REVIEW ARTICLE

Drug Safety 2009; 32 (7): 561-578
0114-5916/09/0007-0561/$49.95/0

Pharmacokinetic Changes of Psychotropic Drugs in Patients with Liver Disease

Implications for Dose Adaptation

Chantal Schlatter, Sabin S. Egger, Lydia Tchambaz and *Stephan Krähenbühl*

Division of Clinical Pharmacology & Toxicology, University Hospital, Basel, Switzerland

Contents

Abstract

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

Of the 116 psychotropic drugs available on the Swiss market by the year 2006, only 12 were predominantly eliminated through the kidney. For five substances, no Q_0 value (the dose fraction metabolized or excreted extrarenally) could be determined because of lack of pharmacokinetic data. Of 99 drugs with predominant hepatic metabolism, 29.3% were categorized as high, 25.2% as intermediate and 38.4% as low extraction drugs, while seven substances could not be classified. Pharmacokinetic studies in patients with liver disease were available for 55 of these 99 drugs eliminated predominantly by the liver (Q_0-value ≥ 0.5). Only a few kinetic studies in patients with liver disease were found for antipsychotics, antiparkinsonian drugs and antidepressants, except for selective serotonin reuptake inhibitors and some newer antidepressants. The expected changes in pharmacokinetics were generally in good agreement with the changes reported in pharmacokinetic studies. For

12 drugs, the observed changes in pharmacokinetics from clinical studies were different from the changes expected based on their classification. However, for low extraction drugs metabolized by cytochrome P450 isozymes, clearance may be reduced by up to 50%.

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

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

The factors affecting drug disposition in patients with chronic liver disease have been discussed in numerous reviews.[1-8] In these reviews, drugs are classified according to their hepatic extraction, which determines mainly the hepatic clearance of drugs. Since, until now, no *in vivo* surrogate parameter exists to predict hepatic clearance of drugs, predictions concerning dose adjustment in patients with liver disease can only be made based on the pharmacokinetic properties of the drugs administered.[4] Dose recommendations made in this article are based on the classification of the drugs according to their hepatic extraction (E_h). Only the basic principles underlying this classification will be reviewed. For further information, refer to the publication of Delco et al.[4] or Tchambaz et al.[9]

Hepatic clearance (Cl_{hep}) is defined as the volume of blood from which a drug is removed completely by the liver per unit time. Hepatic clearance can be expressed as (equation 1):

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

where Q is the blood flow across the liver, f_u is the unbound fraction (free fraction) and Cl_i is the intrinsic clearance of the drug. The equation is based on the assumption that the liver is a well-stirred compartment, a model used already in a previous review of dose adaptation of antineoplastic drugs in patients with liver disease.[9]

When $(f_u \times Cl_i) >> Q$, equation 1 can be simplified to $Cl_{hep} \approx Q$. In this case, the blood flow across the liver becomes rate-limiting for hepatic clearance of a drug. Due to their high hepatic extraction (>60%), this class of drugs has a low bioavailability (<40%) and is insensitive to changes in protein binding or activity of drug-metabolizing enzymes. Porto-systemic shunts resulting from portal hypertension[10] and a reduction in portal venous perfusion of hepatocytes resulting from increased vascular resistance and/or capillarization in patients with cirrhosis will lead to changes in hepatic clearance of high extraction drugs.[1] A variable amount of portal blood is therefore not cleared by hepatocytes in patients with cirrhosis and, as a consequence, bioavailability of orally administered drugs may increase substantially. Therefore, the initial dose of orally administered high extraction drugs has to be reduced according to the expected increase in bioavailability and the maintenance dose according to bioavailability and impaired hepatic blood flow across the liver. Since the extent of porto-systemic shunting is usually not known in patients with cirrhosis, the oral bioavailability of high extraction drugs is assumed to be 100%.[4] Accordingly, taking into account the assumed increase in bioavailability, the reduced dose may be calculated as follows: reduced dose = (normal dose × normal bioavailability)/100.[4] For intravenous administration, the maintenance dose has

to be reduced, as only the reduction in hepatic blood flow has to be considered.

In contrast, the hepatic clearance of drugs for which $(f_u \times Cl_i) << Q$ is mainly determined by the capacity of the liver to metabolize these substances. For such drugs, equation 1 can be simplified to $Cl_{hep} \approx (f_u \times Cl_i)$. Liver cirrhosis can alter Cl_i of these drugs by affecting the activity of cytochrome P450 (CYP) isozymes and/or glucuronyl transferases, whereby oxidation seems to be more sensitive than glucuronidation.[7,8] Because of a low hepatic extraction (<30%) during the first passage across the liver, such drugs have a high bioavailability (>70%), if bioavailability is not limited by processes different from first pass hepatic metabolism. Treatment can be started with normal initial doses, because no significant alteration in bioavailability is expected. Maintenance doses may be reduced as a result of impaired hepatic clearance, especially for drugs mainly metabolized by CYP isozymes. Hepatic clearance of low extraction drugs highly bound to albumin may additionally be influenced by changes in plasma protein binding. In patients with liver cirrhosis, protein binding may be diminished due to lower levels of serum albumin resulting from impaired albumin synthesis[11] and/or due to accumulation of endogenous compounds (e.g. bilirubin), competing for plasma protein binding sites. As a consequence, the f_u of a drug may increase and offset the reduction of intrinsic clearance, leading apparently to unchanged or even increased hepatic clearance.[4] Considering the total drug concentration (free and protein bound fraction), this reasoning is correct, but regarding only the free concentration, f_u would equal 1 and hepatic clearance for low extraction drugs would approach intrinsic clearance (Cl_i).[4,12] Dose adjustment for low extraction drugs with high protein binding should therefore be made according to the free plasma concentration of the drug (e.g. phenytoin, valproate) or according to pharmacodynamic parameters (e.g. phenprocoumon).

Drugs with an intermediate hepatic extraction (30–60%) show characteristics of both groups. The hepatic clearance of such drugs can be influenced by all the parameters included in equation 1. Initial doses should therefore be reduced according to the expected increase in bioavailability and maintenance dose should be further adjusted according to the expected decrease in intrinsic hepatic clearance.

Drugs acting on the central nervous system (e.g. anxiolytics, sedatives, antidepressants, antipsychotics, antiepileptics) are often prescribed to patients with liver cirrhosis because of a variety of psychiatric symptoms or illnesses associated with liver cirrhosis.[13] Benzodiazepines may be used for the management of alcohol deprivation, for insomnia or as a pre-medication before upper-gastrointestinal endoscopy. A study evaluating drug use in patients with liver cirrhosis showed that, beside the benzodiazepines, antipsychotics, antidepressants and/or antiepileptics were also frequently prescribed.[14] In fact, chronic depressive symptoms are not uncommon in patients with cirrhosis.[15]

Most of the psychotropic drugs are lipophilic and are extensively metabolized through the liver, involving also biotransformation by CYP isozymes.[13] In patients with cirrhosis, the decrease in hepatic clearance and hepatic extraction results in an increased risk for dose-related adverse drug reactions of psychotropic drugs. But not only pharmacokinetic changes should be considered when prescribing centrally acting drugs, pharmacodynamic changes have also been reported in patients with liver cirrhosis.[1]

Prescribing to patients with liver cirrhosis requires careful drug selection and dose adjustment based on the pharmacokinetic profile may prevent adverse effects. Classification according to pharmacokinetic properties and results from clinical trials in patients with liver cirrhosis and/or other liver diseases can therefore help to select and administer drugs more rationally in this group of patients. The aims of this work were therefore (i) to collect pharmacokinetic data on psychotropic drugs (antiepileptics, antiparkinsonian drugs, antipsychotics, anxiolytics, sedatives, hypnosedatives, antidepressants, psychostimulants and antidementia drugs) and to classify the drugs based on their pharmacokinetic profile; (ii) to formulate recommendations for dose adjustment in patients with liver cirrhosis;

(iii) to compare the dose recommendations based on this classification with recommendations from the product information and from published clinical studies; and (iv) to evaluate and discuss the actual level of information available for dose adjustment in patients with liver disease.

1. Literature Search Methodology

We searched MEDLINE for studies dealing with pharmacokinetics, hepatic adverse effects and/or dose adjustment in patients with liver disease for all psychotropic drugs registered in Switzerland in 2006. To perform our literature search, combinations of key terms including 'pharmacokinetics', 'metabolism', 'cytochromes', 'drug toxicity' and 'liver diseases' in combination with 'central nervous system agents' and the specific generic name of each psychotropic drug were used. The references of the publications found were screened for additional relevant studies. In addition to MEDLINE literature searches, standard reference sources such as the *Swiss Compendium of Drugs*[16] containing product information of the drugs registered in Switzerland, the *Physicians' Desk Reference*,[17] as well as *Therapeutic Drugs*,[18] *DRUGDEX® System*,[19] *Avery's Drug Treatment*,[20] *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*[21] and *Hepatotoxicity*[22] were used to locate data regarding pharmacokinetics, hepatic adverse effects, dose-dependent adverse effects and dose recommendations of the psychotropic drugs investigated.

