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Schmerztherapie bei Leberinsuffizienz

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List of Abbreviations

11-OH-THC 11-hydroxytetrahydrocannabinol

Aa. arteries

AA 4-amino-antipyrine

AAA 4-acetyl-amino-antipyrine

AAG α_1-acid glycoprotein

ALT alanine aminotransferase

AST aspartate aminotransferase

CBD cannabidilol

Cl_h hepatic drug clearance

Cl_{int} intrinsic clearance of unbound drug

COX cyclooxygenase

CR controlled release

CYP cytochrome-P_{450}-enzymes

DILI drug induced liver injury

EH hepatic extraction ratio

FAA 4-formyl-amino-antipyrine

fu fraction of unbound drug in the blood

h hour(s)

IASP International Association for the Study of Pain

INR International Normalized Ratio

IR immediate release

iv intravenous

L litre

LI Liver Insufficiency

MAA moiety 4-methyl-amino-antipyrine

M3G morphine-3-glucuronide

M6G morphine-6-glucuronide

MELD model for end-stage liver disease

mg milligram

min minute(s)

MMT methadone maintenance treatment

NAPQI N-acetyl-p-benzoquinoneimine

NMDA N-methyl D-aspartate

NSAID(s) non-steroidal anti-inflammatory drug(s)

OLT orthotopic liver transplantation

po peroral

Q_h hepatic blood flow

r rectal

s second(s)

sl sublingual

$t_{1/2}\beta$ elimination half-life

td transdermal

THC $\triangle^9$-tetrahydrocannabinol

THC-COOH 11-nor-9-carboxy-tetrahydrocannabinol

UGT glucuronyltransferase

V. vein

VPA valproic acid

Vv. veins

WHO World Health Organization

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Zusammenfassung

Medikamentöse Schmerztherapie bei schwerkranken Patienten ist eine klinische Herausforderung. Die Leber spielt im Metabolismus von Medikamenten eine zentrale Rolle. Lebererkrankungen führen zu Veränderungen im hepatischen Blutfluss, der enzymatischen Clearance, der Synthese von Plasmaproteinen und dem Bindungsverhalten von Medikamenten an Plasmaproteine, sowie zu einem veränderten Ansprechen der Endorgane auf die verabreichten Medikamente.

In einer systematischen Literatursuche wurde nach pharmakokinetische Veränderungen bei Lebererkrankungen und nach Dosierungs-Richtlinien gesucht.

Remifentanil, Pregabalin und Gabapentin werden nicht in der Leber metabolisiert, daher sind keine Dosisanpassungen notwendig. Diclofenac, Ibuprofen, Meloxicam, Fenanyl und Sufentanil werden vorrangig zur vorsichtigen Verwendung empfohlen. Die Dosierungen von Nimesolid, Etoricoxib, Celecoxib, Paracetamol, Alfentanil, Dihydrocodein, Hydromorphon, Methadon, Morphin, Oxycodon, Pethidin, Piritramid and Tramadol müssen reduziert werden. Codein, Tilidin, Carbamazepin und Valproatsäure sollen vermieden werden. Metamizol, Rofecoxib, Buprenorphin, Nalbuphin, Oxymorphon, Amitriptylin, Duloxetin, Lamotrigin, Topiramat, Kortikosteroide, Ketamin und Cannabinoide sind nicht ausreichend untersucht worden. Weitere Studien zu ihrem Verhalten bei Leberinsuffizienz sind notwendig.

Die vorhandene Literatur ist vielfach nicht präzise und schwer vergleichbar, daher sollen die Empfehlungen stets an die individuellen Bedürfnisse der Patienten angepasst werden.

Abstract

Pain medication in patients with severe illness is a clinical challenge. The liver plays an important role in the metabolism of drugs. Liver disease alters the hepatic blood flow, the intrinsic clearance, the amount of plasma proteins and drug binding to plasma proteins and the end-organ response.

A systematic search was performed to identify pharmacokinetic alterations in liver diseases and dosage guidelines.

