness. Confusion, anxiety, syncope, insomnia. Gastrointestinal adverse effects. *Tolcapone:* Hypotension, hallucinations, dyskinesias, nausea. Increase of aminotransferases.

Anti-Alzheimer agents	
Anticholinesterases: *donepezil, tacrine, rivastigmine, galanthamine*	*Tacrine:* Abdominal cramping, anorexia, nausea, vomiting and diarrhea, elevations of serum transaminases. *Donepezil, rivastigmine, galantamine:* Nausea, diarrhea, vomiting, and insomnia.

Table 4

Kinetic data, hepatic adverse effects and dose recommendations in patients with liver disease of the central nervous system agents on the market in Switzerland by the end of the year 2001

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Psychostimulants										
Amphetamines										
Amfepra-mon	4	nk Reduction to hydroxy derivatives (22)	-	2	-	-				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* To avoid in patients with liver disease.
Dexamfe-tamine	4	1 CYP 2D6 (27), oxidative deamination, hydroxylation to active metabolite, conjugation (18)	6.11	12	15-40	-				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* To avoid in patients with liver disease.
Methylphe-nidate	1	0.95 Oxidase, de-esterase via non microsomal esterase to retalinic acid (18)	2	5.6	20	25	28	0.3	*Case reports*: hepatocellular injury (21), liver failure after high doses (28).	No official dose adjustment recommendations available for patients with liver disease. *Recommendation*: Start with a third of normal dose (normal dose: 20-30mg/d) in patients with liver cirrhosis. Increase dose carefully.
Phenter-mine	4	0.3 Renal elimination	3.5	20	-	-				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Monitor renal function and adjust the dose accordingly.
Phenylpro-panolamine	3	0.15 Renal elimination	4	4	0	99				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Monitor renal function and adjust the dose accordingly.
Other psychostimulants										

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Mazindol	4	0.9 Conjugation (29), (30)	-	36	77	-				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Mazindol is extensively metabolised by the liver (29, 30), therefore better to avoid in patients with liver disease.
Modafinil	3	0.95 Inductor of CYP3A4, inhibitor of CYP2C19 (22)	0.9	10.5	62	80	37	0.04	*Sporadic*: cholestatic liver injury (22).	*Studies*: Half-life is doubled in patients with liver cirrhosis (22). *Recommendation:* 50% dose reduction (100-200mg/d) for patients with liver disease (22)
Antidepressants										
Tricyclic antidpressants										
Amitripty-line	2	1 Hydroxylation (CYP2D6), N-demethylation (CYP3A4 to Nortriptyline), conjugation (18)	14	21	95	48	51	0.57	*Rare*: hepatocellular injury and cholestatic liver injury (21), (22).	*Studies*: Altered kinetics (plasma levels and AUC 2-3 times higher) and strong sedative response in a patient with porto-caval anastomosis and cirrhosis (31). *Recommendation*: Caution in patients with porto-caval shunts. Start with 50% of normal dose (normal dose: 75mg/d) and adjust dose according to patient response (31).
Clomipra-mine	2	1 Hydroxylation, demethylation to active metabolite, glucuronidation (18)	15	20	98	50	45	0.5	*Occasionally*: hepatocellular injury (22) *Rare*: liver failure (22).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* According to kinetic behavior, initial doses should be reduced by 50% (normal dose: 100 mg/d) and maintenance dose adjusted according to patients response.
Dibenzepin	1	nk N-demethylation to active metabolite (22)	4.2	5	85	25				No official dose adjustment recommendations available for patients with liver disease. *Recommendation:* Based on the low bioavailability, initial doses should not exceed 25% of normal (normal dose: 300 mg/d) in patients with liver cirrhosis. Maintenance doses should be adjusted according to patients response.
Doxepin	1	1 Demethylation,	20	17	95	27	65	0.72	*Rare*: hyperbilirubinemia	*Recommendation*: Dose adjustment is recommended in patients with severe liver disease, but no specification

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
		oxidation to active metabolite, hydroxylation, glucuronidation (18),							(22), cholestatic and/or hepatocellular liver injury (21).	(22). Based on the kinetic data, initial doses should not exceed 25% of normal (normal dose: 30-50mg/d), and maintenance doses should be adjusted according to patient response.
Imipramine	1	1 N-demethylation to desipramine (active metabolite) (18) by CYP 2C19 (32), 1A2 (33), 2D6 (34), 3A4 (35)	15	16	85	42	54.6	0.61	*Sporadic*: cholestatic and hepatocellular liver injury (21), (22).	No dose adjustment recommendations available for patients with liver disease. *Recommendation*: Considering low bioavailability, initial dose should not exceed 50% of normal (normal dose: 100 mg/d). Careful up-titration and monitoring of the patient response.
Lofepra-mine	1	1 CYPs (36), N-dealkylation, hydroxylation, glucuronidation , desipramine (active metabolite) (18)	-	2.2	99	<10	686	>1	*Rare*: elevation of liver enzymes (no specification) (22). *Case report*: liver failure (36).	*Studies*: Decreased metabolic clearance in patients with severe liver disease (not quantified) (22). No dose adjustment recommendations available for patients with liver disease. *Recommendation*: Start with <25% of normal dose (normal dose: 100 mg/d). Careful up-titration and monitoring of the patient response
Melitracen	4	0.7 Hydroxylation, N-demethylation, to litracen (active metabolite) (22)	-	19	89	-			*Sporadic*: cases of cholestatic liver injury (22).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* To avoid in patients with liver disease.
Nortripty-line	2	1 Inhibitor of CYP2D6 (37). Demethylation, hydroxylation to active metabolite (by CYP2D6) (18), partial biliary	18	31	95	51	31	0.34	*Occasionally*: hepatocellular and hepatic injury (21).	No dose adjustment recommendations available for patients with liver disease. *Recommendation*: Start with 50% of normal dose (normal dose: 75 mg/d) in patients with liver cirrhosis. Careful up-titration.

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t_{½}$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
		excretion (38)								
Opipramol	2	0.9 2D6 (22) deshydroxyethyl metabolite (22)	10	8	91	40			*Sporadic*: hepatic failure (22).	No dose adjustment recommendations available for patients with liver disease. *Recommendation*: Starting dose should be reduced by 50% in cirrhotics (normal dose: 50-100mg/d), careful up-titration.
Trimipra-mine	2	0.9 Hydroxylation, demethylation to active metabolite (CYP2D6), glucuronidation (22), (18)	31	23	90	41	67	0.67	*Rare:* hepatocellular and/or cholestatic liver injury (22).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* initial dose should not exceed 50% of normal (normal dose: 150 mg/d). Increase dose carefully according to effect and toxicity.
Tetracyclic antidepressants										
Maprotiline	2	1 Hydroxylation (18), N-demethylation by 2D6 (to active metabolite), (39),	25	45	90	68	63.5	0.71	*Sporadic*: hepatocellular injury, steatosis,phospho-lipidosis (21).	*Recommendation*: The official recommendation is to avoid in patients with liver failure (18, 22). In patients with liver cirrhosis, the initial dose should be reduced to 50% of normal (normal dose: 100 mg/d), careful up-titration.
Mianserin	2	0.95 2D6 (40), N-oxidation, hydroxylation to active metabolite, N-demethylation to active metabolite (18)	10	40	85	68	63.5	0.67		No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Start with 50% of normal dose (normal dose: 60 mg/d) in patients with liver cirrhosis. Increase dose carefully.
Mirtazapine	2	1 demethylation to active metabolite, oxidation (by CYP1A2, 2D6, 3A, (22)	4.8	16.3	85	50	38.3	0.43	*Sporadic*: hepatocellular injury (22).	*Studies*: AUC and half-life increased by 50% in patients with liver insufficiency (22). *Recommendation:* Reduce dose by 50% (normal dose: 30mg/d) in patients with liver cirrhosis (22).

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
SSRI										
Citalopram	3	0.95 Weak inhibitor of 2D6. N-demethylation to active metabolite (CYP 2D6), N-oxidation and deamination (18)	14	33	80	80	18.1	0.19	*Rare*: hepatocellular injury (elevation of serum transaminases) (41).	*Studies*: Oral clearance reduced by 40% and elimination half-life in cirrhotics about twice that of the normal subjects, accumulation possible (42). *Recommendation*: In patients liver cirrhosis maintenance dose should not exceed 10-30 mg/d (22).
Fluoxetine	4	1 N-demethylation to norfluoxetine (active metabolite) (CYP2D6) (18)	30	48	78	-			*Rare*: hepatocellular injury, hyperbilirubinemia (21), (22). Elevations of bilirubin, of transaminases, alkaline phosphatase and gammaglutamyl-transferase reported (43).	*Studies*: Increased elimination half-life of fluoxetine (from 2-3 days to 7 days) and of norfluoxetine (from 7-9 days to 12 days) in patients with alcoholic liver cirrhosis (20, 44). Increased volume of distribution by 150% and plasma clearance two times higher in patient with alcoholic liver cirrhosis (45). *Recommendation*: Reduce dose by 50% or increase dosage interval from 1 to 2 days in patients with liver cirrhosis (22, 45).
Fluvoxa-mine	2	1 Oxidative deamination, oxidative demethylation (CYP 2D6) (18), (22)	25	15	77	53	89.9	1	*Rare*: elevation of liver enzymes (no specification) (22). *Case report*: elevation of gamma-glutamyl transferase (46).	*Studies*: AUC increased by 50% due to longer elimination half-life (25h) (47); (18) and 30% decrease in clearance in patients with liver cirrhosis (20). *Recommendation*: Reduce initial dose to 50% of normal (normal dose: 100mg/d) and monitor maintenance therapy carefully in patients with cirrhosis (18, 47).
Paroxetine	2	0.95 oxidation (CYP2D6) (18)	13	17	95	50	36.1	0.38	*Rare*: hepatocellular injury (21), (22).	*Studies*: Doubled plasma levels in patients with alcoholic liver cirrhosis (48). *Recommendation*: Dose adjustment recommended (10mg/d or 20mg/2d) (22). Initial dose should be at the lower end of the range recommended for subjects

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
										without liver disease (48).
Sertraline	4	1 N-demethylation, glucuronidation, oxidative deamination (CYP2D6, 3A4). Inhibition of CYPs 2D6, 3A4, 2C9 (18), (22)	25	23	98	-	160	>1	*Rare*: hepatocellular injury (21). *Case reports*: liver failure (22).	*Studies*: AUC increased by 4 times, half-life by 2.5 times and Cmax by 1.7 times in patients with liver cirrhosis (49), (22). *Recommendation*: Reduce initial dose to 25% of normal (normal dose: 50mg/d) (22). Careful increase of dose according to effect and toxicity (49).
Serotonin precursor										
Oxitriptan	4	nk conversion to serotonin (5-hydroxytriptophan-decarboxylase) (22)	-	-	19	-				No dose adjustment recommendations available for patients with liver disease.
MAO-A inhibitor										
Moclobe-mide	2	1 N-oxidation, hydroxylation (18) by CYP2C19, 2D6 (22)	1.2	1.7	50	55	58	0.64	*Case report*: cholestatic liver injury (50).	*Studies*: Clearance decreased by 25% and three times prolonged half-life in patients with liver cirrhosis (51). *Recommendation*: Reduce initial dose by 50% in patients with liver cirrhosis (300mg/d) (or increase dosage interval) (51). Careful up-titration according to effect and toxicity.
Other antidepressants										
Nefazodo-ne	1	1 Inhibitor of CYP3A (18), N-dealkylation, hydroxylation to hydroxynefazodone (active metabolite) (22) by CYP3A (52)	0.5	3.5	99	20			*Case reports*: liver failure (53); (54); (55). The drug has been withdrawn from the market due to liver toxicity.	*Studies*: Increased AUC of nefazodone by 60% in patients with liver cirrhosis (56, 57). *Recommendation*: Dose adjustment recommended in patients with severe liver disease (Child B and C) (18, 56, 57, 58). Initial dose should be reduced to 25% of normal (normal dose: 200mg/d). Careful up-titration according to effect and toxicity.