The psychotropic drugs were categorized as outlined in the previous section and according to a previous review of antineoplastic agents by Tchambaz et al.[9] The classification is based on the hepatic extraction and/or bioavailability of a given drug. Because data for hepatic extraction is rare in the literature, hepatic extraction was estimated using the following equation (equation 2):

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

where Q_0 is the dose fraction metabolized or excreted extra-renally (1-Q_0 is the dose fraction excreted non-metabolized by the kidney), Cl_{sys} is the systemic clearance (determined in plasma) and Q the plasma flow across the liver. Q was assumed to be 900 mL/min[9] and the values for Q_0 and Cl_{sys} were obtained from the literature. If bioavailability and calculated hepatic extraction were not consistent, drugs were classified according to the measured value for absolute bioavailability except when bioavailability was lower than expected from hepatic extraction due to incomplete intestinal absorption.

Table I. Classification of liver injury[23]

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

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

Dose recommendations are based on the original articles from clinical studies, on the product information published in the *Swiss Compendium of Drugs*[16] or the *Physicians' Desk Reference*[17] and based on the classification of the drugs according to their hepatic extraction. For low extraction drugs with high protein binding, assessment of total drug clearance may be misleading since intrinsic clearance and protein binding account for hepatic clearance as outlined previously.[4,12] Therefore, clearance of unbound drug was considered relevant for dose recommendation. The available strengths and oral dosage forms of the drugs marketed in Switzerland were also taken into account for the dosage recommendations made.

Drug-induced liver disease was classified according to Bénichou[23] if enough data was available for classification (table I). In addition to the hepatic adverse effects, the most important dose-dependent adverse reactions of the psychotropic drugs were retrieved from the standard literature or suitable publications.[16-19,24-26] They can usually be deduced from the pharmacological effect and receptor affinity of a drug. Occurrence of dose-dependent symptoms may serve as an indicator for drug accumulation in the case of

insufficient dose adaptation to impaired liver function.

2. Findings

A total of 116 psychotropic drugs were available on the Swiss market by the year 2006 (antiepileptics [n = 18]; antiparkinsonian drugs [n = 13]; antipsychotics [n = 22]; anxiolytics, sedatives and hypnosedatives [n = 29]; antidepressants [n = 24]; psychostimulants [n = 6] and antidementia drugs [n = 4]).

Data about pharmacokinetic properties of the drugs were either extracted from the standard literature[16-21,24] or were based on published pharmacokinetic studies or reviews.[27-67] Only 12 of 116 psychotropic drugs (10%) are predominantly eliminated through the kidney (Q_0-value <0.5): amantadine, lithium, phentermine, phenylpropanolamine, pramipexole, sulpiride, tiapride and the newer antiepileptics gabapentin, levetiracetam, pregabalin, topiramate and vigabatrin. For five substances, no Q_0 value could be determined because of lack of pharmacokinetic data. The remaining drugs are predominantly eliminated by the liver either through CYP-dependent metabolism and/or through conjugation. CYP isozymes involved in the phase I metabolism of antipsychotics are mainly CYP2D6, 3A4 and to a lesser extent 1A2. CYP2D6 plays a major role in the metabolism of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Whereas most of the benzodiazepines are metabolized through CYP2C19 and/or 3A4, the major metabolic pathway of oxazepam, lorazepam and temazepam is glucuronidation.

Based on their bioavailability and/or hepatic extraction, of 99 substances predominantly eliminated by the liver (Q_0-value ≥0.5), 29 substances were classified as high extraction drugs, 25 as drugs with intermediate hepatic extraction and 38 as low extraction drugs (table II). Only seven substances could not be classified because of lack of pharmacokinetic data. Most of the antiepileptic drugs were classified as low extraction drugs, except oxcarbazepine, the only high extraction drug in this therapeutic drug class. Benzodiazepines were also commonly classified as low extraction drugs, except flurazepam, midazolam and triazolam. In contrast, 8 of 10 antiparkinsonian drugs hepatically metabolized, namely biperiden, bromocriptine, cabergoline, dihydroergocryptine, entacapone, levodopa, pergolide and selegiline were classified as high extraction drugs. However, the maintenance dose of antiparkinsonian drugs is commonly found by slow up-titration. As treatments are therefore usually started at low doses, initial doses do not have to be reduced additionally in patients with liver cirrhosis.

Hepatic adverse drug effects have been reported for 88 of the 116 drugs studied (76%).[16-19,22,68-99] Phenothiazines may cause cholestatic liver injury, while some older antiepileptic drugs are associated with induction of acute intermittent porphyria in predisposed patients. The use of benzodiazepines may induce hepatic encephalopathy in patients with cirrhosis. For other drug classes, no specific pattern of hepatic adverse reactions has been reported. Tricyclic antidepressants, for example, have been associated with hepatocellular as well as cholestatic liver injuries.

Pharmacokinetic studies (either located through MEDLINE searches of the literature[33,45,49,80,87,100-161] and/or in the respective product information[16,17] or other standard reference sources[18,19]) evaluating the kinetic properties of drugs in patients with liver disease, could be found for 56% of the drugs with known predominant hepatic elimination (55 of 99). Of the individual therapeutic groups assessed, for three of four antidementia drugs (75%), pharmacokinetic data in patients with liver cirrhosis was available. The only exception was memantine, for which 50% of the dose is eliminated unchanged through the kidney. Also, for a high proportion of the anxiolytics, hypnosedatives and sedatives (20 of 28 drugs; 71%) as well as for antiepileptics (9 of 13 drugs; 69%), pharmacokinetic information in patients with liver disease was available. Only sparse information about pharmacokinetic changes in patients with liver disease was available for the antipsychotic drugs. Clinical studies in patients with liver disease could only be found for 5 of 17 drugs (29%):

Table II. Psychotropic drugs with Q_0-value ≥0.5 listed by hepatic extraction category (n = 99)

Drug class	Drugs classified according to their hepatic extraction			
	High[a]	Intermediate[b]	Low[c]	Unknown[d]
Antiepileptic drugs	Oxcarbazepine		Barbexaclone, carbamazepine, clonazepam, ethosuximide, lamotrigine, phenobarbital (phenobarbitone), phenytoin, primidone, tiagabine, valproate	Methsuximide, sulthiame
Antiparkinsonian drugs	Biperiden, bromocriptine, cabergoline, dihydroergocryptine, entacapone, levodopa, pergolide, selegiline	Ropinirole	Tolcapone	
Antipsychotics	Chlorpromazine, chlorprothixene, fluphenazine, perphenazine, promazine, quetiapine	Amisulpride, clozapine, flupentixol, haloperidol, levomepromazine, olanzapine, risperidone, zuclopenthixol	Aripiprazole, sertindole	Clothiapine
Anxiolytics, sedatives and hypnosedatives	Buspirone, clomethiazole, flurazepam, hydroxyzine, promethazine, zaleplon	Diphenhydramine, midazolam, triazolam, zolpidem	Alprazolam, bromazepam, chlordiazepoxide, clobazam, clorazepate, diazepam, flunitrazepam, lorazepam, lormetazepam, meprobamate, methaqualone, nitrazepam, oxazepam, prazepam, temazepam, zopiclone	Chloral hydrate, ketazolam
Antidepressants	Bupropion, dibenzepin, doxepin, mianserin, sertraline	Amitriptyline, clomipramine, escitalopram, fluvoxamine, imipramine, maprotiline, mirtazapine, moclobemide, nortriptyline, paroxetine, trimipramine, venlafaxine	Citalopram, fluoxetine, reboxetine, trazodone	Melitracen, opipramol
Psychostimulants	Methylphenidate, sibutramine		Amfepramone, modafinil	
Antidementia drugs	Rivastigmine		Donepezil, galantamine, memantine	

a High extraction drugs: hepatic extraction >60%, oral bioavailability <40% in case of complete intestinal absorption (or lower, if intestinal absorption is not complete).

b Intermediate extraction drugs: hepatic extraction 30–60%, oral bioavailability 40–70%.

c Low extraction drugs: hepatic extraction <30%, oral bioavailability >70%. In this category, protein binding may be relevant: for drugs with high binding to albumin, hepatic clearance may increase.

d Unknown: hepatic extraction not classifiable due to lack of pharmacokinetic data.