Remifentanil, pregabalin and gabapentin are not metabolised in the liver, therefore no dosage adjustments are necessary. Diclofenac, ibuprofen, meloxicam, fentanyl and sufentanil are primary recommended and should be used carefully. Dosage of nimesolide, etoricoxib, celecoxib, paracetamol, alfentanil, dihydrocodeine, hydromorphone, methadone, morphine, oxycodone, pethidine, piritramide and tramadol must be reduced. Codeine, tilidine, carbamazepine and valproate acid should be avoided. Metamizole, rofecoxib, buprenorphine, nalbuphine, oxymorphone, amitriptyline, duloxetine, lamotrigine, topiramate, corticosteroids, ketamine and cannabinoids are not well studied and require further investigation.

The existing data is often not precise and hardly comparable, therefore the recommendations should always be adjusted to the individual patients' needs.

1 Introduction

Pain management is a very important issue, especially in patients with severe illness and in elderly patients. The majority of patients seek a doctor due to pain [1, 2]. Organ dysfunction makes pain management difficult, especially in liver insufficiency, since the liver is the major organ involved in the metabolism of drugs.

Several authors [3–7] have investigated and described the correlation between pain management and drug metabolism in liver disease, but none of them have presented a full overview on pain medication in subjects with impaired liver function. This review aims to gather all information currently available concerning pain medication according to the World Health Organization pain ladder and liver impairment.

1.1 Definition of Pain

The current International Association for the Study of Pain (IASP) definition of pain states that pain is *an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage* [8]. Pain is experienced very subjectively and consists of biological, psychological and social aspects.

1.2 Therapy of Pain according to the WHO

In 1986, the World Health Organization (WHO) invented their nowadays well-known pain ladder [2]. The first step is the administration of non-opioid medication. If the pain persists or gets worse, a weak opioid should be administered. The third step is the administration of a strong opioid.

Recently, Vargas-Schaffer suggested to add invasive therapeutic options as the fourth step to the WHO pain ladder [2].

Parallel to all four steps, adjuvants can be used if necessary. The therapy of adverse effects is also administered parallelly to all four steps.

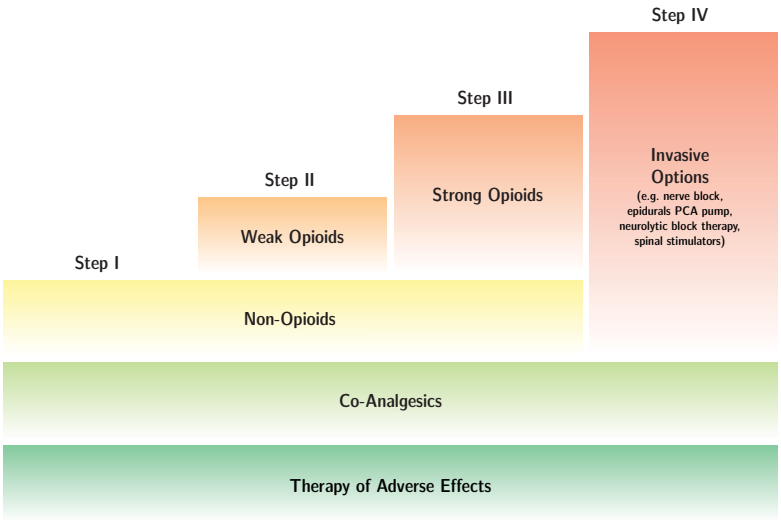

Figure 1: *Modified WHO Pain Ladder [2].*

1.3 Drug Metabolism in the Liver

The liver plays an important and central role in the metabolism of drugs. It takes care of pre-systemic elimination of orally administered drugs (first-pass effects) and conversion from inactive pro-drugs to active metabolites (e.g. codeine). During phase I- and II-reactions it eliminates drugs, inactivates them and makes them more water soluble in order to excrete them via bile and/or the urinary tract and through the synthesis of plasma proteins.

Enzymes The most important class of enzymes for the phase-I-metabolism of drugs in the liver are the cytochrome-P_{450}-enzymes (CYP). They are located in the membrane of the endoplasmic reticulum. The liver holds about 90–95% of all CYP enzymes in the body [9]. Further enzymes of the phase-I-metabolism are alcohol dehydrogenases, aldehyde dehydrogenases, xanthine oxidase, amine oxidases, monoamine oxidases, diamine oxidase and other metabolic enzymes [9].