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Trazodone	3	1 Hydroxylation (by CYP3A4) to 1-m-chlorophenylpipe-razine (active metabolite, CYP2D6) (18), (24)	1.5	6	95	75	8.8	0.1	*Rare*: cholestatic and/or hepatocellular injury, chronic hepatitis (21).	*Recommendation:* Start with dose in the low range of normal (normal dose: 50-100mg) in patients with liver disease. Careful up-titration according to effect and toxicity.
Venlafaxine	2	0.95 O-demethylation (CYP2D6) to O-demethylvenlafa-xine (active metabolite), N-demethylation (CYP3A3/4) (22), glucuronidation, inhibitor of CYP2D6 (18),	6	5	27	45	92.4	0.98	*Case reports*: hepatocellular injury, hepatitis (59); (60).	*Studies*: Elimination half-life prolonged by about 30%, and clearance decreased by 50% in patients with liver cirrhosis. Patient with more severe liver cirrhosis (Child C) had a more substantial decrease in clearance (about 90%) (20). *Recommendation:* Initial dose should not exceed 50% of normal (normal dose: 100mg/d) in cirrhotic patients. Careful up-titration according to efficacy and toxicity (20). Drug should be avoided in patients with cirrhosis Child C.
Anxiolytics, hypnotics and sedatives										
Benzodiazepines										
Alprazolam	3	0.8 CYP3A (61), Alpha-OH-alprazolam (active metabolite) (18)	1.1	12	70	88	3.1	0.03	Risk of hepatic encephalopathy in patients with liver cirrhosis (18). *Rare*: cholestatic liver injury (21).	*Studies*: Elimination half-life increased by 50% and clearance of the drug reduced by 50% in patients with alcoholic liver cirrhosis. Changes in elimination half-life and clearance indicated that the metabolism of the drug is slowed in patients with alcoholic cirrhosis (62). *Recommendation*: Daily dose should be reduced by 50% in patients with alcoholic liver cirrhosis (62), recommended initial dose in patients with liver disease is 0.25mg given 2 or 3 times daily (20).
Bromaze-pam	2	1 Hydroxylation to hydroxybromaze--	0.7	16	70	60	2.5	0.03		*Recommendation*: Dose reduction adjustment recommended in patient with liver disease (22). Maintenance dose should not exceed 50% of normal

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
		pam (22)								(normal dose:10mg/d) in patients with liver disease. Careful up-titration according to efficacy and toxicity.
Brotizolam	3	1 Hydroxylation (by CYPs) (63)	0.7	5	90	70	7	0.08		*Studies*: Elimination half-life about two times longer in patients with liver cirrhosis than in controls (64). *Recommendation*: Dose adjustment recommended in patients with liver disease: 50% of a normal dose (0.125-0.250mg) (22). Alternative benzodiazepines, which are primarly conjugated (e.g. oxazepam, lorazepam) may be preferred in these patients.
Clobazam	3	1 N-dealkylation to active metabolite, hydroxylation (18)	1	20	90	>86	1	0.01		*Studies*: Elimination half-life about twice in patients with liver cirrhosis or viral hepatitis compared to normal subjects (65). *Recommendation*: Maintenance dose should be reduced by 50% (normal dose: 20-30mg/d) (22).
Cloraze-pate	3	1 N-desmethyldiaze-pam (active metabolite) (18)	1.3	2	98	91	0.71	0.01	Risk of hepatic encephalopathy in cirrhotic patients (22).	*Recommendation*: Smallest effective initial dose recommended for patients with liver disease (5mg/d) (22).
Cloxazolam	4	nk Chlor-N-desmethyl-diazepam (active metabolite) (22)	-	-	95	-				*Recommendation*: Dose adjustment recommended in patients with severe liver disease (no specification) (22).
Diazepam	3	1 N-demethylation (CYP 2C19), hydroxylation (CYP 3A4), glucuronidation, N-desmethyldiaze-pam, oxazepam and temazepam are active metabolites (18)	1.5	43	98	100	2.6	0.02	*Rare*: cholestatic liver injury (21).	*Studies*: Elimination half-life of diazepam five-fold increased in patients with liver cirrhosis compared to the controls (66,67). Differences in EEG response at similar plasma concentrations in patients with liver cirrhosis suggested differences in cerebral sensitivity (68). Repeated administration may cause accumulation and deeper sedation in patients with liver cirrhosis and hepatitis (69). *Recommendation*: Dose adjustment recommended in patients with liver disease (69).Based on a clinical study, a reduction by approx. 50% is recommended

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
										(68).The kinetic data suggest that the maintenance dose should not exceed 25% of normal (normal dose:10mg/d). Due to the long half-life, there will be accumulation and encephalopathy may be more accentuated.
Flunitraze-pam	3	1 N-demethylation to active metabolite (CYP 2C19), hydroxylation (CYP 3A) (70), amination (71)	3	29	78	85			Risk of hepatic encephalopathy in patients with liver cirrhosis (18).	*Studies*: Plasma levels and pharmacokinetic parameters not altered in patients with hepatic failure (liver cirrhosis or hepatitis (72). No dose adjustment recommendations available for patients with liver disease. Recommendation: Considering the extensive hepatic metabolism, dosage should be reduced by 50% of normal (normal dose: 1mg/d).
Flurazepam	1	1 N-desalkylation, hydroxylation (active metabolites) (18)	3.4	2	95	30			*Rare*: cholestatic liver injury (21).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Considering low bioavailability, dosage should be reduced to 30% of normal (normal dose: 15-30mg/d). Monitor for drug accumulation.
Ketazolam	4	1 N-demethylation to oxazepam, diazepam (active metabolites) (18)	-	2	93	-				*Recommendation*: Careful dosage recommended in patients with liver cirrhosis due to possible accumulation of metabolites and induction of hepatic encephalopathy (22).
Lorazepam	3	1 Glucuronidation (18)	1.3	14	90	93	4.6	0.05	Risk of hepatic encephalopathy (22), (18).	*Studies*: No changes in the kinetics in patients with acute viral hepatitis. Half- life and V_d increased (100%), protein binding decreased in patients with alcoholic liver cirrhosis (73). *Recommendation*: Dose adjustment recommended, 50% of normal dose (normal dose: 2mg/d) in patients with liver cirrhosis, monitor patients well. Injection to avoid in patients with liver failure (22).
Lormetaze-pam	3	0.85 N-demethylation, glucuronidation	4.6	2	85	90				*Studies*: No changes in the kinetics in patient with liver disease (22) and with liver cirrhosis (75). *Recommendation*: Dose adjustment not

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
		(22). Partial biliary excretion 0.3-2.8% (74)								necessary in single oral and multiple dose therapy in patients with liver cirrhosis (75).
Midazolam	2	1 3A (76), hydroxylation to active alpha-hydroxy-midazolam (18)	1	1.9	96	44	27.7	0.31		*Studies*: Increased AUC by 60% in patients with alcoholic liver cirrhosis and increased pharmacological effects (77). Prolonged pharmacodynamic effects in patients with compensated alcoholic liver cirrhosis (78). Decreased clearance by 50% and doubled half-life in patients with alcoholic liver cirrhosis. Benzodiazepine of choice for patients who require endoscopic procedure (79). Doubled bioavailability in patients with liver cirrhosis (80). *Recommendation*: Dose adjustment recommended (80). 50% of normal dose (normal dose: 7.5-15mg/d) in patients with Child A or B cirrhosis, to avoid in patients with Child C cirrhosis (22).
Nitrazepam	3	1 N-reduction (18)	2	30	50	78	4	0.04	*Case report:* cholestatic liver injury (21).	*Studies*: No significant differences in elimination half-life, clearance and volume of distribution in patients with liver cirrhosis. Free fraction increased in patients with liver cirrhosis by 35% (81). *Recommendation*: Dose adjustment recommended in patients with liver cirrhosis (no quantification) (81). 50% dose reduction of normal (normal dose: 2.5-5mg/d)
Oxazepam	3	1 Glucuronidation (18)	1	7	98	90	8	0.09	Risk of hepatic encephalopathy (22), (18)	*Studies*: Kinetics not changed in patients with liver cirrhosis or acute viral hepatitis (82, 83). *Recommendation*: Dose adjustment not recommend for patients with liver cirrhosis or hepatitis (excellent sedative for patients with liver disease) (82). Others recommend to decrease the dose and to monitor patients (no quantification) (22).
Prazepam	3	1 Dealkylation to Norprazepam (active metabolite)	14	1.3	97	86	10	0.1		*Recommendation*: Contraindicated in patients with severe liver disease due to possible encephalopathy (22).