Q_0 = extra-renal dose fraction.

aripiprazole, promazine, quetiapine, risperidone and sertindole. The best studied drug class were the SSRIs. For all of the six substances available in Switzerland (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), data about pharmacokinetics in patients with liver cirrhosis could be found. In table III, pharmacokinetic data, dosage recommendations as well as hepatic and the most important dose-dependent adverse reactions are provided for drugs with a high hepatic extraction where pharmacokinetic studies were available. For all the other drugs, data about pharmacokinetics, classification of the drugs, hepatic and dose-dependent adverse reactions and dose recommendations are available; please see the online Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A11, or access

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

Drugs	Kinetic parameters[a,b,c]	Hepatic adverse effects	Studies performed and dose recommendations
Antidepressants			
Bupropion	Metabolism: hydroxylation (CYP2B6), reduction.[17] Active metabolite: hydroxybupropion. Q_0: >0.95 V_d: 28 L/kg $t_{½}$: 21 h PB: 84% Cl_{sys}: 160 L/h E: >0.9	*Rare:* abnormal liver tests, jaundice, hepatitis.[16,98,99]	*Studies:* $t_{½}$ of hydroxybupropion was prolonged (32 h vs 21 h; $p < 0.05$) in patients with alcoholic liver disease compared with healthy volunteers.[158] AUC was higher for bupropion and hydroxybupropion but did not reach significance. *Product information:* No significant difference in the pharmacokinetics between patients with mild to moderate liver cirrhosis and healthy controls. C_{max} increased by 70%, $t_{½}$ by 40% and AUC by 200% in patients with severe liver cirrhosis compared with healthy controls. $t_{½}$ of metabolites prolonged about 2- to 4-fold. Contraindicated in patients with severe liver cirrhosis. Recommended daily dose for patients with mild to moderate liver disease 150 mg. *Personal recommendation:* According to pharmacokinetic data and clinical studies, start with lowest available dose (150 mg/d). Adjust maintenance dose or dosage interval according to dose-dependent adverse effects[16,18,19] (seizures, agitation, insomnia, tremor, nausea, anorexia, tachycardia, hypertension). Because of expected massive increase in bioavailability, bupropion should be avoided in patients with severe liver cirrhosis (Child-Pugh class C)
Sertraline	Metabolism: *N*-demethylation (CYP2D6, 2C9, 2B6, 2C19, 3A4), hydroxylation, oxidative deamination, *N*-carbamoyl glucuronidation[58] Active metabolite: *N*-desmethylsertraline Q_0: 1 V_d: 25 L/kg $t_{½}$: 23 h PB: 98% Cl_{sys}: 96 L/h E: >0.9	*Rare:* hepatocellular injury[22] *Case reports:* liver failure[16]	*Studies*: AUC increased 4-fold, $t_{½}$ 2.5-fold and C_{max} 1.7-fold in patients with liver cirrhosis after intake of sertraline 100 mg as a single oral dose.[152] C_{max} of desmethylsertraline was 1.5-fold decreased ($p < 0.05$) and t_{max} significantly longer. Significant correlation between sertraline plasma concentration and serum albumin observed. It was recommended to start with sertraline 50 mg/day and increase dosage only after 15 days, if necessary. *Product information*: start treatment in patients with liver cirrhosis Child-Pugh class A and B with 50% of normal initial dose. Contraindicated in patients with liver cirrhosis Child-Pugh class C. *Personal recommendation*: According to pharmacokinetic data and product information, it is recommended to start with 50% of normal dose (25 mg/d). Adjust maintenance dose according to dose-dependent adverse reactions[16,18] (nausea, diarrhoea, insomnia, nervousness, tachycardia, serotonin syndrome). Do not up-titrate the dose before 2 weeks after treatment beginning or dose adjustment
Antipsychotics			
Chlorpromazine	Metabolism: hydroxylation (CYP2D6, 1A2), *N*-demethylation, *N*-oxidation, deamination, sulfoxidation,[18,37] partial biliary excretion[16] Q_0: 1	Risk of hepatic encephalopathy in patients with liver cirrhosis[80] *Sporadic:* cholestatic liver injury[22]	*Studies:* Changes in EEG associated with drowsiness and increased sensitivity in patients with liver cirrhosis, particularly in patients with previous history of encephalopathy.[80,112] Should be avoided in patients with liver cirrhosis due to the risk of hepatic encephalopathy[80] *Product information:* contraindicated in patients with cholestatic liver injury

Continued next page

Table III. Contd

Drugs	Kinetic parameters[a,b,c]	Hepatic adverse effects	Studies performed and dose recommendations
	V_d: 22 L/kg $t_{½}$: 30 h PB: 95% F: 32% Cl_{sys}: 36.1 L/h E: 0.67		*Personal recommendation:* According to pharmacokinetic data, start with 25–50% of normal initial dose. Adjust maintenance dose according to dose-dependent adverse effects[16,18] (extrapyramidal reactions, seizures, hyperprolactinaemia, anticholinergic effects, orthostatic hypotension, prolongation of QT interval)
Promazine	Metabolism: hydroxylation, *N*-oxidation, *N*-demethylation (CYP1A2, 2C19), sulfoxidation (CYP1A2, 3A4)[18,38] Q_0: 1 $t_{½}$: 15 h (variable) PB: 92% F: 16%	Phenothiazines may cause intrahepatic cholestasis[18]	*Studies:* In patients with cirrhosis (Child-Pugh class A and B), total and free plasma clearance decreased by 76% and 89%, $t_{½}$ was 2-fold and AUC 2.9-fold higher compared with healthy subjects.[114] Unbound fraction was also significantly higher (35.5% vs 10.4%). No change in pharmacokinetics during acute phase of viral hepatitis B, but more adverse effects observed (sedation, postural hypotension, dizziness).[113] Adjust dosage in patients with cirrhosis (no specific dosage recommendation)[114] *Product information:* Caution in patients with liver disease.[16] Use not recommended in patients with liver disease because phenothiazines may cause intrahepatic cholestasis[18] *Personal recommendation:* According to the pharmacokinetic parameters, start with 25% of normal initial dose. Adjust dosage according to dose-dependent adverse reactions[16,18] (extrapyramidal reactions, seizures, hyperprolactinaemia, anticholinergic effects, orthostatic hypotension, prolongation of QT interval)
Quetiapine	Metabolism: dealkylation, hydroxylation (CYP3A4, 2D6 [minor]), sulfoxidation, glucuronidation[41] Q_0: 0.95 V_d: 10 L/kg $t_{½}$: 6 h PB: 83% F: 9% Cl_{sys}: 79.8 L/h E: >0.9	*Rare:* jaundice, transient and reversible elevations in serum transaminase (primarily ALT)[16,19] *Case report:* subfulminant liver failure[83]	*Studies:* Compared with healthy controls, clearance decreased by 25% in patients with liver cirrhosis, AUC and C_{max} increased by 40% and $t_{½}$ prolonged by 77%.[116] The authors concluded that patients with hepatic liver cirrhosis may be given quetiapine 25 mg as a starting dose, and dose escalation should be conducted with caution *Product information:* Recommendations based on the study from Thyrum et al.[116] conducted by Astra Zeneca. Start with quetiapine 25 mg on the first day. Up-titrate carefully in increments of 25–50 mg/d to an effective dose, depending on clinical response and dose-dependent adverse reactions *Personal recommendation:* According to pharmacokinetic data and clinical study, start with 25 mg and up-titrate carefully according to clinical effect and dose-dependent adverse reactions[16,17] (drowsiness, weight gain, orthostatic hypotension, prolongation of QT interval. Rare: extrapyramidal symptoms)
Anxiolytics, hypnosedatives, sedatives			
Buspirone	Metabolism: CYP3A,[16] dealkylation, hydroxylation, glucuronidation[18] Active metabolite: 1-pyrimidinyl piperazine		*Studies:* C_{max} about 16-fold higher in patients with liver cirrhosis than in controls.[129] $t_{½}$ in patients with cirrhosis about twice that of healthy subjects.[129] Should be used with caution in patients with liver disease.[129] At steady state, C_{max} was 9- and 12-fold higher in patients with compensated

Continued next page

Table III. Contd

Drugs	Kinetic parameters[a,b,c]	Hepatic adverse effects	Studies performed and dose recommendations
	Q_0: 1 V_d: 5 L/kg $t_{½}$: 2.4 h PB: 95% F: 4% Cl_{sys}: 92.5 L/h E: >0.9		(n = 6) and decompensated (n = 6) cirrhosis compared with controls (n = 12), $t_{½}$ was increased by 169% and 204%, respectively, and AUC increased by 752% and 1773%, respectively.[130] Intensity and frequency of adverse effects were similar in patients with cirrhosis and controls. No significant difference in pharmacokinetics of 2-pyrimidinyl piperazine between patients with cirrhosis and controls. However, due to high intra- and inter-subject variability of the plasma buspirone concentration data, dosing recommendations could not be made[130] *Product information:* Contraindicated in patients with liver disease *Personal recommendation:* According to pharmacokinetic data, start with lowest possible dose (5 mg) due to variable bioavailability in patients with porto-systemic shunts. Adjust maintenance dose according to dose-dependent adverse reactions[16] (drowsiness, dizziness, nausea, nervousness). Dose interval may be reduced from 3 times to 1–2 times daily
Clomethiazole	Metabolism: CYP2A6, 3A4/5, 2B6, 1A1, 2C19[16] Q_0: 0.95 V_d: 9 L/kg $t_{½}$: 6 h PB: 65% F: 10% Cl_{sys}: 100 L/h E: >0.9	Elevation of transaminases *Rare:* jaundice, cholestatic hepatitis[16]	*Studies:* Clearance decreased by 30%, bioavailability 10-fold higher in patients with advanced alcoholic liver cirrhosis compared with healthy subjects.[145] Dose reduction recommended (no specification).[145] After continuous infusion of clomethiazole, systemic clearance decreased by 50% and $t_{½}$ prolonged by 90% in patients with liver cirrhosis (Child-Pugh class B and C).[146] No statistically significant difference between subjects with mild liver impairment and healthy controls *Product information:* Avoid in patients with severe liver disease. Clomethiazole should not be given to patients with alcohol dependence with liver cirrhosis, because of fatal respiratory depression in combination with alcohol *Personal recommendation:* Oral administration should be avoided in patients with liver cirrhosis since bioavailability is unpredictable. Start intravenous therapy with 25–50% of normal dose and adjust dose according to dose-dependent adverse effects[16,18] (nasal and conjunctival irritation, sedation, cardiovascular and respiratory depression). Lorazepam, oxazepam and temazepam are better alternatives
Hydroxyzine	Metabolism: metabolism to cetirizine (active),[45] 70% of the dose eliminated by biliary excretion[16] Q_0: 1 V_d: 16 L/kg $t_{½}$: 20 h Cl_{sys}: 41.1 L/h E: 0.76	*Rare:* hepatic or cholestatic jaundice[16]	*Studies:* $t_{½}$ was 36.6 h, clearance 36.3 L/h and V_d 23 L/kg in patients with primary biliary cirrhosis.[45] $t_{½}$ of cetirizine was 25 h. Increase normal dosage interval of 2–3 times daily to once per 24 h or less[45] *Product information:* in patients with liver cirrhosis, clearance was reduced by about 66%. $t_{½}$ was increased to 37 h and serum concentrations of cetirizine were higher compared with healthy individuals. Dosage reduction is indicated in patients with moderate impaired liver function. Contraindicated in patients with severe liver insufficiency *Personal recommendation:* According to the pharmacokinetic data, start with 50% of normal initial dose (12.5 mg). Adjust maintenance dose according to dose-dependent adverse reactions[16] (anticholinergic effects, sedation)