Glucuronosyltransferases, glutathione S-transferases, N-acetyl transferases, sulfotransferases, methyltransferases and other enzymes catalyse phase-II-reactions [9]. The most important one for the metabolism of drugs is uridine diphosphate glucuronyltransferase (UGT); UGT 2B7, for example, is the enzyme that builds morphine-6- and morphine-3-glucuronide from morphine [9].

Excretion After their metabolisation in the liver, drugs are either eliminated by the bile or the urine. Liver diseases might alter the biliary excretion of drugs, so that dosage modification for those drugs might be necessary [10].

1.3.1 Hepatic Drug Clearance

In his review from 2008, Verbeeck [10] summarises the important determinants for hepatic drug clearance:

The hepatic drug clearance (Cl_h) depends on the hepatic blood flow (Q_h) and the hepatic extraction ratio (E_h).

$$Cl_h = Q_h \times E_h \tag{1.1}$$

The hepatic extraction ratio itself depends on the liver blood flow, the intrinsic clearance of unbound drug (Cl_{int}) and the fraction of unbound drug in the blood (fu):

$$Cl_h = Q_h \times \frac{fu \times Cl_{int}}{Q_h + fu \times Cl_{int}} \tag{1.2}$$

Concluding, the hepatic drug clearance is mainly dependent on 1. the **hepatic blood flow**, 2. the **intrinsic clearance** (the hepatic enzyme activity[1]) and 3. the **drug binding capacity of the blood** (mainly from plasma proteins) [7, 10].

High-, Intermediate- and Low-Clearance Drugs

According to their elimination in the liver, drugs can be categorised into three groups [10]:

- highly extracted drugs with an extraction ratio of > 0.7,
- low extracted drugs with an extraction ratio of < 0.3, and

[1] metabolising and transport enzymes

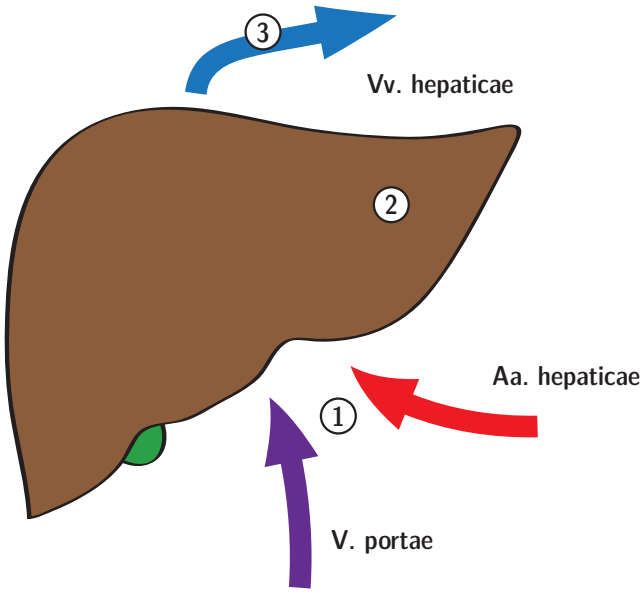

Figure 2: *The main determinants of drug metabolism in the liver are the hepatic blood flow (1), the intrinsic clearance (2) and the drug binding in the blood (3). Further information is given in the text.*

- intermediate extracted drugs with an extraction ratio between 0.3 and 0.7.

The limiting factor in the hepatic clearance of highly extracted drugs is the liver blood flow. Porto-systemic-shunting will effect the elimination of these drugs [10]. The plasma binding and intrinsic hepatic clearance are the most influential parameters in poorly extracted drugs [10]. The hepatic elimination of intermediate extracted drugs is affected by all three main determinants: hepatic blood flow, intrinsic clearance and drug binding capacity [10].

1.4 Liver Insufficiency

1.4.1 Effects of Liver Insufficiency on Hepatic Drug Metabolism

Liver insufficiency alters – depending substantially on the aetiology – mainly four parameters in the hepatic metabolism: the hepatic blood flow (e.g. hepatic hypertension causing porto-systemic shunts), the intrinsic clearance or enzyme activity, the amount of plasma proteins and drug binding to plasma proteins, and the end-organ response [7, 10–13].