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
		(22)								
Temaze-pam	3	1 Glucuronidation, demethylation, enterohepatic circulation (18)	1.4	13	96	80	4	0.04	Risk of hepatic encephalopathy (22).	*Studies*: No significant changes of the pharmacokinetics in patients with alcoholic liver cirrhosis (84). Slower absorption and delayed hypnotic activity possible in patients with liver cirrhosis (85). *Recommendation*: Usually doses (10-20mg/d)) can be used in patients with undecompensated cirrhosis (7). Caution in patients with liver cirrhosis due to possible induction of encephalopathy (84).
Triazolam	2	1 Hydroxylation to α-hydroxytriazolam (CYP3A) (86) , glucuronidation (18)	1.6	3	80	53	23.5	0.26	Risk of hepatic encephalopathy in patients with liver cirrhosis (22). *Rare*: cholestatic liver injury (21).	*Studies*: Risk of disproportional sedative effects in patients with cirrhosis, which may be due to decreased clearance by 60%, and hypersensitivity of the brain (87). Mild to moderate hepatic dysfunction does not uniformly result in altered kinetics and drug responses (88). *Recommendation:* Should be better avoided in patients with liver cirrhosis. However if night time sedation with triazolam is deemed appropriate, patients with severe liver dysfunction can receive 0.125mg as a start dose (89).
Imidazopyridine/cyclopyrrolone derivatives										
Zolpidem	3	1 Hydroxylation, oxidation (by CYP3A4) (18), partial biliary excretion (90)	0.5	2	93	70	18.2	0.2	*Case report*: hepatitis (91).	*Studies*: Increased half-life up to 10h in patients with liver cirrhosis (22). *Recommendation*: Initial dose should not exceed 50% of normal dose (5mg). Careful up-titration, if necessary (22, 92).
Zopiclone	3	0.95 N-oxidation (by CYP3/4), N-demethylation, oxidative decarboxylation (22)	1.4	5	45	80	14.8	0.16		*Studies*: Decreased clearance by 40% and prolonged half-life (>10h) in patients with liver disease (22). Response to zopiclone delayed and possibly exaggerated in cirrhosis (93). *Recommendation*: Precautions required when using in patients with liver cirrhosis (93). Start with 3.75mg in cirrhotics patients Child C or with 7.5mg in cirrhotics

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
										patients Child A/B (94).
Pyrazolopyrimidine										
Zaleplon	1	1 Aldehyde oxidase, CYP3A4, glucuronidation (22)	1.4	1	60	31	66	0.73		Studies: Oral clearance reduced by 70% and 87% in patients with mild or moderate hepatic insufficiency, respectively 4-fold increase in Cmax and 7-fold increase in AUC (20). Recommendation: recommended dose in patients with mild to moderate hepatic insufficiency is 5mg. To avoid in patients with severe hepatic impairment (20).
Antihistamines										
Diphenhy-dramine	3	0.9 N-demethylation, inhibitor of 2D6 (18)	4.5	8.5	90	72	26	0.26		*Studies*: Elimination half-life increased by 163% and protein binding increased by 15% in patients with alcoholic liver cirrhosis (95). No apparent increase in cerebral sensitivity in patients with alcoholic liver cirrhosis (95). *Recommendation*: A single intravenous dose (0.8mg/kg) showed to be safe and effective in patients with liver cirrhosis (95). Based on the kinetic studies, dose should be reduced by 50% (normal dose: 50mg/d).
Doxylamine	4	nk CYP (22), N-dealkylation, N-acetyl conjugation (96)	-	10.1	-	-				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* To avoid in patients with liver disease.
Hydroxy-zine	4	nk Cetirizine (active metabolite) (97), biliar excretion 70% (22)	16	3-20	78	-				*Studies*: Prolonged elimination half-life (36.6h) and increased volume of distribution (23 L/kg) in patients with primary biliary cirrhosis (97). No dose adjustment recommendations available for patients with liver disease. *Recommendation*: Increase normal dosage interval of 3-4 times daily to once per 24 hours or less (98). Start with low dose, careful up-titration.
Prometha-	1	1	14	12	85	25	68	0.76		No dose adjustment recommendations available for

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
zine		Sulfoxidation, N-dealkylation (CYP2D6), biliar excretion (18)								patients with liver disease. *Recommendation: R*educe the dose in patients with liver disease to 25% of normal (10mg/d).
Aldehyde										
Chloral-hydrate	4	1 Alcohol dehydrogenase to trichloroethanol (active metabolite) (18)	0.6	8	40	-				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* To avoid in patients with liver disease.
Carbamate										
Meproba-mate	4	0.9 hydroxylation (22)	0.6	10	20	-	3	0.03	*Rare*: hepatocellular injury (21).	*Studies*: Increased half-life (18-24h) in patients with liver cirrhosis and hepatitis (99). No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Start with reduced dose in patient with liver disease, 25% of normal (normal dose: 1200mg/d).
Other anxiolytics, hypnotics and sedatives										
Buspirone	1	1 3A (22), oxidative dealkylation to 1-Pyrimidinyl-piperazine (active), hydroxylation, glucuronidation (18)	5	2.4	95	4	92.5	1		*Studies*: Cmax about 16 times higher in patients with liver cirrhosis than in controls. Elimination half-life in cirrhotics about twice that of normal subjects (100). *Recommendations*: Should be used with caution in patients with liver disease (100). 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 (101). To avoid in patients with liver disease (20).
Clomethia-zole	1	0.95 2A6, 3A4/5,2B6,1A1,2C 19 (22)	-	6	65	10	100	1		*Studies*: Plasma clearance decreased by 30% and bioavailability 10 times greater (116%) in patients with alcoholic liver cirrhosis (102). *Recommendation*: Dose adjustment recommended in patients with alcoholic liver cirrhosis (no specification)

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
										(102). To avoid in patients with severe liver disease (22). Initial doses should be reduced by at least 50% (normal dose: 200-400 mg/d) and increases should be made cautiously.
Methaqua-lone	3	0.9 hydroxylation, oxidation, conjugation (20)	6	35	80	75	8	0.08		No dose adjustment recommendations available for patients with liver disease. *Recommendation:* 50% dose reduction of normal (normal dose: 250mg) in patients with liver disease.
Antipsychotics										
Phenothiazines										
Chlorpro-mazine	1	1 Hydroxylation, N-demethylation, N-oxidation, deamination, sulfoxidation (18), partial biliar excretion (22)	22	30	95	32	36.1	0.40	Risk of hepatic encephalopathy in patients with liver cirrhosis (103). *Sporadic*: cholestatic liver injury (21).	*Studies*: Changes in EEG associated with drowsiness and increased sensitivity in patients with liver cirrhosis, particularly when previous history of encephalopathy (103). *Recommendation*: Should be avoid in patients with liver cirrhosis due to risk of hepatic encephalopathy (103).
Fluphena-zine	1	1 Hydroxylation to active metabolite, glucuronidation (18), biliar excretion, enterohepatic circulation (22)	25	20.3	90	25.5	42	0.47	Risk of hepatic encephalopathy (22). *Rare*: cholestatic liver injury (21).	*Recommendation*: Dose adjustment recommended in patients with liver disease (22). Initial oral dose should not exceed 25% of normal (normal dose: 10mg/d)
Levomepro-mazine (methotri-meprazine)	4	1 Sulfoxidation, glucuronidation, demethylation (22)	30	25	-	-			*Rare*: cholestatic liver injury (22).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* To avoid in patients with liver disease.
Perphena-zine	1	1 N-oxidation, hydroxylation, sulfoxidation,	20	21	90	20	107	1.19	Risk of hepatic encephalopathy (18) *Sporadic*: cholestatic liver	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Start with reduced dose in cirrhosis patients, 20% of normal (normal dose: 10mg/d), careful

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
		glucuronidation (18)							injury (21).	up-titration.
Promazine	4	1 Hydroxylation, N-oxidation, conjugation (18), N-demethylation (CYP1A2, 2C19), sulfoxidation (CYP1A2,3A4) (104)	-	-	92	-			Risk of hepatic encephalopathy (18)	*Recommendation*: Use not recommended in patients with liver disease due to possible encephalopathy (18).
Thiorida-zine	2	1 Sulfoxidation, N-demethylation, hydroxylation (CYP2D6), conjugation, extensive biliary excretion (18)	10	20	97	60			Risk of hepatic encephalopathy (22). *Sporadic*: cholestatic liver injury (21).	*Recommendation*: Initial dose should be at the lower end of the range (up 10mg/d) recommended for subjects without disease (22). Increased dose carefully according to the effects and/or toxicity.
Thioxanthenes										
Chlorpro-thixene	1	0.95 Sulfoxidation, N-demethylation, hydroxylation, N-oxidation (22), (105)	15.5	12	99	12			*Sporadic*: cholestatic liver injury (21).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* To avoid in patients with liver disease.
Flupentixol	1	1 Sulfoxidation, N-dealkylation, glucuronidation, biliar excretion, enterohepatic circulation (18)	14	35	99	40			*Occasionally*: hyperbilirubinemia (22).	*Recommendation*: Careful dosing due to possible accumulation in patients with impaired liver function (22). Due to low bioavailability, initial oral dose should not exceed 50% of normal (normal dose: 3-15mg/d).

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Zuclopen-thixol	2	1 Sulfoxidation, N-dealkylation (2D6) (22), glucuronidation, enterohepatic circulation (18)	20	20	99	50			*Case reports*: hepatocellular injury (106); (107).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Start with 50% of normal dose (normal dose: 2-50mg depending on the indication) in cirrhotic patients. Careful up-titration according to the effects/toxicity.
Piperidine										
Penfluridol	3	nk N-dealkylation, enterohepatic circulation, biliar excretion 80% (22)	-	100	-	75			*Rare*: hepatocellular injury, cholestatic liver injury (22).	No dose adjustment recommendations available for patients with liver disease. *Recommendation*: Avoid drug in patients with cholestatic liver injury. Start with a dose at the lower end of the range recommended for subjects without liver disease (20mg/d), careful up-titration.
Dibenzodiazepines										
Clozapine	2	1 N-demethylation to active metabolite (CYP1A2, 3A4) (108), N-oxidation (18)	5	16	95	55	25.6	0.3	*Rare*: cholestatic and/or hepatocellular liver injury (21).	*Recommendation*: Monitoring of liver function recommended in patients with liver disease. (22). According to kinetic behavior, maintenance dose should be reduced by approx. 50% (normal dose: 100-200mg/d).
Quetiapine	1	0.95 3A4 (22)	10	6	83	9	79.8	0.84	*Sporadic*: hepatocellular injury (22).	*Studies:* Clearance decreased by 25% in patients with alcoholic liver cirrhosis, plasma levels and AUC increased by 40% (20), (22). *Recommendation:* Patients with hepatic impairment should be started on 25mg/d. Up-titrate carefully in increments of 25-50mg/d to an effective dose, depending on clinical response and tolerability (109), (20).
Thienobenzodiazepines										
Olanzapine	2	>0.85 oxidation (by CYP1A2, 2D6,	14	37	93	60	18.2		*Frequent*: hepatocellular injury (110).	*Recommendation*: Since prolonged half-life probable in patients with liver disease, dose reduction recommended (no specification) (22). Starting dose