Continued next page

Table III. Contd

Drugs	Kinetic parameters[a,b,c]	Hepatic adverse effects	Studies performed and dose recommendations
Zaleplon	Metabolism: aldehyde oxidase, desalkylation (CYP3A4), followed by glucuronidation[16] Q_0: 1 V_d: 1.4 L/kg $t_{½}$: 1 h PB: 60% F: 31% Cl_{sys}: 70 L/h E: >0.9		*Studies:* No clinical studies available in patients with liver disease *Product information:* Oral clearance reduced by 70% and 87% in compensated and decompensated patients with cirrhosis, respectively, up to 4-fold increase in C_{max} and up to 7-fold increase in AUC in comparison with healthy subjects.[17] Contraindicated in patients with liver insufficiency.[16] *Personal recommendation:* According to pharmacokinetic data and product information, start with lowest possible dose in patients with mild to moderate hepatic insufficiency (5 mg). Adjust dosage according to dose-dependent adverse reactions[16,17] (somnolence, drowsiness, asthenia). Zaleplon should be avoided in patients with severe hepatic impairment. Better alternatives are available: lorazepam, oxazepam and temazepam

a Q_0 = the fraction metabolized or excreted extra-renally (1-Q_0: fraction excreted unchanged by the kidney).

b V_d = For calculation of volume of distribution, bodyweight was assumed to be 70 kg.

c E = Hepatic extraction was calculated as described in equation 2 (see section 1 of the text).

AUC = area under the concentration-time curve; **Cl_{sys}** = systemic clearance; **C_{max}** = maximum concentration; **CYP** = cytochrome P450; **E** = hepatic extraction; **F** = bioavailability; **PB** = fraction bound to proteins; **Q_0** = extra-renal dose fraction; **$t_{½}$** = dominant half-life; **t_{max}** = time to maximum concentration; **V_d** = volume of distribution.

through our homepage at http://kpharm.unibas.ch ['Publications'].

3. Discussion

Dose adjustment of hepatically eliminated drugs is necessary to avoid dose-dependent adverse reactions. However, no surrogate parameter is available for reliable quantification of the degree of impairment of hepatic metabolism. Neither routine liver function tests, nor quantitative tests of liver function with model substrate markers such as plasma clearance of antipyrine, galactose, indocyanine green or lidocaine (lignocaine), nor the Child-Pugh classification[162] have proved to be useful for the determination of the capacity of the liver to metabolize drugs.[7,8] Probe drugs may quantify the activity of specific CYP isozymes, but they may not adequately predict metabolism of drugs degraded by different CYP isozymes as well as hepatic extraction and protein binding of specific drugs. Therefore, dose adjustment based on the hepatic extraction of drugs has been proposed in patients with liver diseases, provided that the pharmacokinetic properties of a drug are available.[4]

Our classification of the psychotropic drugs according to hepatic extraction is based on the assumption that the liver is a well-stirred compartment, a model used frequently as an approach for describing hepatic clearance[7,163] and used by us in a previous review of dose adaptation of antineoplastic drugs in patients with liver disease.[9] As with other models for hepatic clearance such as the parallel-tube model or the dispersion model, it is assumed that (i) no diffusion barriers exist and that the distribution into the liver is perfusion limited; (ii) only unbound drug may be hepatically extracted; and (iii) the metabolic enzymes are distributed homogenously across the liver.[163,164] The main difference between these models concerns the concentration gradient of the drug within the liver sinusoids. The parallel-tube model assumes a decrease of drug concentration in an exponential fashion along the sinusoids, whereas the dispersion model assumes an axial dispersion and the well-stirred model an equal drug concentration within every part of the liver. Ito and Houston[164] could show

that there are only minimal differences for the prediction of the *in vivo* hepatic drug clearance from *in vitro* data between these three models. Therefore, and also for its mathematical simplicity, we used the well-stirred model for the prediction of hepatic drug clearance.

Of 116 psychotropic drugs studied, for five substances no Q_0 value could be obtained and another seven substances with predominant hepatic metabolism could not be classified according to their hepatic extraction. These drugs can be replaced in patients with liver cirrhosis by adequate alternatives without any problems. Because of the high proportion of centrally acting drugs eliminated predominantly through the liver, the dosage has to be reduced for most of them in patients with liver cirrhosis in order to prevent dose-dependent adverse effects. When comparing the results from clinical pharmacokinetic studies in patients with liver cirrhosis and other liver diseases (available for 55 drugs) with the estimates based on measured or calculated hepatic extraction, the recommendations were not fully congruent for only 12 drugs. It must be pointed out that for low extraction drugs, the observed reduction in drug clearance in patients with liver disease may be as high as 50% for drugs metabolized primarily by CYP isozymes.

For oxcarbazepine and cabergoline, both classified as high extraction drugs, higher changes would have been predicted based on their estimated hepatic extraction than observed in clinical studies. These differences between the expected and observed changes in patients with cirrhosis may be explained mainly by the metabolic pathway of the substances. Oxcarbazepine, for example, undergoes 10-keto reduction by cytosolic arylketone reductases to the monohydroxy derivative[31] and is not metabolized by CYP isozymes that are known to be affected by liver cirrhosis. Similarly, for cabergoline the contribution of CYP-mediated metabolism is minimal.[16] As a result, dose adjustment cannot only be based on the classification of the hepatic extraction of a drug, but is also influenced by the way an individual drug is metabolized. The decrease in hepatic metabolism seems to be affected by different factors such as the CYP isozymes involved, the severity of the liver disease and presence or absence of cholestasis.[8,165,166]

According to an *in vivo* study using a cocktail of probe drugs for the drug-metabolizing enzymes CYP1A2 (caffeine), CYP2C19 (mephenytoin), CYP2D6 (debrisoquine) and CYP2E1 (chlorzoxazone) to assess the effect of liver disease on activity of CYP isozymes, patients with moderate to severe liver cirrhosis (Child-Pugh score >6) showed a significant reduction of the metabolism of all CYP isozymes evaluated.[165] The reduction in metabolic ratio ranged from 60% for chlorzoxazone (CYP2E1) to 80% for mephenytoin (CYP2C19) compared with healthy controls. Generally, CYP2C19 and CYP1A2 seem to be more sensitive to liver disease than other CYP isozymes, whereas CYP2C9 and CYP2D6 seem to be less affected.[8,167] Reasons for reduced hepatic metabolism of drugs in patients with cirrhosis may be a reduction in absolute cell mass and/or a difference in hepatic expression of CYP isozymes affecting their activity,[7,166] but also impaired delivery of certain drugs and oxygen to the site of metabolism due to sinusoidal capillarization may result in a reduction of intrinsic clearance.[1]

Although pharmacokinetic data in patients with liver disease is available for 55 of the 99 substances with predominant hepatic metabolism studied, there is a gap in information for a large number of centrally acting drugs. Only a few studies in patients with liver cirrhosis are available for antipsychotics, antiparkinsonian drugs and most of the antidepressants, except for SSRIs and some newer antidepressants. In general, information about pharmacokinetic properties in patients with liver disease is lacking, especially for older drugs, while for newer drugs results from pharmacokinetic studies are often included in the product information. There appears to be an effort by the pharmaceutical companies to provide information about the pharmacokinetics of drugs in vulnerable patient groups, such as patients with liver disease. Information about pharmacokinetics in patients with renal or hepatic disease, as well as for elderly patients, should be included in the product information for every new drug released on the market.