Enzyme Activity The more severe the liver disease, the greater the reduction of drug metabolism [7, 10, 13]. However, it has been reported that in liver disease those enzymes responsible for conjugation reactions (phase-II-reactions) are less affected than those enzymes for oxidation reaction. Periportal areas, where phase-II-reaction enzymes are mainly located, seem to be less susceptible than centrilobular areas, the main location of phase-I-reaction enzymes [10, 12, 14].

Chandok and Watt [7] described in their review the correlation between the severity of liver disease and enzyme activity: patients with asymptomatic chronic liver disease, but without cirrhosis showed no alterations in the hepatic metabolism of drugs. Patients with severe liver disease, but without cirrhosis were likely to have reduced hepatic metabolism of drugs. Patients with well compensated cirrhosis and near-normal synthetic function had an impaired hepatic drug metabolism. The worst impaired drug metabolism occurred in subjects with an abnormal synthetic function of the liver or decompensated cirrhosis (see also Table 1). These findings go along with the study of Sotaniemi et al. [11], who investigated hepatic drug metabolism in 67 subjects with alcoholic liver disease and normal kidney function.

Table 1: *Impaired Hepatic Metabolism of Drugs in Liver Disease [7].*

Severity of Liver Disease	**Effects on Drug Metabolism**
asymptomatic chronic liver disease without cirrhosis	no liver dysfunction
severe liver disease without cirrhosis	metabolism may be altered
compensated cirrhosis and normal synthetic function	impaired drug metabolism
abnormal synthetic function or decompensated cirrhosis	worst impaired drug metabolism

Blood Flow Some liver diseases also cause alterations in the hepatic blood flow. Porto-systemic shunts lead to an increased oral bioavailability by avoiding the pre-systemic hepatic metabolism. These changes will affect highly–intermediately eliminated drugs, consequently, their elimination becomes limited by the intrinsic clearance of the liver. Low hepatic clearance drugs will not be affected that much by changes in the liver blood flow [15].

The main factor for alterations in drug metabolism in the liver seems to be cirrhosis: Morgan and McLean [16] concluded in their review from 1995 that mainly cirrhosis is associated with a significant impaired hepatic elimination. Verbeeck [10] stated that *cirrhosis and cholestasis (. . .) may lead to situations where dosage adjustment is absolutely necessary*.

Comorbidity Patients with advanced cirrhosis often present with impaired renal function as well. Poor nutrition and a reduced muscle mass lead to a reduced creatinine production, therefore their serum creatinine levels may appear normal [7, 10].

Protein binding and kinetics of drugs in liver disease Reduced serum protein concentrations will lead to an increased free fraction of highly protein bound drugs. Effects, adverse effects and toxicity will be increased [7, 10].

1.4.2 Measuring Liver Insufficiency

There are many causes of liver disease (see examples in Table 2). Regardless of the aetiology, a sufficient description of the severity of the liver insufficiency is necessary in every case.

Table 2: *Some Liver Diseases [17].*

Gilbert syndrome	Dubin-Johnson syndrome	Viral hepatitis A, B, C, D, E
Sarcoidosis	Tuberculosis	Primary biliary cirrhosis
Autoimmune hepatitis	α_1 Antitrypsin deficiency	Wilson disease
Acute alcoholic hepatitis	Steatohepatitis	Drug-induced liver disease
Ischemic hepatitis	Portal vein thrombosis	Hepatocellular carcinoma
Metastatic tumors	Abscess	Cysts

Measuring liver insufficiency is difficult. Other than in kidney failure, there is no endogenous marker to evaluate the hepatic clearance. Easy to use clinical tests for testing the residual liver function are not yet available either [7, 10].

The golden standard in the evaluation of liver disease is liver biopsy [17]. However, it is an intricate and invasive procedure which is associated with a number of side effects, e.g. bleeding in patients with reduced synthesis of blood clotting

factors. Another disadvantage is the relatively long processing time. Therefore it is important to have a fast and secure test to evaluate liver insufficiency.