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
		, glucuronidation (22)								should be reduced by 50% (normal dose: 10mg/d) in cirrhotic patients, careful up-titration.
Indol derivative										
Sertindole	3	1 Oxidation, N-dealkylation (CYP2D6, 3A) (22), (111)	20	72	98	74				*Studies*: Clearance decreased by 50% in patients with liver cirrhosis (22). *Recommendation:* According to (112) dosage should be reduced by 50% to offset the expected 50% decrease in clearance. Initial dose should be at the lower end of the range recommended for subjects without liver disease (8-12 mg/d), Careful increase according to toxicity effect (22).
Benzamides										
Amisulpride	2	nk Hydroxylation, oxidation, N-dealkylation (113).	5.8	12	16	48				*Recommendation*: No dose adjustment recommended in patients with liver cirrhosis as the drug undergoes only modest hepatic meabolism (22)
Sulpiride	1	0.3 Renal elimination	1.5	8	40	30			*Rare*: cholestatic liver injury (21).	No dose adjustment recommendations available for patients with liver disease. *Recommendation*: Monitor the renal function and adjust the dose accordingly.
Benzisoxazole										
Risperi-done	2	1 9-hydroxylation (by 2D6) to active metabolite, oxidative N-dealkylation (18)	1.5	3.2	88	66	22.7	0.25	*Rare:* cholestatic and hepatocellular liver injury (20)	*Studies*: No change in single-dose kinetics in patients with liver cirrhosis (20). Increased free fraction by 35% in patients with liver disease (22). *Recommendation*: Initial dose 2x0.5mg/d, careful up-titration to 2x1-2mg/d (20,22).
Butyrophenones										
Haloperidol	2	1 CYP 1A2, 2D6, 3A, inhibitor of CYP2D6, reduced	17	18	92	60	49.6	0.55	*Case report*: cholestatic liver injury (115).	*Recommendation*: Dose adjustment recommended in patients with liver disease (no specification) (22). Dose should be reduced by 50% (normal dose: 3-9mg/d) in patients with liver disease.

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
		haloperidol (active) inhibitor of CYP 2D6 (114)								
Pipampe-rone	4	Oxidative N-dealkylation, amide hydrolysis	-	6	-	-			*Rare*: hepatocellular injury (22).	*Recommendation:* Patients with liver disease should be started on 10mg daily. Careful up-titration in increments of 10mg daily to an effective dose (22).
Lithium salts										
Lithium	3	0.02 Renal elimination	0.7	22	100	100	1.5	0	*Case reports*: ascites, hyperbilirubinemia (116), (117).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Monitor the renal function and adjust dose accordingly.
Antiepileptic drugs										
Benzodiazepine										
Clonaze-pam	3	1 CYP3A4 (118), N-reduction (18)	3	23	85	98	6.5	0.07	*Rare*: hepatocellular injury (21).	*Studies*: Plasma protein binding reduced in cirrhotic patients (119). *Recommendation*: Dose adjustment recommended in patients with severe liver disease (no specification) (22). Patients with liver cirrhosis may be sensitive to sedative effects of benzodiazepines (120). Dose should be reduced by 50% (normal dose: 8mg/d) in patients with liver disease.
Barbiturates										
Barbexa-clone	4	nk Hydroxylation to hydroxyphenobar-bital (121)	-	-	45	-				*Recommendation:* Dose reduction recommended in patients with liver disease. The dose should be chosen according to the therapeutic concentration (therapeutic range:10-40 μg/mL) (22).
Phenobar-bital	3	0.7 Inductor of 3A and 2B6 (122). Oxidation (2C19), glucuronidation (18)	0.7	99	50	100	0.26	0.01	*Sporadic*: hepatocellular injury, cholestatic liver injury (21). Induction of acute intermittant porphyria (22).	*Studies*: "Modest" impairment in the elimination in cirrhosis and/or severe viral hepatitis (123). *Recommendation*: Monitoring of plasma levels recommended in patients with liver disease and prolonged therapy (123). In patients with severe liver disease, it may be contraindicated, in particular if serum levels are not monitored. The dose should be chosen

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
										according to the therapeutic concentration, closely monitoring (therapeutic range:10-40 μg/ml) (22).
Primidone	3	0.6 Oxidation to phenobarbital and converstion to phenylethylmalo-namide (active metabolite) (18)	0.6	10	20	90	2	0.01	*Case report*: coma reported in one patient with acute hepatitis (18). *Very rare*: hepatocellular injury (21).	*Studies*: Kinetics not changed in patients with acute viral hepatitis (124). *Recommendation*: No dose adjustment recommended in patients with acute viral hepatitis (124). Since impaired elimination of primidone described in patients with sever liver disease, dose adjustment recommended (no specification) (22). Monitoring of plasma levels may be helpful (18). Dose should be reduced by 50% (normal dose: 500-1500mg/d) in patients with liver disease.
Carbamazepines and derivatives										
Carbama-zepine	3	1 Epoxidation to active epoxide metabolite, CYP3A4, autoinduction, hydroxylation, glucuronidation (18)	1.4	15	75	>70	5.46	0.06	*Frequent*:: hepatocellular injury (elevation of serum transaminases) *Rare*: cholestatic liver injury. *Very rare:* granulomas (21).	*Studies:* Metabolism and kinetics not affected by mild to moderate hepatic impairment. The kinetics have not been evaluated in severe hepatic impairment (20). *Recommendation:* Should not be used in cases of aggravated liver dysfunction or active liver disease (20).
Oxcarba-zepine	4	nk hydroxycarbaze-pine (active metabolite), cytosylic enzymes, (22)	0.75	28	40	-	283		*Sporadic*: elevation of γ-glutamyltranspeptidase (125). *Very rare*: hepatocellular injury (22)	Recommendation: Dose adjustments not required in patients with mild to moderate hepatic impairment (20).
Succinimide										
Ethosuxi-mide	3	0.8 Oxidation (18)	0.7	45	5	100 -	0.8	0.01		No dose adjustment recommendations available for patients with liver disease.

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Methsu-ximide	4	1 Oxidation, hydroxylation, N-demethylation to active metabolite (22)	-	2.5	-	-			May precipitate hepatic acute porphyria (126)	*Recommendation*: Contraindicated in patients with hepatic porphyria. Caution in patients with liver disease, monitoring of liver functions recommended (22).
Hydantoin										
Phenytoin	3	1 Hydroxylation (CYP2C9), glucuronidation, CYP induction (18), enterohepatic circulation (22)	0.7	24	90	90			*Rare*: hepatocellular or mixed injury, granuloma (21).	*Studies*: Increased percentage (one-third) of unbound phenytoin in patients with acute viral hepatitis, however no change in half-life or plasma clearance (127). Patients with hepatic disease may show early signs of toxicity (20). *Recommendation*: Dose adjustment recommended in patients with liver cirrhosis (22). No dose adjustment recommended in patients with acute viral hepatitis (127). In both cases, the free concentration should be determined.
Fatty acid derivatives										
Tiagabine	3	nk metabolism by CYP3A (22), enterohepatic circulation (128)	1	8	90	90	8.4			*Studies*: Increased half-life (11-15h, 50-100% increase) in patients with liver disease (22,129). Increased incidence of neurological adverse effects in patients with liver disease: dizziness, tremor, nausea, somnolence, incoordination (129). *Recommendation*: Patients should be monitored closely for potential neurological adverse effects (129). Starting dose should not exceed 50% of normal dose (normal dose: 30mg/d).
Valproic acid	3	0.95 Glucuronidation, β-oxidation (18), biliary excretion 7% (130)	0.2	14	90	100	0.5	0.01	*Frequent*: transient hepatocellular and/or cholestatic liver injury (22). *Case reports:* fulminant liver failure	*Studies:* Prolonged half-life by 1.5 time and increased volume of distribution by 1.5 time, decreased protein binding by 10% in patients with liver cirrhosis. Decreased clearance by 50% in patients with liver cirrhosis and by 16% in patients with acute hepatitis (135). *Recommendation*: To avoid in patients with liver

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
									(131), (132). Hepatic liver injury (133), (134).	cirrhosis or significant hepatic insufficiency (18, 20), and in patients with mitochondrial diseases (131).
Vigabatrin	3	0.45 no CYPs	1	7	0	80	5.6	0.03	*Case report*: liver failure (136).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Dose should be reduced by 50% (normal dose: 2g/d) in patients with liver disease. Careful up-titration according to toxicity effect.
Other antiepileptics										
Gabapentin	2	0.35 Renal elimination	0.8	6.5	0	60	6.7	0.03	*Case reports*: acute liver toxicity with a mixed pattern of cytolosis and cholestasis (elevations of aminotransferases, GGT and ALP) (137), cholestatic liver injury (138).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Monitor the renal function and adjust dose accordingly. For patients with creatinine clearance of 15ml/min or less dosage should be adjusted proportionally (e.g. by clearance of 7.5ml/min dose should be one-half of the dose by clearance of 15ml/min) (20).
Lamotrigine	3	0.9 N-glucuronidation (18)	1.1	35	55	98	1.6	0.02	*Case reports:* 2 cases of mixed liver injury (139), (140).	*Recommendation*: Since clearance is decreased in patients with liver cirrhosis, dose should be reduced: 50% in patients with Child B (12.5-25mg/d), 75% in Child C cirrhosis(10-15mg/d) (22). Very careful up-titration in patients with liver cirrhosis.
Levetirace-tam	3	0.3 Renal elimination	0.6	7	5	100	4	0.01		*Studies:* Decreased total body clearance by 50% in patients with severe hepatic impairment (22). *Recommendation*: Monitoring of renal function. 50% dose reduction (normal dose: 500-1500mg/d) recommended for patients with severe liver disease and creatinine clearance <70 ml/min (22).
Topiramate	3	0.1 Renal elimination	0.6	21	9-17	70	1.3	0.01	*Sporadic*: cases of liver failure (22).	*Studies*: Reduced clearance in patients with liver disease (no specification) (22). No dose adjustment recommendations available for patients with liver disease.