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

As indicated by Butler and Begg,[12] assessment of clearance of low extraction drugs with high protein binding should include measurement of free drug clearance, as free drug clearance is independent of changes in protein binding. However, for most of the 64 psychotropic drugs with protein binding ≥80%, no information about free drug clearance was available. Comparing total and free drug plasma clearance of drugs for which information was available (nitrazepam, promazine, tolcapone, lorazepam and chlordiazepoxide), a more accentuated decrease in clearance could be observed for free compared with total drug clearance. For future pharmacokinetic studies this should be taken into consideration.

Another problem to address when considering dose adjustment of psychotropic drugs in patients with liver disease is the conversion of many substances to active metabolites that may also be affected by impaired hepatic metabolism. Of 42 substances with known active metabolites, information concerning pharmacokinetics of metabolites could only be obtained for 14 substances. For the active metabolites of oxcarbazepine, risperidone, aripiprazole, clobazam and buspirone, no differences in pharmacokinetics were detected in patients with liver disease. For the active metabolites of sibutramine, diazepam, hydroxyzine, venlafaxine, bupropion and fluoxetine, the area under the concentration-time curve and elimination half-life were increased and clearance was decreased in patients with cirrhosis compared with healthy controls. In contrast, formation of active metabolites of flunitrazepam and sertraline was diminished in patients with liver cirrhosis. Because of the limited data available, dose recommendations that also take into consideration changes in pharmacokinetics of active metabolites is difficult. In clinical practice, the possibility of an additive increase in effect due to accumulation of active metabolites should be kept in mind, possibly requiring an even larger decrease in dosage than estimated based on the parent drug alone.

Clinical studies, as well as the product information, often did not provide precise dose recommendations for patients with liver disease, suggesting only dose reduction of a specific drug without quantifying the reduction. In clinical studies, the change in pharmacokinetics seemed generally higher in patients with liver cirrhosis than in those with active or chronic hepatitis,[106,111,126,127,132] and is generally also more pronounced with increasing Child-Pugh score.[33,108,130,146,154,159] Dose adjustment is therefore especially important in patients with moderate and severe liver cirrhosis. The combination of the results from pharmacokinetic studies with the estimates based on hepatic extraction may be helpful to support clinicians in the selection of an adequate dosage of drugs in patients with liver cirrhosis. However, prospective clinical trials testing the appropriateness of such dose recommendations are mostly lacking and therefore our propositions should not be interpreted as definitive dose guidelines.

For centrally acting drugs, not only dose adjustment based on pharmacokinetic properties is necessary, but also changes in pharmacodynamics should be considered. For example, patients with cirrhosis have a greater cerebral sensitivity to a number of drugs acting on the central nervous system, e.g. benzodiazepines or antipsychotics.[6,13] Although the mechanism underlying this hypersensitivity remains to be explained, there is evidence that it is not caused only by pharmacokinetic alterations. Patients with hepatic encephalopathy require special consideration, as benzodiazepines and/or drugs with anticholinergic properties may worsen cognitive function.[112,133] Nevertheless, administration of benzodiazepines is indicated for treatment of alcohol withdrawal, anxiety or before endoscopic procedures or surgery in such patients. With the exception of flurazepam, midazolam and triazolam, benzodiazepines are all categorized as low extraction drugs. Since CYP-mediated metabolism is generally more affected

by liver disease than glucuronidation,[7,8] we consider lorazepam, oxazepam and temazepam as the benzodiazepines of choice for patients with liver cirrhosis.

4. Conclusions

Dose recommendations that are based on the hepatic extraction and/or bioavailability of a drug are generally in good agreement with the data from pharmacokinetic studies in patients with liver cirrhosis. Classification of drugs according to hepatic extraction is therefore a useful approach for dose adjustment in patients with liver cirrhosis, when appropriate clinical studies are lacking. For a large number of centrally acting drugs, clinical pharmacokinetic studies and precise dose recommendations are not available. Pharmaceutical companies should be urged to perform pharmacokinetic studies in patients with liver cirrhosis and to provide precise dosage recommendations for new drugs and for critical drugs (e.g. drugs with a high hepatic extraction) already on the market. However, not only changes in pharmacokinetics of the parent drug and/or active metabolites, but also the clinical situation of the patient and the therapeutic index of the drug may influence the choice of dose for certain drugs.

Acknowledgements

This work was supported by a grant from the Swiss National Science Foundation to Professor Stephan Krähenbühl (310000-112483).

None of the authors have any conflicts of interest that are directly relevant to the content of this review. The funding organisation had no influence on the study design, analysis and interpretation of data or writing of the review. The authors all contributed equally to this work.

References

1. McLean AJ, Morgan DJ. Clinical pharmacokinetics in patients with liver disease. Clin Pharmacokinet 1991 Jul; 21 (1): 42-69
2. Morgan DJ, McLean AJ. Clinical pharmacokinetic and pharmacodynamic considerations in patients with liver disease: an update. Clin Pharmacokinet 1995 Nov; 29 (5): 370-91
3. Williams RL, Mamelok RD. Hepatic disease and drug pharmacokinetics. Clin Pharmacokinet 1980 Nov-Dec; 5 (6): 528-47
4. Delco F, Tchambaz L, Schlienger R, et al. Dose adjustment in patients with liver disease. Drug Saf 2005; 28 (6): 529-45
5. Herbert MF. Guide to drug dosage in hepatic disease. In: Holford NHG, editor. Drug data handbook. 3rd ed. Auckland: Adis International, 1998: 179
6. Westphal JF, Brogard JM. Drug administration in chronic liver disease. Drug Saf 1997 Jul; 17 (1): 47-73
7. Verbeeck RK, Horsmans Y. Effect of hepatic insufficiency on pharmacokinetics and drug dosing. Pharm World Sci 1998 Oct; 20 (5): 183-92
8. Rodighiero V. Effects of liver disease on pharmacokinetics: an update. Clin Pharmacokinet 1999 Nov; 37 (5): 399-431
9. Tchambaz L, Schlatter C, Jakob M, et al. Dose adaptation of antineoplastic drugs in patients with liver disease. Drug Saf 2006; 29 (6): 509-22
10. Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: an overview. Pharmacol Ther 2001 Mar; 89 (3): 221-31
11. Krahenbuhl S, Marti U, Grant I, et al. Characterization of mechanisms causing hypoalbuminemia in rats with long-term bile duct ligation. J Hepatol 1995 Jul; 23 (1): 79-86
12. Butler JM, Begg EJ. Free drug metabolic clearance in elderly people. Clin Pharmacokinet 2008; 47 (5): 297-321
13. Crone CC, Gabriel GM, DiMartini A. An overview of psychiatric issues in liver disease for the consultation-liaison psychiatrist. Psychosomatics 2006 May-Jun; 47 (3): 188-205
14. Lucena MI, Andrade RJ, Tognoni G, et al. Drug use for non-hepatic associated conditions in patients with liver cirrhosis. Eur J Clin Pharmacol 2003 May; 59 (1): 71-6
15. Morgan MH, Read AE. Antidepressants and liver disease. Gut 1972 Sep; 13 (9): 697-701
16. Documed AG. Arzneimittelkompendium der Schweiz [online]. Available from: http://www.kompendium.ch [Accessed 2009 Mar 16]
17. Murray L. editor. Physicians' desk reference (PDR). 59th ed. Montvale (NJ): Thomson PDR, 2005
18. Dollery C. editor. Therapeutic drugs. 2nd ed. Edinburgh: Churchill Livingstone, 1999
19. Thomson Healthcare. Micromedex(R) healthcare series [online]. Available from: http://www.thomsonhc.com [Accessed 2009 Mar 16]
20. Speight TM, Holford NHG, editors. Avery's drug treatment. 4th ed. Auckland: Adis International, 1997
21. Thummel KE, Shen DD, Isoherranen N, et al. Design and optimization of dosage regimens: pharmacokinetic data. In: Brunton LL, editor. Goodman & Gilman's: the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006
22. Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia (PA): Lippincott Williams & Wilkins, 1999