A typical battery of blood tests may include levels of serum alanine and aspartate aminotransferases (ALT and AST), alkaline phosphatase, direct and total serum bilirubin, albumin and the assessment of prothrombin time [17].

Today, a modified Child-Pugh score [17] is frequently used to estimate the severity of liver function impairment, though it only offers a vague idea of the severity of liver disease. Nevertheless, it includes the main parameters that influence the reduction of liver metabolism (see Table 3).

Although the Child-Pugh classification has recently been replaced by the model for end-stage liver disease (MELD) score, there is a lot more literature based on the Child-Pugh classification.

Table 3: *Child-Pugh Classification of Cirrhosis [17].*

Factor	**Units**	**1**	**2**	**3**
Serum bilirubin	μmol/L	<34	34–51	>51
	mg/dL	<2.0	2.0–3.0	>3.0
Serum albumin	g/L	>35	30–35	<30
	g/dL	>3.5	3.0–3.5	<3.0
Prothrombin time	seconds prolonged	0–4	4–6	>6
	INR	<1.7	1.7–2.3	>2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5–15. Child-Pugh class is either A (a score of 5–6), B (7–9), or C (10 or above). Decompensation indicates cirrhosis with a Child-Pugh score of 7 or more (class B).

2 Material and Methods

A systematic search was performed until March 2011 using *PubMed*, *EMBASE* and *Google Scholar*. The following strings have been used to identify english and german literature: *liver insufficiency*, *liver impairment* and *liver failure*, in combination with each substance name, respectively. After identifying relevant articles, the reference lists of all articles were manually inspected for further relevant references that might not have been found in the primary search.

Additionally, relevant handbooks on pain therapy were reviewed.

3 Results

3.1 Non-Opioids

3.1.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are intensively used in the therapy of mild to moderate pain. Their effects and side-effects consist in the inhibition of the cyclooxygenase (COX). Two isoenzymes were identified so far: the 'constitutive' COX-1 and the 'inducible' COX-2 [18]. NSAIDs have a very high plasma protein binding, a very low volume of distribution and are eliminated via biotransformation in the liver [19].

NSAIDs are known to cause liver injury and liver failure [5, 18, 20–23]. The epidemiological risk to develop clinically apparent liver injury is 1–8 cases per 100,000 patient years of NSAID use [21]. All NSAIDs can cause liver injury [21].

Elevated liver enzymes in patients during NSAID therapy are common (up to 15%) [5] and generally settle within 4–6 weeks after cessation of the drug [21]. Incidents of liver injury most commonly happen within the first 6–12 weeks of NSAID therapy [21].

Health care professionals and patients with chronic liver disease should be permanently aware of the risks of NSAID therapy [20] and should stop NSAID therapy when pathological liver function tests occur [5]. Subjects which develop NSAID induced liver toxicity should stop taking NSAIDs permanently [21].

Diclofenac

Diclofenac has analgesic and antipyretic effects and is well absorbed from the gastrointestinal tract. It has a short half-life of about 1.5 hours. Diclofenac is bound extensively to plasma albumin [24], metabolised in the liver to glucoroconjugated and sulphate metabolites [24] and is eliminated via the urinary system [24, 25].

In the presence of liver disease, dosage adjustments may not be necessary [24].

Diclofenac is known to cause the most cases of liver injury within NSAIDs [21], accounting for approximately 1–5 cases per 100,000 persons taking diclofenac [20]. Banks et al. [26] investigated 180 cases that were associated with diclofenac-induced liver injury. Therefore, diclofenac should used carefully in the presence of liver disease and discontinued if elevated liver enzymes occour.

Ibuprofen

After oral administration, ibuprofen is absorbed completely and binds extensively to plasma albumin [27]. Ibuprofen undergoes hepatic metabolism and the glucuronide conjugate metabolites are excreted in the urine [27].

Ibuprofen is relatively safe, although some cases of ibuprofen-induced hepatotoxicity have been reported [20, 28].

3.1.2 Preferential Inhibitors of COX-2

Meloxicam

Meloxicam is completely absorbed after oral administration and highly bound ($>$ 99.5%) to plasma proteins [29]. The drug is metabolised in the liver to four inactive main metabolites. The elimination half-life of meloxicam is approximately 20 hours [29, 30].