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
										Recommendation: Adjust according to renal function. By creatinine clearance <70ml/min/1.73 square meters), one-half of the usual adult dose (normal dose: 200-400mg/d) is recommended (20).
Anti-Parkinson agents										
Anticholinergic agents										
Biperiden	1	1 Hydroxylation (18)	24	1.5	95	33.5				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Considering the low bioavailability, initial doses should be reduced by at least 50% and increases should be made cautiously.
Procycli-dine	3	nk	-	12	-	75				*Recommendation*: Caution in patients with liver disease (22). A twice daily dosage instead of the usual thrice daily dosage had been suggested(141).
Trihexy-phenidyl	4	1	-	5	-	-			*Sporadic*: two cases of cholestatic liver injury (21).	*Recommendation*: Should be used with caution (22). At this time no data are available.
Levodopa										
Levodopa	1	1 Dopa decarboxylase to dopamine (active metabolite) (18)	1	1.4	5	33			*Frequent*: elevation of AST levels (incidence 9%) (21). *Case reports*: two cases of mixed liver injury with jaundice reported (21).	No dose adjustment recommendations available for patients with liver disease.
Amantadine										
Amanta-dine	3	0.1 Renal elimination (18)	7.5	15	67	90	20.2	0.02	*Rare*: reversible elevation of liver enzymes (no specification) (22), (20). None (21).	*Recommendation:* Should be used with caution in patients with liver disease (22). Monitor the renal function and adjust dose accordingly.

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
MAO-B inhibitor										
Selegiline	4	1 Oxidative dealkylation (CYP1A2,3A4) to amphetamine, methamphetamine and desmethylselegili-ne (18), (142)	4.3	1.9	94	-	6300	>1	*Sporadic*: elevation of liver enzymes (no specification) (22).	No dose adjustment recommendations available for patients with liver disease.
Dopamine agonists										
Apomor-phine	1	nk Conjugation (22)	2	0.1	100	1.7				No dose adjustment recommendations available for patients with liver disease.
Bromocrip-tine	1	1	2	7	96	6	56	0.62	*Rare*: two cases of hyperbilirubineamia (21).	No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Since bromocriptine undergoes hepatic metabolism, to avoid in patients with liver cirrhosis.
Dihydroer-gocryptine	4	nk Partial biliar excretion (22)	16	14	50	-				No dose adjustment recommendations available for patients with liver disease.
Lisuride	1	1 Hydroxylation, oxidation, N-desalkylation biliar excretion (18)	2.3	2.2	70	15	48	0.53		*Recommendation*: Dose reduction recommended in patients with liver disease (decreased elimination, increased plasma levels) (22). Start with <25% of normal dose, careful up-titration.
Pergolide	4	1 Pergolide sulfoxide, pergolide sulfone (both active in animals) (22)	24	27	90	-				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Drug is best avoided in patients with liver cirrhosis.
Pramipexo-	3	0.15	7.1	11.6	15	90	56.7	0.1	*Rare*:	*Recommendation*: No dose adjustment recommended

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
le		Renal elimination							elevation of transaminase levels (143).	in patients with liver disease, but in patients with renal disease (22). Monitor the renal function and adjust accordingly.
Orthopramide										
Tiapride	3	0.25 Renal elimination	1.4	5	0	70				No dose adjustment recommendations available for patients with liver disease. *Recommendation:* Monitor the renal function and adjust accordingly.
COMT inhibitors										
Entacapo-ne	2	1 Isomerisation (22), 90% biliar excretion (144), (145), (146), inhibitor of 2C9 (22)	2.6	0.28	98	42	43.3	0.48	*Rare*: elevation of liver enzymes (no specification) (22).	No dose adjustment recommendations available for patients with liver disease. *Studies:* 2-fold higher AUC and maximum concentration value in patients with a history of alcoholism and hepatic impairment after a single dose of entacapone (20). *Recommendation:* Due to low bioavailability, initial dose should be reduced by 50-70% (normal dose: 1000mg/d).
Anti-Alzheimer agents										
Anticholinesterases										
Donepezil	4	0.95 2D6, 3A (147), glucuronidation (22)	12	59.7	96	-	12.2	0.13		*Studies*: Clearance reduced by 20% in patients with alcoholic cirrhosis (22). Kinetics not significantly changed in patients with compensated liver cirrhosis (148). *Recommendation*: Normal initial doses (5mg) in patients with liver disease. (22). Maintenance doses may be increased according to clinical needs and adverse effects
Galanta-mine	3	0.8 N-oxidation, N-demethylation, O-demethylation (CYP 2D6, 3A), glucuronidation,	2.5	5.7	18	88.5				*Studies*: Kinetic not altered in patients with Child A cirrhosis. AUC and elimination half-life increased by 30% in patients with Child B cirrhosis (22). *Recommendation*: In patient with moderately impaired hepatic function (Child A, B) the dose should not exceed 16mg daily. Avoid in patients with severe liver

Drug	*Cat*[1]	*Kinetic parameters*							*Hepatic adverse effects*[9]	*Studies performed and dosage recommendations*
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*t½*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
		epimerisation, active metabolites (22), biliar excretion 0.2% (149)								disease (Child C) (20). Carefull uptitration while monitoring adverse effects (22).
Tacrine	1	1 Hydroxylation (CYP1A2) (18)	5	2.5	55	17			*Frequent*: hepatocellular injury (21).	*Recommendation*: Contraindicated in patients with liver disease due to hepatic toxicity (22).
Rivastig-mine	1	1 Cholinesterase (22)	2	1	40	36			Changes in the pharmacokinetics in patients with liver disease should not have effects on the incidence of adverse effects (22).	*Studies*: Clearance decreased by 50% and activity of cholinesterase, AUC doubled in patients with liver cirrhosis (22). *Recommendation:* Dose adjustment is not recommended in patient with mild liver disease, but may be indicated in patients with Child B or C cirrhosis (22). Dose should not exceed 30% of normal dose (normal dose: 9mg/d).

[1]*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
[2]Q_0: extrarenal dose fraction= fraction metabolized or excreted by bile (1 - Q_0: fraction excreted unchanged by the kidney)
[3]V_d: volume of distribution in L per kg. For calculation, body weight was assumed to be 70 kg.
[4] *t½:* dominant half-life
[5]*PB*: Fraction bound to proteins (protein binding in %)
[6]*F*: Bioavailability
[7]Cl_{sys}: systemic clearance (L/min)
[8]*E*: hepatic extraction, calculated as described in equation 3
[9]*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: compare Table 2

Discussion

In order to compare the prediction of the kinetic behavior (estimated using hepatic extraction) with kinetic studies carried out in patients with liver disease, we studied the psychoanaleptics (including psychostimulants, antidepressants and anti-Alzheimer drugs), psycholeptics (antipsychotics, anxiolytics, hypnotics and sedatives), anti-Parkinson drugs and antiepileptics on the market in Switzerland.

As explained in the introduction, classification according to pharmacokinetic properties and conducted clinical trials in patients with liver disease can help to select and administer drugs more rationally in such patients. The hepatic extraction (E) is important to predict the kinetic behavior of drugs and to avoid dose-dependent drug toxicity in patients with impaired liver function. However, our studies shows 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 clinical studies performed in patients with liver disease.

Most of the clinical studies have investigated the kinetic behavior of drugs in patients with liver cirrhosis and, less frequently, hepatitis. There are few data of dosage recommendations for patients with liver pathology other than liver cirrhosis.

Another deficiency of the reported studies is that the majority are single-dose studies and do not provide information for the adaptation of the maintenance dosage. In fact, patients who need psychotropic drugs are usually treated for a prolonged period of time: drugs can cumulate increasing the risk of dose-related adverse effects (as shown in Table 3) or leading to stronger pharmacodynamic effects. Often clinical studies do not provide quantitative dosage adjustments or remain vague. In most cases, it is obvious that the dosage should be adjusted, but the problem is by how much. Another point to take into consideration is that adjusting drug dosage in patients with liver disease should be based on both pharmacokinetics and pharmacodynamic changes, since the effects of some drugs are altered due to changes in their dynamics. For example, hepatic patients have a greater cerebral sensitivity to a number of drugs acting on the central nervous system (CNS). Although the mechanism underlying this hypersensitivity remains to be explained, there is evidence that this is not caused only by pharmacokinetic alterations.

In our study, we can conclude that there is a lack of data concerning the safe use of drugs acting on the CNS in patients with liver disease: on the one hand data about

the hepatic extraction and on the other hand clinical studies which should also provide information about pharmacodynamic changes in these patient population.

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Project 4

IV Comparison of bioavailability of propranolol and serum bile acid concentration in patients with liver cirrhosis

4.1 Introduction

Some high-extraction (or flow-limited) drugs are frequently used in patients with liver cirrhosis (i.e. propranolol, clomethiazole). Hepatic clearance of high-extraction drugs is mainly determined by blood flow across the liver (1). By definition, when given orally, only a small proportion of high-extraction drugs reaches systemic circulation (low systemic bioavailability).

Patients with liver cirrhosis generally have reduced hepatic blood flow and portal-systemic shunts impair contact between portal blood and hepatocytes so that a variable amount of portal blood cannot be cleared by hepatocytes. These two mechanisms lead to reduced hepatic clearance and increased systemic bioavailability of high-extraction drugs. This may potentially lead to toxic reactions, depending on the toxicity profile of the drugs. Therefore, in general both the loading as well as the maintenance dose of flow-limited drugs must be reduced in patients with liver cirrhosis (2).

Bile acids are removed from portal blood in healthy subjects by flow-limited hepatic uptake. They are excreted in bile either unchanged and/or in conjugated form. In cirrhosis, plasma bile acid concentrations are elevated due to impaired hepatic uptake and/or elimination (3,4,5). It was concluded that intrahepatic shunting was the main determinant of serum bile acid concentrations in patients with liver cirrhosis and this was supported by Ohkubo (4) who measured the extent of intrahepatic shunting and found that serum bile acids correlated well with the degree of shunting.

Since, as discussed above, bioavailability of high-extraction drugs is a function of the magnitude of portal-systemic shunts, we hypothesize that the bioavailability of propranolol and other high-extraction drugs shows a linear correlation with serum bile acid concentrations in patients with liver cirrhosis.

4.2 Subjects and methods

Control subjects and patients with liver cirrhosis

3 healthy individuals (the control group) and 14 patients with liver cirrhosis were studied. The control subjects were all in good health and had no evidence of liver disease, as assessed by medical history and physical examination. The 14 patients

with liver cirrhosis were recruited from outpatients regularly seen at the Hepatology Unit of the University Hospital of Basel.

Details of the patients with liver disease and the control subjects are listed in Table 4.1. Medicaments taken by the patients in with cirrhosis during the month preceding the study are shown in Table 4.1. Patients were assessed by conventional liver tests (serum concentration of albumin, bilirubin, prothrombin time, serum activity of alanine aminotransferase). In healthy subjects, conventional liver tests were not performed.

Study design

The study was approved by the Ethics Committee of Basel. After having obtained written consent, patients and control subjects were evaluated 2-4 weeks prior to the study by clinical examination and by doing the liver function tests detailed above. The study had an open cross-over design and consisted of two individual sessions. Patients and volunteers received randomly either 0.66 mg propranolol given as an intravenous infusion over 10 minutes using a perfusor pump or 40 mg propranolol given as an oral tablet. Propranolol was administered at 7.30 AM. A light standard meal was served 2 hours after the administration of propranolol. The interval between the individual sessions was at least 7 days.