23. Bénichou C, editor. Adverse drug reactions: a practical guide to diagnosis and management. Chichester: John Wiley & Sons Ltd, 1994
24. Bircher J, Sommer W. Klinisch-pharmakologische Datensammlung. 2. Auflage ed. Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH, 1999
25. Buckley PF. Receptor-binding profiles of antipsychotics: clinical strategies when switching between agents. J Clin Psychiatry 2007; 68 Suppl. 6: 5-9
26. Trindade E, Menon D, Topfer LA, et al. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. CMAJ 1998 Nov 17; 159 (10): 1245-52
27. Nisoli E, Carruba MO. An assessment of the safety and efficacy of sibutramine, an anti-obesity drug with a novel mechanism of action. Obes Rev 2000 Oct; 1 (2): 127-39
28. Hvidberg EF, Dam M. Clinical pharmacokinetics of anticonvulsants. Clin Pharmacokinet 1976; 1 (3): 161-88
29. Bachmann K, He Y, Sarver JG, et al. Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of ethosuximide by human hepatic microsomal enzymes. Xenobiotica 2003 Mar; 33 (3): 265-76
30. Seree EJ, Pisano PJ, Placidi M, et al. Identification of the human and animal hepatic cytochromes P450 involved in clonazepam metabolism. Fundam Clin Pharmacol 1993; 7 (2): 69-75
31. May TW, Korn-Merker E, Rambeck B. Clinical pharmacokinetics of oxcarbazepine. Clin Pharmacokinet 2003; 42 (12): 1023-42
32. DeVane CL. Pharmacokinetics drug interactions, and tolerability of valproate. Psychopharmacol Bull 2003; 37 Suppl. 2: 25-42
33. Lau AH, Gustavson LE, Sperelakis R, et al. Pharmacokinetics and safety of tiagabine in subjects with various degrees of hepatic function. Epilepsia 1997 Apr; 38 (4): 445-51
34. Deleu D, Northway MG, Hanssens Y. Clinical pharmacokinetic and pharmacodynamic properties of drugs used in the treatment of Parkinson's disease. Clin Pharmacokinet 2002; 41 (4): 261-309
35. Kvernmo T, Hartter S, Burger E. A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. Clin Ther 2006 Aug; 28 (8): 1065-78
36. Taavitsainen P, Anttila M, Nyman L, et al. Selegiline metabolism and cytochrome P450 enzymes: in vitro study in human liver microsomes. Pharmacol Toxicol 2000 May; 86 (5): 215-21
37. Yoshii K, Kobayashi K, Tsumuji M, et al. Identification of human cytochrome P450 isoforms involved in the 7-hydroxylation of chlorpromazine by human liver microsomes. Life Sci 2000; 67 (2): 175-84
38. Wojcikowski J, Pichard-Garcia L, Maurel P, et al. Contribution of human cytochrome p-450 isoforms to the metabolism of the simplest phenothiazine neuroleptic promazine. Br J Pharmacol 2003 Apr; 138 (8): 1465-74
39. Mauri MC, Volonteri LS, Colasanti A, et al. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet 2007; 46 (5): 359-88
40. Eiermann B, Engel G, Johansson I, et al. The involvement of CYP1A2 and CYP3A4 in the metabolism of clozapine. Br J Clin Pharmacol 1997 Nov; 44 (5): 439-46
41. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. Clin Pharmacokinet 2001; 40 (7): 509-22
42. Caccia S. Biotransformation of post-clozapine antipsychotics: pharmacological implications. Clin Pharmacokinet 2000 May; 38 (5): 393-14
43. Sporkert F, Augsburger M, Giroud C, et al. Determination and distribution of clotiapine (Entumine) in human plasma, post-mortem blood and tissue samples from clotiapine-treated patients and from autopsy cases. Forensic Sci Int 2007 Aug 6; 170 (2-3): 193-9
44. Venkatakrishnan K, Greenblatt DJ, Von Moltke LL, et al. Alprazolam is another substrate for human cytochrome P450-3A isoforms [letter]. J Clin Psychopharmacol 1998 Jun; 18 (3): 256
45. Simons FE, Watson WT, Chen XY, et al. The pharmacokinetics and pharmacodynamics of hydroxyzine in patients with primary biliary cirrhosis. J Clin Pharmacol 1989 Sep; 29 (9): 809-15
46. Kilicarslan T, Haining RL, Rettie AE, et al. Flunitrazepam metabolism by cytochrome P450S 2C19 and 3A4. Drug Metab Dispos 2001 Apr; 29 (4 Pt 1): 460-5
47. Von Moltke LL, Greenblatt DJ, Harmatz JS, et al. Triazolam biotransformation by human liver microsomes in vitro: effects of metabolic inhibitors and clinical confirmation of a predicted interaction with ketoconazole. J Pharmacol Exp Ther 1996 Feb; 276 (2): 370-9
48. Hellstern A, Hildebrand M, Humpel M, et al. Minimal biliary excretion and enterohepatic recirculation of lormetazepam in man as investigated by a new nasobiliary drainage technique. Int J Clin Pharmacol Ther Toxicol 1990 Jun; 28 (6): 256-61
49. Gaillot J, Le Roux Y, Houghton GW, et al. Critical factors for pharmacokinetics of zopiclone in the elderly and in patients with liver and renal insufficiency. Sleep 1987; 10 Suppl. 1: 7-21
50. Langtry HD, Benfield P. Zolpidem: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 1990 Aug; 40 (2): 291-313
51. Akutsu T, Kobayashi K, Sakurada K, et al. Identification of human cytochrome p450 isozymes involved in diphenhydramine N-demethylation. Drug Metab Dispos 2007 Jan; 35 (1): 72-8
52. Ganes DA, Midha KK. Identification in in vivo acetylation pathway for N-dealkylated metabolites of doxylamine in humans. Xenobiotica 1987 Aug; 17 (8): 993-9
53. Koyama E, Chiba K, Tani M, et al. Reappraisal of human CYP isoforms involved in imipramine N-demethylation and 2-hydroxylation: a study using microsomes obtained from putative extensive and poor metabolizers of S-mephenytoin and eleven recombinant human CYPs. J Pharmacol Exp Ther 1997 Jun; 281 (3): 1199-210
54. Eap CB, Bender S, Gastpar M, et al. Steady state plasma levels of the enantiomers of trimipramine and of its metabolites in CYP2D6-, CYP2C19- and

CYP3A4/5-phenotyped patients. Ther Drug Monit 2000 Apr; 22 (2): 209-14
55. Knapp DR, Gaffney TE, McMahon RE, et al. Studies of human urinary and biliary metabolites of nortriptyline with stable isotope labeling. J Pharmacol Exp Ther 1972 Mar; 180 (3): 784-90
56. Brachtendorf L, Jetter A, Beckurts KT, et al. Cytochrome P450 enzymes contributing to demethylation of maprotiline in man. Pharmacol Toxicol 2002 Mar; 90 (3): 144-9
57. Grasmader K, Verwohlt PL, Rietschel M, et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004 Jul; 60 (5): 329-36
58. DeVane CL, Liston HL, Markowitz JS. Clinical pharmacokinetics of sertraline. Clin Pharmacokinet 2002; 41 (15): 1247-66
59. Rao N. The clinical pharmacokinetics of escitalopram. Clin Pharmacokinet 2007; 46 (4): 281-90
60. Bonnet U. Moclobemide: evolution, pharmacodynamic, and pharmacokinetic properties. CNS Drug Rev 2002 Fall; 8 (3): 283-308
61. Mihara K, Otani K, Tybring G, et al. The CYP2D6 genotype and plasma concentrations of mianserin enantiomers in relation to therapeutic response to mianserin in depressed Japanese patients. J Clin Psychopharmacol 1997 Dec; 17 (6): 467-71
62. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. Clin Pharmacokinet 2000 Dec; 39 (6): 413-27
63. Westra P, van Thiel MJ, Vermeer GA, et al. Pharmacokinetics of galanthamine (a long-acting anticholinesterase drug) in anaesthetized patients. Br J Anaesth 1986 Nov; 58 (11): 1303-7
64. Jann MW, Shirley KL, Small GW. Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. Clin Pharmacokinet 2002; 41 (10): 719-39
65. Robinson DM, Keating GM. Memantine: a review of its use in Alzheimer's disease. Drugs 2006; 66 (11): 1515-34
66. Abernethyl DR, Divoll M, Greenblatt DJ, et al. Absolute bioavailability of imipramine: influence of food. Psychopharmacology (Berl) 1984; 83 (1): 104-6
67. Blin O. The pharmacokinetics of pergolide in Parkinson's disease. Curr Opin Neurol 2003 Dec; 16 Suppl. 1: S9-12
68. Reynolds Jr NC, Miska RM. Safety of anticonvulsants in hepatic porphyrias. Neurology 1981 Apr; 31 (4): 480-4
69. Chounta A, Tsiodras S, Zouridakis S, et al. Sibutramine use associated with reversible hepatotoxicity. Ann Intern Med 2005 Nov 15; 143 (10): 763-4
70. Mehta H, Murray B, LoIudice TA. Hepatic dysfunction due to intravenous abuse of methylphenidate hydrochloride. J Clin Gastroenterol 1984 Apr; 6 (2): 149-51
71. Farago F. Trigeminal neuralgia: its treatment with two new carbamazepine analogues. Eur Neurol 1987; 26 (2): 73-83
72. Chitturi S, George J. Hepatotoxicity of commonly used drugs: nonsteroidal anti-inflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, psychotropic drugs. Semin Liver Dis 2002; 22 (2): 169-83
73. Kellermann K, Soditt V, Rambeck B, et al. Fatal hepatotoxicity in a child treated with vigabatrin. Acta Neurol Scand 1996 May; 93 (5): 380-1
74. Sauve G, Bresson-Hadni S, Prost P, et al. Acute hepatitis after lamotrigine administration. Dig Dis Sci 2000 Sep; 45 (9): 1874-7
75. Bjoro K, Gjerstad L, Bentdal O, et al. Topiramate and fulminant liver failure [letter]. Lancet 1998 Oct 3; 352 (9134): 1119
76. Lasso-de-La-Vega MC, Zapater P, Such J, et al. Gabapentin-associated hepatotoxicity. Am J Gastroenterol 2001 Dec; 96 (12): 3460-2
77. Richardson CE, Williams DW, Kingham JG. Gabapentin induced cholestasis. BMJ 2002 Sep 21; 325 (7365): 635
78. Brockmann K, Hanefeld F. Progressive elevation of liver enzymes in a child treated with sulthiame. Neuropediatrics 2001 Jun; 32 (3): 165-6
79. Hubble JP, Koller WC, Cutler NR, et al. Pramipexole in patients with early Parkinson's disease. Clin Neuropharmacol 1995 Aug; 18 (4): 338-47
80. Maxwell JD, Carrella M, Parkes JD, et al. Plasma disappearance and cerebral effects of chlorpromazine in cirrhosis. Clin Sci 1972 Aug; 43 (2): 143-51
81. Dincsoy HP, Saelinger DA. Haloperidol-induced chronic cholestatic liver disease. Gastroenterology 1982 Sep; 83 (3): 694-700
82. Ozcanli T, Erdogan A, Ozdemir S, et al. Severe liver enzyme elevations after three years of olanzapine treatment: a case report and review of olanzapine associated hepatotoxicity. Prog Neuropsychopharmacol Biol Psychiatry 2006 Aug 30; 30 (6): 1163-6
83. El Hajj I, Sharara AI, Rockey DC. Subfulminant liver failure associated with quetiapine. Eur J Gastroenterol Hepatol 2004 Nov; 16 (12): 1415-8
84. Cohen LS, Cohen DE. Lithium-induced hyperbilirubinemia in an adolescent. J Clin Psychopharmacol 1991 Aug; 11 (4): 274-5
85. Hazelwood RE. Ascites: a side effect of lithium [letter]? Am J Psychiatry 1981 Feb; 138 (2): 257
86. Krebs S, Dormann H, Muth-Selbach U, et al. Risperidone-induced cholestatic hepatitis. Eur J Gastroenterol Hepatol 2001 Jan; 13 (1): 67-9
87. Morgan DD, Robinson JD, Mendenhall CL. Clinical pharmacokinetics of chlordiazepoxide in patients with alcoholic hepatitis. Eur J Clin Pharmacol 1981 Mar; 19 (4): 279-85
88. Karsenti D, Blanc P, Bacq Y, et al. Hepatotoxicity associated with zolpidem treatment. BMJ 1999 May 1; 318 (7192): 1179
89. van Vliet AC, Frenkel M, Wilson JH. Acute liver necrosis after treatment with opipramol. Ned Tijdschr Geneeskd 1977 Aug 20; 121 (34): 1325-7
90. Cai Q, Benson MA, Talbot TJ, et al. Acute hepatitis due to fluoxetine therapy. Mayo Clin Proc 1999 Jul; 74 (7): 692-4
91. Lopez-Torres E, Lucena MI, Seoane J, et al. Hepatotoxicity related to citalopram. Am J Psychiatry 2004 May; 161 (5): 923-4