In the presence of liver failure, there is no need for dose adjustments in mild to moderate (Child-Pugh I–II) hepatic impairment [31]. There is no data in severe (Child-Pugh III) hepatic impairment [31].

Nimesulide

Nimesulide is a selective COX-2-inhibitor. After oral administration, the drug is rapidly absorbed [32]. The drug undergoes pre-systemic first-pass metabolism, resulting in an oral bioavailability of about 54–65%, which is similar to rectal administration [32]. The volume of distribution is 0.18–0.39 L/kg, elimination half-life is 1.8–4.73 hours [32]. Nimesulide is extensively bound to plasma proteins (99%), mainly albumin [32]. Its major metabolite is the 4'-hydroxy derivate [32].

The pharmacokinetics of nimesulide are significantly altered in the presence of liver insufficiency: the elimination of the parent drug and the metabolite is reduced and this requires a 4–5-times dose reduction in patients with hepatic insufficiency [32].

Several cases of liver injury have been reported during nimesulide therapy [33–38]. Therefore, regular liver tests are recommended.

3.1.3 Selective Inhibitors of COX-2

Celecoxib

Celecoxib is moderately absorbed after oral administration and extensively bound to plasma albumin [39]. Its apparent volume of distribution is 455 ± 166 L, the elimination half-life approximately 11 hours [39]. Celecoxib is metabolised in the liver by CYP2C9, its metabolites are eliminated via the urine and the faeces [39].

In the presence of liver insufficiency, the steady-state plasma concentration is *increased by approximately 40% and 180% in patients with mild and moderate hepatic impairment, respectively* [39].

Etoricoxib

Etoricoxib is a selective inhibitor of the COX-2 and moderately absorbed after orally administration [40]. It is highly bound to plasma albumin [40]. Its volume of distribution is 120 L, the elimination half-life is approximately 20 hours after a single dose [40]. Etoricoxib is metabolised in the liver via CYP3A4 and excreted via the biliary and urinary system [40].

Agrawal et al. [41] investigated the effects of liver insufficiency on etoricoxib metabolism after single and multiple oral and intravenous doses and recognised that neither absorption, nor binding to plasma proteins is affected by hepatic disease. Patients with mild (Child-Pugh score of 5–6) and moderate liver insufficiency (Child-Pugh score of 7–9) tolerated etoricoxib well. However, a decreased systemic clearance was recognised. The authors suggest a *60 mg once-daily dosing regimen for mild hepatic insufficiency patients and a 60 mg every-other-day dosing regimen for moderate hepatic insufficiency patients.* [41]. There is no data for subjects with Child-Pugh score > 9.

Rofecoxib

Rofecoxib is a selective COX-2 inhibitor with a high bioavailabiliy [42]. It is metabolised in the liver via O-glucuronidation by uridine diphosphate-glucuronosyl transferase (UGT) 2B7 and 2B15 [42].

The metabolism of rofecoxib might be altered in the presence of liver insufficiency, however, no concrete data has been identified to guide dosage adjustments in such cases.

3.1.4 Metamizole

Metamizole (dipyrone) undergoes hepatic first-pass effect. The bioavailability of the resulting active metabolite moiety 4-methyl-amino-antipyrine (MAA) is 85% [43]. The elimination half-life of MAA is 2.6 to 3.5 hours [43]. MAA is further metabolised into 4-formyl-amino-antipyrine (FAA) and to 4-amino-antipyrine (AA). AA is further metabolised into 4-acetyl-amino-antipyrine (AAA) [43].

No recommendations of metamizole administration in the presence of liver insufficiency have been identified.

3.1.5 Paracetamol/Acetaminophen

In the USA, the UK and in Sweden the most common cause of acute liver failure is caused due to acetaminophen intoxication [22, 44].