Blood sampling

An i.v. catheter was inserted in a vein on the forearm and a venous blood sample (5 ml) was collected into heparinized tubes which were centrifuged at 3000 rpm for 10 minutes and then stored at - 20°C. In case of intravenous propranolol administration, blood sampling was done through an indwelling catheter placed in a vein of the contralateral arm. After a single oral dose of 40 mg propranolol or an i.v. dose of 1 mg propranolol applied as infusion over 10 minutes using a perfusor pump, blood samples were collected at 5 minutes, 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 14, 24, 36 and 48 hours. After i.v. application of propranolol, additional samples were collected at 10 minutes and 0.75 hours. At 24 and 48 hours patients arrived at 8:00 a.m. after an overnight fast (see day 1) and two blood samples (5 ml each) were obtained by venepuncture. Blood pressure and heart rate were determined at the same time points when blood was obtained.

Determination of propranolol

Propranolol plasma levels were measured using a high pressure liquid chromatography (HPLC)-assay. A simple and method was developed to determine low propranolol concentration in heparinised human plasma using pronethanol as internal standard. The mobile phase (optimized for separation of pronethanol and propranolol) was aqueous phosphoric acid pH 2.5 (containing 2.5 mM octansulfonic acid sodium and 0.01 M potassium dihydrogenphosphat):acetonitrile (68:33, v/v). The flow-rate was kept at 0.8 ml/min and the analysis accomplished in less than 12 min. The column effluent was monitored with a fluorescence detector at an excitation wavelength of 230 nm and an emission wavelength of 340 nm. Extraction was performed from 1 ml (intravenous kinetics) or from 0.200 ml human plasma (oral kinetics). As internal standard, for the intravenous kinetics a 100-µl volume of aqueous pronethanol solution (120 ng/ml) was added to 1 ml human plasma, whereas for the oral kinetics 20 µl of aqueous pronethanol solution (600 ng/ml) was added to 200 µl human plasma. After addition of 300 µl (1.4 M) sodium dihydrogencarbonate and vortex mixing for 15 s, 9 ml of extraction medium (hexan:ethylacetat 1:1, v/v) were given to the sample and shaken for 20 min. After centrifugation of the tubes (3000 N/min, 5 min), the aqueous layer was frozen and the organic layer extracted with 300 µl (0.01M) sulfuric acid. The samples were shaken for 20 min. After centrifugation (3000 N/min, 5 min), 250 µl of the organic layer were transferred into autosampler vials, which were closed after 30 minutes and put in the autosampler. An aliquot of 10 µl was injected into the HPLC system. The separation took place in a 3 µm Luna Pheny-Hexyl column (150x4.60 mm i.d., Phenomenex, Germany) protected by a phenyl (phenypropyl) guard column (4x3 mm i.d., Phenomenex, Germany) and thermostated at 37°C

The limit of detection for propranolol was 0.15 ng/ml and the limit of quantification 0.5 ng/ml. The mean precision was found to be 2.4% and 7.9% for the intra- and interday precision, respectively. The mean accuracy for both inter- and intra-day precision was found to be 102 and 106%. The analytical recoveries of the drug from heparinised human plasma were determined at four concentrations such as 48, 13, 6 and 1.5 ng/ml and its mean percent of recovery ranged from 85.0 to 95.5%.

Determination of bile acids

The total plasma bile acid pool was determined in the plasma samples obtained at 0, 24 and 48 hours after propranolol administration using a commercially available spectrophotometric assay (Wako, Osaka, Japan). Conventional liver function tests, other biochemical determinations and hematological investigations were performed by standard methods in the Departments of Clinical Chemistry of the University Hospital of Basel.

Pharmacokinetic calculations

Analysis of the plasma samples provided two individual plasma concentration-time curves for each subject for propranolol. Values below the limit of quantification (0.5 ng/ml) were set at zero for the calculation. The plasma concentration-time curves (AUC) was obtained by using a non compartment al model (TopFit, version 2.0).

The area under the plasma concentration / time curve (AUC) of propranolol concentration after oral and i.v. administration were calculated as follows:

$$AUC\ (0\text{-}\infty) = AUC(0\text{-}t) + C(t)/\ k_e$$

in which t is 48 hours and k_e is the elimination rate constant calculated as the slope of the plasma concentration-time curve after semilogarithmic transformation. AUC(0-t) was calculated by use of the trapezoidal rule with linear interpolation.

Bioavailability (F) of propranolol was calculated as follows:

$$F = (AUC_{oral}\ X\ dose_{iv})/(AUC_{iv}\ X\ dose_{oral})$$

T_{max} and C_{max} values were determined from raw data. Elimination half -life and clearance were estimated using non-linear-regression analysis as follows:

$$CL = F\ X\ dose/AUC$$

With F set at 1 for intravenous administration. The apparent volume of distribution of propranolol was calculated as:

$$V_d = F\ X\ dose/(AUC\ X\ k_e)$$

Statistical analysis

Data are expressed as mean with standard variation. Group means were compared by two-tailed unpaired t-test using the SPSS statistical program (SPSS for Windows, version 10.1, SPSS Inc., Chicago IL, USA). The level of significance was p=0.05. Linear regression analysis was performed by the least squares method, α of 0.05 was considered to be statistically significant.

4.3 Results and discussion

The total serum bile acid concentrations and pharmacokinetic parameters of propranolol were investigated following oral and intravenous administration to patients with biopsy proven cirrhosis (n=14) and in healthy control subjects (n=3).

Results of conventional liver function tests are shown in Table 4.1. As shown in this table the patients were older than the control subjects. The main results of the pharmacokinetics of propranolol are shown in Table 4.2. The concentration-time profiles of propranolol could adequately be described by non-compartmental analysis. Although large variations were observed between individual patients, the intravenous pharmacokinetic parameters did not differ significantly between patients and healthy subjects. However, as expected, the oral pharmacokinetic parameters showed a significantly (by 7 times) increased area under the curve (AUC) in patients with liver cirrhosis as compared to control subjects. The elimination half-life ($t_{1/2}$) was prolonged by 6 times in cirrhotic patients as compared to controls and the bioavailability (F) was found to be 60% in patients with liver cirrhosis and 12% in control subjects. This last finding accords with other reports in the literature (6,7).

Table 4.1. Details of patients and control subjects. *Normal values in parentheses.*

Subj.	Sex	Age (y)	Diagnosis[a]	BW[a] (kg)	Albumin (35-52g/l)	Bilirubin (5-26 μmol/l)	AST[a] (11-36 IU/l)	Alkaline phosphatase (normal: 43-106 IU/l)	INR[a] (<1.3)	Past history			Child's score	Medica-tion[b]
										Encepha-lopathy	Ascites	Variceal bleeding		
Patients with liver cirrhosis														
1	m	57	AC	57	35	46	49	142	1.1	-	-	-	A / 7	1,2,3,4
2[c]	f	51	*d*	76	35	9	175	79	1.1	-	-	-	A / 6	5,6
3	m	27	NAC (HBV)	57	28	183	237	124	1.5	-	-	-	B / 8	4,7,8,9, 10
4	m	54	AC	76	17	178	234	327	1.4	+	+	-	C / 12	11,12,13, 14,15
5	f	47	NAC	59	31	18	107	167	1.4	-	-	-	A / 6	16
6	m	37	NAC (HCV)	70	35	11	85	102	1.0	-	-	-	A / 6	17
7	m	50	AC	d	28	133	63	235	2.2	-	-	-	C / 12	18
8	f	49	AC	53	24	44	37	286	*d*	-	+	-	B / 9	2,3,11,12 18,19
9	m	50	AC	89.5	27	393	200	314	1.3	+	+	-	C / 11	3,11,12
10	m	60	NAC (HBV)	94	35	29	101	261	1.2	-	-	-	A / 6	2,20,21, 22,23,24
11[c]	m	60	AC	92	31	20	21	104	1.3	-	-	-	A / 6	
12	m	51	AC	58	25	117	98	286	1.1	-	-	-	B / 9	2,3,11,12 15,25,26

Subj.	Sex	Age (y)	Diagnosis[a]	BW[a] (kg)	Albumin (35-52g/l)	Bilirubin (5-26 µmol/l)	AST[a] (11-36 IU/l)	Alkaline phosphatase (43-106 IU/l)	INR[a] (<1.3)	Past history			Child score	Medication[b]
										Encephalopathy	Ascites	Variceal bleeding		
13	m	58	AC	63	24	8	20	50	1.1	-	+	+	B / 8	13,15,18, 27,28,29, 30
14	m	67	NAC	80	36	17	142	101	1.1	-	-	-	A / 5	21, 31
Mean		**51**		**71.1**	**29.36**	**86.14**	**112.07**	**184.14**	**1.29**					
SD		**10**		**13.9**	**5.45**	**104.64**	**72.18**	**93.10**	**0.30**					
Healthy control subjects														
REP	m	20	-	74	ND	ND	ND	ND	ND	-	-	-	-	.
GEC	m	20	-	75	ND	ND	ND	ND	ND	-	-	-	-	.
TCL	f	27	-	63	ND	ND	ND	ND	ND	-	-	-	-	.
Mean		**22**		**71**	ND	**ND**	**ND**	**ND**	**ND**					
SD		**3**		**5**										

[a] *Abbreviations*: AST, serum aspartate aminotransferase; AC, alcoholic cirrhosis; BW, body weight; INR, international normalized ratio; NAC, nonalcoholic cirrhosis (due to viral hepatitis); ND, not determined; SD: standard deviation

[b] *Medicaments used during the month preceding the study*: 1, lamivudine; 2, torasemide; 3, spironolactone; 4, calcium and colecalciferol; 5, losartan;6, calcitriol; 7, ciclosporin; 8, mycophenolic acid; 9, prednisone; 10, omeprazole; vitamine B-complex; 12, thiamine, 13, ciprofloxacine; 14, vitamine K; 15, lactose; 16, morphine; 17, diflucane; 18, propranolol; 19, amoxicillin; 20, acetylsalicylic acid; 21, atenolol; 22, valsartan; 23, simvastatin; 24, insulin; 25, acid folic; 26, potassium chloride; 27, furosemide; 28, pantoprazole; 29, tazobactam; 30,dalteparin; 31, hydrochlorothiazide

[c] patients with cholecystectomy

[d] missing data

Table 4.2. Pharmacokinetic parameters of propranolol in patients and control subjects