92. Green BH. Fluvoxamine and hepatic function. Br J Psychiatry 1988 Jul; 153: 130-1
93. Timmings P, Lamont D. Intrahepatic cholestasis associated with moclobemide leading to death. Lancet 1996 Mar 16; 347 (9003): 762-3
94. Otani K, Kaneko S, Tasaki H, et al. Hepatic injury caused by mianserin. BMJ 1989 Aug 19; 299 (6697): 519
95. Hui CK, Yuen MF, Wong WM, et al. Mirtazapine-induced hepatotoxicity. J Clin Gastroenterol 2002 Sep; 35 (3): 270-1
96. Horsmans Y, De Clercq M, Sempoux C. Venlafaxine-associated hepatitis [letter]. Ann Intern Med 1999 Jun 1; 130 (11): 944
97. Cardona X, Avila A, Castellanos P. Venlafaxine-associated hepatitis [letter]. Ann Intern Med 2000 Mar 7; 132 (5): 417
98. Hu KQ, Tiyyagura L, Kanel G, et al. Acute hepatitis induced by bupropion. Dig Dis Sci 2000 Sep; 45 (9): 1872-3
99. Alvaro D, Onetti-Muda A, Moscatelli R, et al. Acute cholestatic hepatitis induced by bupropion prescribed as pharmacological support to stop smoking: a case report. Dig Liver Dis 2001 Nov; 33 (8): 703-6
100. Jones DE, Newton JL. An open study of modafinil for the treatment of daytime somnolence and fatigue in primary biliary cirrhosis. Aliment Pharmacol Ther 2007 Feb 15; 25 (4): 471-6
101. Alvin J, McHorse T, Hoyumpa A, et al. The effect of liver disease in man on the disposition of phenobarbital. J Pharmacol Exp Ther 1975 Jan; 192 (1): 224-35
102. Pisani F, Perucca E, Primerano G, et al. Single-dose kinetics of primidone in acute viral hepatitis. Eur J Clin Pharmacol 1984; 27 (4): 465-9
103. Blaschke TF, Meffin PJ, Melmon KL, et al. Influence of acute viral hepatitis on phenytoin kinetics and protein binding. Clin Pharmacol Ther 1975 Jun; 17 (6): 685-91
104. Pacifici GM, Viani A, Rizzo G, et al. Plasma protein binding of clonazepam in hepatic and renal insufficiency and after hemodialysis. Ther Drug Monit 1987 Dec; 9 (4): 369-73
105. Vasudevan AE, Goh KL, Bulgiba AM. Impairment of psychomotor responses after conscious sedation in cirrhotic patients undergoing therapeutic upper GI endoscopy. Am J Gastroenterol 2002 Jul; 97 (7): 1717-21
106. Klotz U, Rapp T, Muller WA. Disposition of valproic acid in patients with liver disease. Eur J Clin Pharmacol 1978 Mar 17; 13 (1): 55-60
107. Krahenbuhl S, Brandner S, Kleinle S, et al. Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure. Liver 2000 Jul; 20 (4): 346-8
108. Marcellin P, de Bony F, Garret C, et al. Influence of cirrhosis on lamotrigine pharmacokinetics. Br J Clin Pharmacol 2001 May; 51 (5): 410-4
109. Brockmoller J, Thomsen T, Wittstock M, et al. Pharmacokinetics of levetiracetam in patients with moderate to severe liver cirrhosis (Child-Pugh classes A, B, and C): characterization by dynamic liver function tests. Clin Pharmacol Ther 2005 Jun; 77 (6): 529-41
110. Whiteman PD, Fowle AS, Hamilton MJ, et al. Pharmacokinetics and pharmacodynamics of procyclidine in man. Eur J Clin Pharmacol 1985; 28 (1): 73-8
111. Jorga KM, Kroodsma JM, Fotteler B, et al. Effect of liver impairment on the pharmacokinetics of tolcapone and its metabolites. Clin Pharmacol Ther 1998 Jun; 63 (6): 646-54
112. Read AE, Laidlaw J, McCarthy CF. Effects of chlorpromazine in patients with hepatic disease. Br Med J 1969 Aug 30; 3 (5669): 497-9
113. Hu OY, Tang HS, Sheeng TY, et al. Pharmacokinetics of promazine: I. Disposition in patients with acute viral hepatitis B. Biopharm Drug Dispos 1990 Oct; 11 (7): 557-68
114. Hu OY, Tang HS, Sheeng TY, et al. Pharmacokinetics of promazine in patients with hepatic cirrhosis: correlation with a novel galactose single point method. J Pharm Sci 1995 Jan; 84 (1): 111-4
115. Zhang WV, Ramzan I, Murray M. Impaired microsomal oxidation of the atypical antipsychotic agent clozapine in hepatic steatosis. J Pharmacol Exp Ther 2007 Aug; 322 (2): 770-7
116. Thyrum PT, Wong YW, Yeh C. Single-dose pharmacokinetics of quetiapine in subjects with renal or hepatic impairment. Prog Neuropsychopharmacol Biol Psychiatry 2000 May; 24 (4): 521-33
117. Snoeck E, Van Peer A, Sack M, et al. Influence of age, renal and liver impairment on the pharmacokinetics of risperidone in man. Psychopharmacology (Berl) 1995 Dec; 122 (3): 223-9
118. Klotz U, Antonin KH, Brugel H, et al. Disposition of diazepam and its major metabolite desmethyldiazepam in patients with liver disease. Clin Pharmacol Ther 1977 Apr; 21 (4): 430-6
119. Klotz U, Avant GR, Hoyumpa A, et al. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 1975 Feb; 55 (2): 347-59
120. Andreasen PB, Hendel J, Greisen G, et al. Pharmacokinetics of diazepam in disordered liver function. Eur J Clin Pharmacol 1976 Jun 15; 10 (2): 115-20
121. Branch RA, Morgan MH, James J, et al. Intravenous administration of diazepam in patients with chronic liver disease. Gut 1976 Dec; 17 (12): 975-83
122. Bozkurt P, Kaya G, Suzer O, et al. Diazepam serum concentration-sedative effect relationship in patients with liver disease. Middle East J Anesthesiol 1996 Feb; 13 (4): 405-13
123. Sellers EM, Greenblatt DJ, Giles HG, et al. Chlordiazepoxide and oxazepam disposition in cirrhosis. Clin Pharmacol Ther 1979 Aug; 26 (2): 240-6
124. Roberts RK, Wilkinson GR, Branch RA, et al. Effect of age and parenchymal liver disease on the disposition and elimination of chlordiazepoxide (librium). Gastroenterology 1978 Sep; 75 (3): 479-85
125. Shull HJ, Wilkinson GR, Johnson R, et al. Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. Ann Intern Med 1976 Apr; 84 (4): 420-5
126. Kraus JW, Desmond PV, Marshall JP, et al. Effects of aging and liver disease on disposition of lorazepam. Clin Pharmacol Ther 1978 Oct; 24 (4): 411-9
127. Monjanel-Mouterde S, Antoni M, Bun H, et al. Pharmacokinetics of a single oral dose of clobazam in patients with liver disease. Pharmacol Toxicol 1994 Jun; 74 (6): 345-50

128. Juhl RP, Van Thiel DH, Dittert LW, et al. Alprazolam pharmacokinetics in alcoholic liver disease. J Clin Pharmacol 1984 Feb-Mar; 24 (2-3): 113-9
129. Dalhoff K, Poulsen HE, Garred P, et al. Buspirone pharmacokinetics in patients with cirrhosis. Br J Clin Pharmacol 1987 Oct; 24 (4): 547-50
130. Barbhaiya RH, Shukla UA, Pfeffer M, et al. Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. Eur J Clin Pharmacol 1994; 46 (1): 41-7
131. Jochemsen R, Van Beusekom BR, Spoelstra P, et al. Effect of age and liver cirrhosis on the pharmacokinetics of nitrazepam. Br J Clin Pharmacol 1983 Mar; 15 (3): 295-302
132. Drouet-Coassolo C, Iliadis A, Coassolo P, et al. Pharmacokinetics of flunitrazepam following single dose oral administration in liver disease patients compared with healthy volunteers. Fundam Clin Pharmacol 1990; 4 (6): 643-51
133. Bakti G, Fisch HU, Karlaganis G, et al. Mechanism of the excessive sedative response of cirrhotics to benzodiazepines: model experiments with triazolam. Hepatology 1987 Jul-Aug; 7 (4): 629-38
134. Kroboth PD, Smith RB, Van Thiel DH, et al. Nighttime dosing of triazolam in patients with liver disease and normal subjects: kinetics and daytime effects. J Clin Pharmacol 1987 Aug; 27 (8): 555-60
135. Robin DW, Lee M, Hasan SS, et al. Triazolam in cirrhosis: pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 1993 Dec; 54 (6): 630-7
136. Hildebrand M, Hellstern A, Humpel M, et al. Plasma levels and urinary excretion of lormetazepam in patients with liver cirrhosis and in healthy volunteers. Eur J Drug Metab Pharmacokinet 1990 Jan-Mar; 15 (1): 19-26
137. Ghabrial H, Desmond PV, Watson KJ, et al. The effects of age and chronic liver disease on the elimination of temazepam. Eur J Clin Pharmacol 1986; 30 (1): 93-7
138. Ochs HR, Greenblatt DJ, Verburg-Ochs B, et al. Temazepam clearance unaltered in cirrhosis. Am J Gastroenterol 1986 Jan; 81 (1): 80-4
139. Trouvin JH, Farinotti R, Haberer JP, et al. Pharmacokinetics of midazolam in anaesthetized cirrhotic patients. Br J Anaesth 1988 Jun; 60 (7): 762-7
140. MacGilchrist AJ, Birnie GG, Cook A, et al. Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. Gut 1986 Feb; 27 (2): 190-5
141. Pentikainen PJ, Valisalmi L, Himberg JJ, et al. Pharmacokinetics of midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. J Clin Pharmacol 1989 Mar; 29 (3): 272-7
142. Chalasani N, Gorski JC, Patel NH, et al. Hepatic and intestinal cytochrome P450 3A activity in cirrhosis: effects of transjugular intrahepatic portosystemic shunts. Hepatology 2001 Dec; 34 (6): 1103-8
143. Parker G, Roberts CJ. Plasma concentrations and central nervous system effects of the new hypnotic agent zopiclone in patients with chronic liver disease. Br J Clin Pharmacol 1983 Sep; 16 (3): 259-65
144. Meredith CG, Christian Jr CD, et al. Diphenhydramine disposition in chronic liver disease. Clin Pharmacol Ther 1984 Apr; 35 (4): 474-9
145. Pentikainen PJ, Neuvonen PJ, Jostell KG. Pharmacokinetics of chlormethiazole in healthy volunteers and patients with cirrhosis of the liver. Eur J Clin Pharmacol 1980 Apr; 17 (4): 275-84
146. Centerholt C, Ekblom M, Odergren T, et al. Pharmacokinetics and sedative effects in healthy subjects and subjects with impaired liver function after continuous infusion of clomethiazole. Eur J Clin Pharmacol 2003 Jun; 59 (2): 117-22
147. Hrdina PD, Lapierre YD, Koranyi EK. Altered amitriptyline kinetics in a depressed patient with porto-caval anastomosis. Can J Psychiatry 1985 Mar; 30 (2): 111-3
148. Benfield P, Heel RC, Lewis SP. Fluoxetine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. Drugs 1986 Dec; 32 (6): 481-508
149. Schenker S, Bergstrom RF, Wolen RL, et al. Fluoxetine disposition and elimination in cirrhosis. Clin Pharmacol Ther 1988 Sep; 44 (3): 353-9
150. Joffe P, Larsen FS, Pedersen V, et al. Single-dose pharmacokinetics of citalopram in patients with moderate renal insufficiency or hepatic cirrhosis compared with healthy subjects. Eur J Clin Pharmacol 1998 May; 54 (3): 237-42
151. Dalhoff K, Almdal TP, Bjerrum K, et al. Pharmacokinetics of paroxetine in patients with cirrhosis. Eur J Clin Pharmacol 1991; 41 (4): 351-4
152. Demolis JL, Angebaud P, Grange JD, et al. Influence of liver cirrhosis on sertraline pharmacokinetics. Br J Clin Pharmacol 1996 Sep; 42 (3): 394-7
153. van Harten J, Duchier J, Devissaguet JP, et al. Pharmacokinetics of fluvoxamine maleate in patients with liver cirrhosis after single-dose oral administration. Clin Pharmacokinet 1993 Feb; 24 (2): 177-82
154. Areberg J, Christophersen JS, Poulsen MN, et al. The pharmacokinetics of escitalopram in patients with hepatic impairment. AAPS J 2006; 8 (1): E14-9
155. Stoeckel K, Pfefen JP, Mayersohn M, et al. Absorption and disposition of moclobemide in patients with advanced age or reduced liver or kidney function. Acta Psychiatr Scand Suppl 1990; 360: 94-7
156. Timmer CJ, Sitsen JM, Delbressine LP. Clinical pharmacokinetics of mirtazapine. Clin Pharmacokinet 2000 Jun; 38 (6): 461-74
157. Tran A, Laneury J, Duchêne P, et al. Pharmacokinetics of reboxetine in volunteers with hepatic impairment. Clin Drug Invest 2000; 19 (6): 473-7
158. DeVane CL, Laizure SC, Stewart JT, et al. Disposition of bupropion in healthy volunteers and subjects with alcoholic liver disease. J Clin Psychopharmacol 1990 Oct; 10 (5): 328-32
159. Zhao Q, Iyer GR, Verhaeghe T, et al. Pharmacokinetics and safety of galantamine in subjects with hepatic impairment and healthy volunteers. J Clin Pharmacol 2002 Apr; 42 (4): 428-36
160. Reyes JF, Vargas R, Kumar D, et al. Steady-state pharmacokinetics, pharmacodynamics and tolerability of donepezil hydrochloride in hepatically impaired patients. Br J Clin Pharmacol 2004 Nov; 58 Suppl. 1: 9-17

161. Tiseo PJ, Vargas R, Perdomo CA, et al. An evaluation of the pharmacokinetics of donepezil HCl in patients with impaired hepatic function. Br J Clin Pharmacol 1998 Nov; 46 Suppl. 1: 51-5

162. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973 Aug; 60 (8): 646-9

163. Wilkinson GR. Clearance approaches in pharmacology. Pharmacol Rev 1987 Mar; 39 (1): 1-47

164. Ito K, Houston JB. Comparison of the use of liver models for predicting drug clearance using in vitro kinetic data from hepatic microsomes and isolated hepatocytes. Pharm Res 2004 May; 21 (5): 785-92

165. Frye RF, Zgheib NK, Matzke GR, et al. Liver disease selectively modulates cytochrome P450-mediated metabolism. Clin Pharmacol Ther 2006 Sep; 80 (3): 235-45

166. George J, Murray M, Byth K, et al. Differential alterations of cytochrome P450 proteins in livers from patients with severe chronic liver disease. Hepatology 1995 Jan; 21 (1): 120-8

167. Branch RA. Drugs in liver disease. Clin Pharmacol Ther 1998 Oct; 64 (4): 462-5

Correspondence: Professor *Stephan Krähenbühl*, Division of Clinical Pharmacology & Toxicology, University Hospital, Hebelstrasse 2, CH-4031 Basel, Switzerland.
E-mail: kraehenbuehl@uhbs.ch