Subj	*Intravenous*[a]							*Oral*[b]							*F(%)*
	C_{max} (ng/ml)	t_{max} (min)	AUC (0-∞) (ng.min/ml)	Cl (ml/min)	V_d (l)	k_e (1/min)	$t_{1/2}$ (min)	C_{max} (ng/ml)	t_{max} (min)	AUC (0-∞) (ng.min/ml)	Cl (ml/min)	V_d (l)	k_e (1/min)	$t_{1/2}$ (min)	
Patients with liver cirrhosis															
1	2.25	10	662.08	997	407	2.45 x10-3	283	89.8	120	40097.25	997	406	2.45 x10-3	283	**99.93**
2	18.7	5	1560.3	423	217	1.95 x10-3	356	59.1	90	48608.17	423	490	8.63 x10-4	803	**51.4**
3	10	10	1338.65	493	163	3.03 x10-3	229	52.1	480	55084.17	493	428	1.15 x10-3	601	**67.90**
4	2.4	10	2982.8	221	276	8.02 x10-4	864	156.1	181	141779.4	221	217	1.02 x10-3	680	**78.43**
5	6.3	10	752.92	877	666	1.32 x10-3	527	24.7	90	22275.62	879	1064	8.24 x10-4	841	**48.82**
6	12.1	5	768.56	859	396	2.17 x10-3	319	50.03	90	14593.68	858	385	2.22 x10-3	312	**31.33**
7	7	7	1686.73	391	228	1.72 x10-3	403	63	180	73506.24	391	616	6.36 x10-4	1090	**71.91**
8	7.4	5	3482.2	190	191	9.9 x10-4	700	61.9	180	86988.89	190	309	6.13 x10-4	1130	**41.22**
9	2.2	10	1482.05	445	500	8.9 x10-4	779	32.7	304	48318.72	289	293	6.8 x10-4	1020	**53.79**
10	8.3	5	942.69	827	424	1.95 x10-3	355	20.3	60	13846.89	701	720	9.72 x10-4	713	**24.24**
11	10.6	5	1373.67	480	358	1.34 x10-3	517	132.4	182	73555.36	481	500	9.61 x10-4	722	**88.35**
12	5.9	8	2700.42	541	824	6.56 x10-4	1060	31.8	60	62609.77	541	1337	4.05 x10-4	1710	**84.63**
13	2.2	18	2349.5	281	375	7.48 x10-4	926	52.5	180	42239.13	281	214	1.31 x10-3	528	**29.66**
14	11.8	5	1002.26	659	261	2.52 x10-3	275	82.2	60	43838.26	658	695	9.48 x10-4	732	**72.17**
Mean	**7.3**	**8.3**	**1699**	**540**	**387**	**1.5x10-4**	**563**	**63.6**	**169**	**55654**	**529**	**548**	**2.24x10-4**	**803**	**59.4**
SD	**4.6**	**3.6**	**876**	**256**	**184**	**0.7x10-4**	**263**	**39**	**111**	**33004**	**248**	**311**	**2.8x10-4**	**364**	**23.5**

Subj	*Intravenous*[a]							*Oral*[b]							*F(%)*
	C_{max} (ng/ml)	t_{max} (min)	AUC (0-∞) (ng.min/ml)	Cl (ml/min)	V_d (l)	k_e (1/min)	$t_{1/2}$ (min)	C_{max} (ng/ml)	t_{max} (min)	AUC (0-∞) (ng.min/ml)	Cl (ml/min)	V_d (l)	k_e (1/min)	$t_{1/2}$ (min)	
Healthy control subjects															
REP	7.2	10	842.58	783	381	2.05 x10-3	338	9.1	90	1222.15	791	90.99	8.7 x10-3	79.7	**2.42**
GEC	14.1	5	1085.51	608	253	2.41 x10-3	288	59.7	120	16581.21	613	145.46	4.22 x10-3	164	**25.43**
TCL	8.9	5	1884.37	350	194	1.81 x10-3	383	22.3	180	8368.37	353	84.99	4.16 x10-3	166	**7.39**
Mean	**10.13**	**6.7**	**1271**	**580**	**276**	**2.21x10-4**	**336**	**30.4**	**130**	**8724**	**467**	**451**	**5.7x10-4**	**137**	**11.8**
SD		**2.4**	**445**	**178**	**78**	**2x10-4**	**39**	**21.4**	**37.4**	**6275**	**183**	**332**	**2.1x10-4**	**40**	**9.89**
P-Values *(Patients vs. healthy control subjects)*															
	NS	***NS***	***NS***	***NS***	***NS***	***NS***	***NS***	***NS***	***NS***	***P<0.05****	***NS***	***NS***	***NS***	***P<0.01****	***P<0.01****

Abbreviations: AUC = area under the concentration-time curve; Cl = clearance; t1/2 = elimination half-life; T max = time point Cmax; Vd = oral volume of distribution

[a] dosis: 0.66 mg except for patient 12 who became 1.46 mg

[b] dosis: 40 mg

*significant differences between patients and control subjects, by two-tailed unpaired t-test (p<0.05, p<0.01)

NS: not significantly different from control

Serum bile acid concentrations determined in the plasma sample obtained at the two sessions before propranolol administration (time 0 hours) are shown in Table 4.3.

Table 4.3. Bioavailability of propranolol and serum bile acid concentrations in patients and control subjects

Subject	**F (%)**	**Serum bile acid concentration (μmol/l)**		
		0h (just before iv administration)	0h (just before oral administration)	0h (mean)
1	**99.9**	8.2	3.7	**6.0**
2	**50.8**	19.0	31.6	**25.3**
3	**67.9**	200.0	139.1	**169.4**
4	**78.4**	25.7	35.1	**30.4**
5	**48.8**	17.4	7.9	**12.7**
6	**31.3**	13.0	3.9	**8.5**
7	**71.9**	82.9	92.5	**87.7**
8	**41.2**	88.5	73.1	**80.8**
9	**53.8**	43.7	36.4	**40.1**
10	**24.2**	9.2	27.8	**18.5**
11	**88.4**	20.7	38.6	**29.7**
12	**84.6**	41.3	74.0	**57.7**
13	**29.7**	28.2	25.9	**27.1**
14	**72.2**	15.3	12.3	**13.8**
REP	**2.4**	3.9	3.7	**3.8**
GER	**25.4**	3.0	2.4	**2.7**
TCL	**7.4**	1.3	2.1	**1.7**

In order to check the reliability of the serum bile acid determination, the serum bile acid concentrations obtained before oral propranolol administration were correlated with those obtained before intravenous propranolol administration. There was a significant linear correlation (Fig. 4.1).

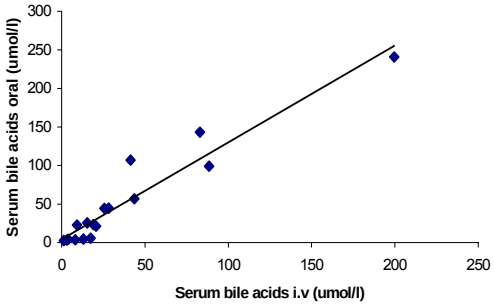

Fig. 4.1. Correlation between bile acid concentrations obtained before intravenous and oral propranolol administration (t=0h). The equation was y = 1.26x + 4.27 (r^2 = 0.92), P<0.05

Since there was good correlation between the bile acid values obtained before oral and intravenous propranolol administration (t = 0h), mean values were used to investigate the correlation with the bioavailability of propranolol in patients (Fig.4.2), and patients and normal subjects (Fig. 4.3).

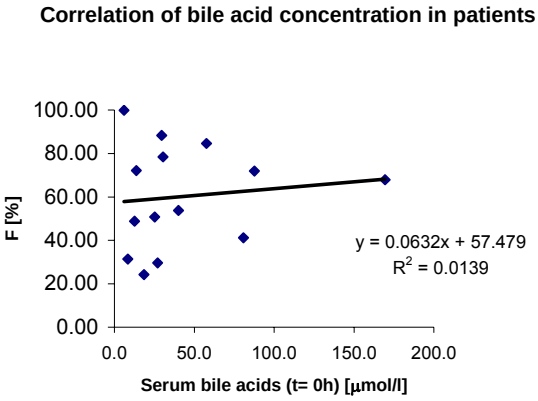

Fig. 4.2. Correlation between the serum bile acid concentration and the bioavailability of propranolol in patients with liver cirrhosis

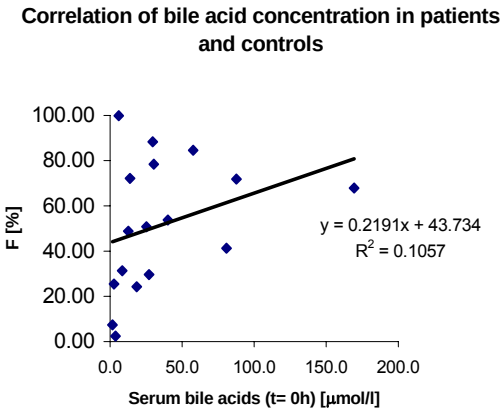

Fig. 4.3. Correlation between the serum bile acid concentration and the bioavailability of propranolol in patients with liver cirrhosis and control subjects

As shown in Fig. 4.2 and 4.3 no significant correlation was found between serum bile acid concentrations and propranolol bioavailability in patients alone or in patients combined with the control group. The relationship of indices of liver function such as Child-score, INR, serum bilirubin and serum albumin with the bioavailability of propranolol in cirrhotic patients was also investigated (Fig. 4.4).

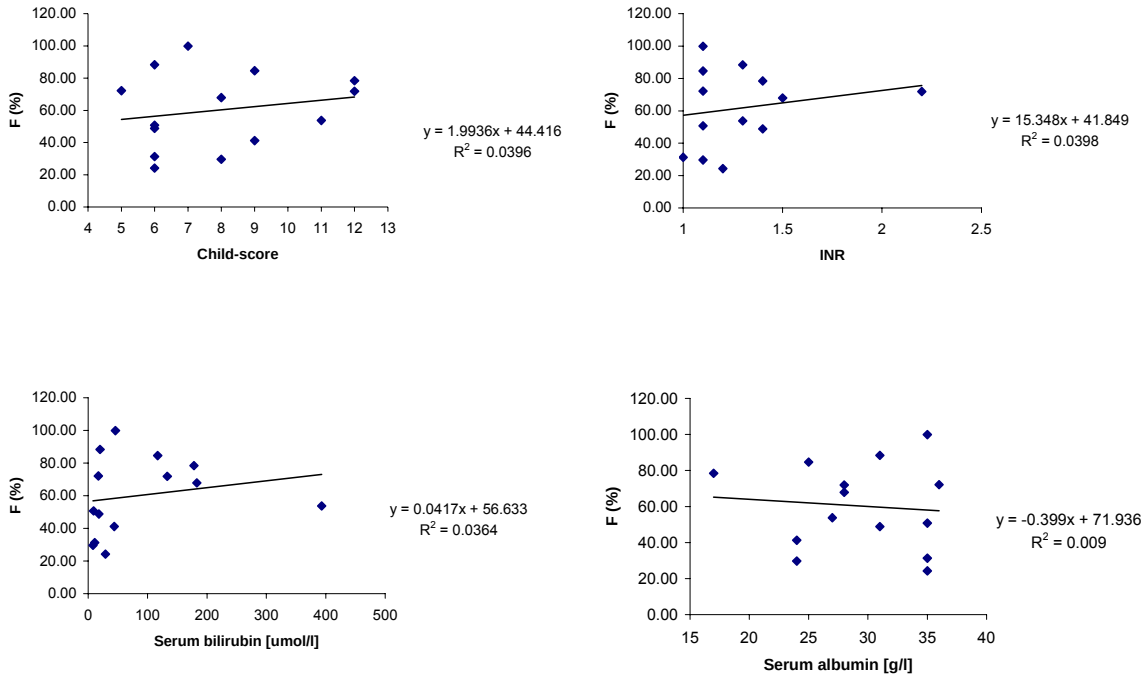

Fig. 4.4 Correlation of serum bile acid concentration with liver function tests in cirrhotic patients

As shown in Fig. 4.4., no statistically significant correlations were found between bioavailability and the various indices of liver function (Child score, INR, serum bilirubin and albumin) in the cirrhotic patients.

However, when the oral clearance of propranolol in patients with liver cirrhosis is correlated with the serum bile acid concentration, an inverse relationship between the two parameters was detectable (Fig. 4.5.A). A small increase in the serum bile acid concentration (in cirrhotic patients a marker of liver function) can be associated with an important decrease in propranolol clearance. When only the data from cirrhotic patients with serum bile acids values under 50 μmol/l were considered, the clearance was negatively correlated (r = 0.919) (Fig 4.5 B.).

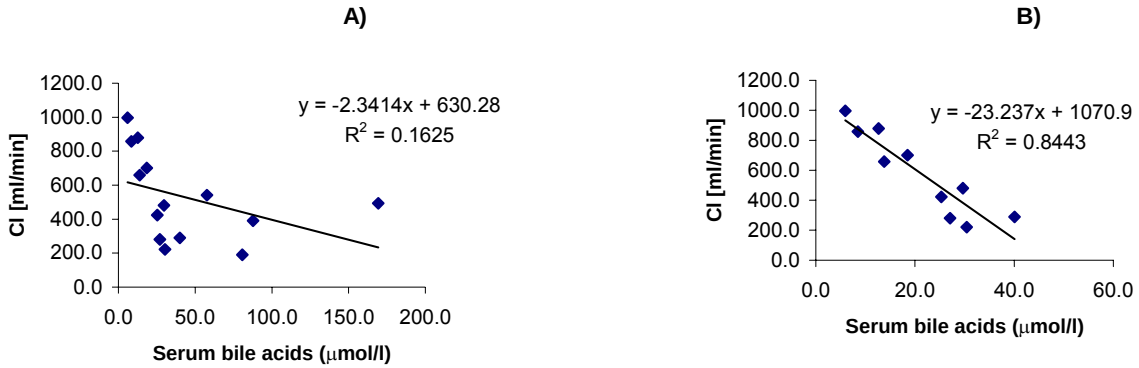

Fig. 4.5 Correlation of serum bile acid concentration with the oral clearance in A) all the 14 cirrhotic patients, and B) with the patients with serum bile acids values <50 μmol/l (n=10)

As shown in Fig. 4.6. similar trends were found when the bile acid concentration was correlated with the intravenous clearance of propranolol in patients.

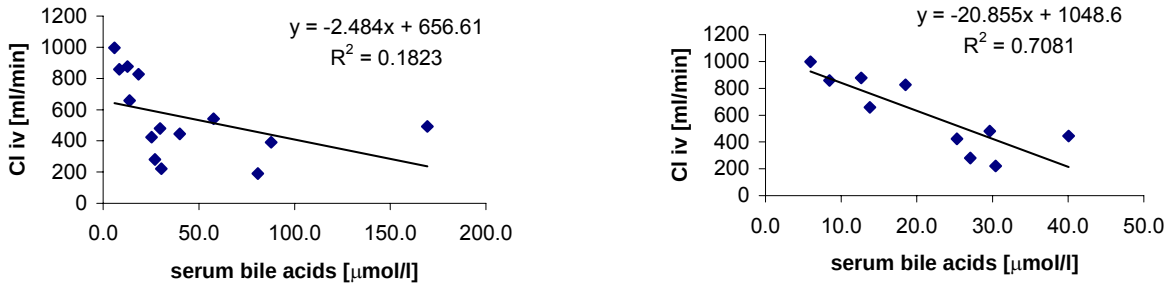

Fig. 4.6 Correlation of serum bile acid concentration with the intravenous clearance in A) all the 14 cirrhotic patients, and B) with the patients with serum bile acids values <50 μmol/l

In control subjects, the bioavailability of propranolol is approximately 26 ± 10 % (7,8,9), indicating that propranolol is a drug with high hepatic extraction. Factors that determine the bioavailability of drugs with high hepatic clearance include liver blood flow and/or shunting of portal blood (1). For a drug like propranolol, increased porto-systemic shunting would be expected to increase its bioavailability. In patients with cirrhosis, the serum bile acid concentration is considered to represent a measure of porto-systemic shunting (4). It has been shown convincingly that there is a linear correlation between the bile acid concentration in portal and peripheral venous blood and the magnitude of portal-systemic shunts in patients with mild to moderate liver cirrhosis (4). A positive linear correlation has previously been found between the serum bile acid concentration in patients with liver cirrhosis and the Cmax of spirapril, a drug with a low to moderate hepatic clearance (10). Despite this previous findings, in the current study we did not find a significant correlation between serum bile acids and bioavailability of propranolol in patients with liver cirrhosis.

The negative correlation between the serum bile acid concentrations and hepatic clearance may be surprising. In patients with liver cirrhosis, propranolol has a bioavailability of 60% (11,7) and is therefore kinetically similar to drugs with medium extraction. In this situation, mainly intrinsic hepatic clearance predicts hepatic clearance of a drug (2). The serum bile acid concentration may therefore reflect not only porto-systemic shunting but also intrinsic hepatic clearance in patients with liver cirrhosis.

4.4 Conclusion and outlook

In the current study we did not find a significant correlation between serum bile acids and bioavailability of propranolol in patients with liver cirrhosis. It is possible that the serum bile acid concentration is not a reliable marker for porto-systemic shunts and can therefore not be used to predict bioavailability of high extraction drugs such as propranolol.

Individual bile acids may provide more information about porto-systemic shunts and may therefore be able to predict bioavailability of propranolol. Individual bile acids will therefore be determined by GC-MS.

4.4 References

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V 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 3.1. (project 1)**, the kinetic and dynamic changes in patients with liver disease of the most important drugs used in these patients were discussed. The conclusion was that 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.

In **chapter 3.2.** and **3.3. (project 2 and project 3)**, the antineoplastic drugs and central nervous system 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.

The correlation between the bioavailability of propranolol and the plasma bile acid concentration in patients with liver cirrhosis was investigated in **chapter IV (project 4)**.
In this study we did not find a significant correlation between serum bile acids and bioavailability of propranolol in patients with liver cirrhosis. It is therefore possible that the serum bile acid concentration is not a reliable marker for porto-systemic shunts

and can therefore not be used to predict bioavailability of high extraction drugs such as propranolol.

Individual bile acids provide more information about porto-systemic shunts and may therefore be able to predict bioavailability of propranolol. Individual bile acids will therefore be determined by GC-MS.

When the clearance of propranolol in patients with liver cirrhosis is correlated with the serum bile acid concentration, an inverse relationship between the two parameters was detectable. When only the data from cirrhotic patients with serum bile acids values under 50 μmol/l were considered, the clearance was negatively correlated.

In patients with liver cirrhosis, propranolol has a bioavailability of 60% and is therefore kinetically similar to drugs with medium extraction. In this situation, mainly intrinsic hepatic clearance predicts hepatic clearance of a drug. The serum bile acid concentration may therefore reflect not only porto-systemic shunting but also intrinsic hepatic clearance in patients with liver cirrhosis.

There was no significant correlation between serum bile acids and bioavailability of propranolol in patients with liver cirrhosis. The serum bile acid concentration seems not to be a reliable marker for porto-systemic shunts and can therefore not be used to predict bioavailability of high extraction drugs in patients with liver cirrhosis.

There are currently not enough data for safe use of cyctostatics and central nervous agents in patients with liver disease. Pharmaceutical companies should 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 advise for dose adaptation.

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Jacob M., **Tchambaz L.**, Krähenbühl A., Wolf P., Krähenbühl S. Dose adaptation of antineoplastic drugs in patients with liver disease (Drug Safety, submitted).

Ratz Bravo AE, **Tchambaz L**, Krähenbühl-Melcher A, Hess L, Schlienger RG, Krähenbühl S. The prevalence of potentially critical drug-drug interactions in ambulatory dyslipidemic patients treated with statins (Drug Safety, submitted).

LECTURES

During my study 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.

Acknowledgements

This work was performed in the group of Clinical Pharmacology and Toxicology, at the University Hospital Basel under the supervision of Prof. Dr. Stephan Krähenbühl.

My thanks are due to all the people without whom there would have been no thesis.

First amongst them, I am grateful to Prof. Stephan Krähenbühl for giving me the opportunity to do my thesis in his group and for the time he invested whenever I needed during projects. I must thank him for his patience and his perception as well as his good ideas and his lucid, practically infallible grasp of what should stay and what should go.

Many thanks to Professor Jürgen Drewe for his invaluable help with my projects, optimism and energy, to Dr. Ralph Mager and Maria Schmidlin for discussions and helping me in EEG recordings.

Additionally, I would like to thank Prof. Peter Hauser for accepting the function of representative of the Faculty.

To Yvonne, Manuel, Louisa and Sandro for their professional help in the clinical study and to Dr. Markus Wenk for introducing me in the hplc and for his great experience.

Thanks also to all the other colleagues and friends from the labs 410-411 and the Division Pharmacology and Toxicology, past and present, I had the pleasure to work with.

All my friends deserve thanks, but I want to give a special mention to Mister Gloor and his family.

Finally, and most deeply, I wish to thank my mother Catherine and my sister Sophie, for understanding my never-ending studies in Basel and supporting me at any time.