Acetaminophen is metabolised in the liver. About 85–90% of the parent drug is inactivated by glucuronidation and sulfatation [45]. About 5% of the parent drug is eliminated unchanged in the urine[45]. The remaining 5–10% of the parent drug is oxidated by CYP-enzymes to reactive electrophile N-acetyl-p-benzoquinoneimine (NAPQI) [45]. NAPQI is normally inactivated by conjugation with glutathione, however, in overdose of paracetamol, NAPQI binds covalent to liver cell proteins, leading to hepatotoxic effects and end in tissue necrosis [5, 45–47].

Although normal doses of acetaminophen do not alter liver function in patients with chronic liver disease [46], it should be used very carefully in the presence of liver disease. Murphy [5] recommends reducing acetaminophen dosage in the presence of cirrhosis and avoiding it in moderate to severe liver failure.

3.2 Opioids

3.2.1 Weak Opioids

Codeine

Codeine is used for mild to moderate pain. After oral administration, the drug is well absorbed, about 50% undergo first-pass-metabolism in the gut and liver [51]. Codeine is metabolised in the liver via three pathways: glucuronidation (major pathway), N-demethylation to norcodeine via CYP3A (10–20%) and O-demethylation to morphine via CYP2D6 (5–15%) [51]. The active metabolite morphine is responsible for the analgesic effect and underlies inter-individual variations due to the known genetic metabolism of CYP2D6 [51].

No literature was found for dosage adjustments in the presence of liver insufficiency, therefore codeine should currently be avoided when liver disease is present [5].

Dihydrocodeine

Dihydrocodeine underlies hepatic first-pass metabolism; the bioavailability after oral administration is about 20%, half-life is 3.3–4.5 hours [65]. Dihydrocodeine is metabolised in the liver to dihydrocodeine glucuronide (27.7%), nordihydrocodeine (15.8%), nordihydrocodeine glucuronide (6.3%) dihydromorphine (0.5%) and dihydromorphine glucuronide (8.4%) [65].

Tegeder et al. suggest using dihydrocodeine with caution in the presence of liver insufficiency due to an increased bioavailability and reduced elimination of the drug [65].

Tramadol

Tramadol is a synthetic opioid analgesic with weak binding to μ-opioid-receptors and reuptake inhibition of serotonin and noradrenaline neurotransmitters [77–79].

Tramadol is rapidly absorbed, the bioavailability after oral administration is about 55–75% [74, 75]. The terminal half-life after peroral adminstration is 5.1–5.5 hours, after intravenous administration 5.2 hours [74, 75]. The drug is metabolised in the liver via N- and O-demethylation and conjugation of O-demethylated compounds to 11 metabolites [80]. Only mono-O-demethyl-tramadol is an active metabolite [3, 5].

Table 4: *Pharmacokinetics of Opioids in Healthy Adults.*

Substance	Common Application	Oral Bioavailability	$t_{\frac{1}{2}}\beta$	Protein Binding	Volume of Distribution	References
Alfentanil	iv		70–94 min	92%	0.86 L/kg	[48–50]
Buprenorphine	sl	50–55%	4–7 h	96%	100–300 L	[3]
Codeine	po, r, im	12–84%	3–3.5 h		3.6 L/kg	[51]
Fentanyl	iv, po, td		219–495 min	84%	4 L/kg	[6, 48, 50, 52, 53]
Hydromorphone	po, iv, im, sc, spinal	12.5–78%				[54]
Methadone	po		4.2–130 h	80%		[55]
Morphine	po, iv, im	15–50%	1.5–4.5 h	20–60%	1–4.7 L/kg	[3, 53, 56–59]
Nalbuphine	po, iv	11.8%	3.7 h			[60]
Oxycodone	po (IR, CR), iv	60–87%	2–8 h	45%	2–3 L/kg	[61–63]
Oxymorphone	po	10%				[64]
Pethidine	po	48–57%	3–7 h	60–80%	2.8-5 L/kg	[3, 53, 65, 66]
Piritramide	po		1–8 h		4.7 L/kg	[67, 68]
Remifentanil	iv		6–48 min	70–92%	0.2–0.4 L/kg	[3, 53, 69, 70]
Sufentanil	iv		1–2.7 h	92.5%	2.9–3.3 L/kg	[50, 53, 71, 72]
Tilidine Nortilidine	po (metabolite)	6% 99%	 3.3–4.9 h			[73] [73]
Tramadol	po, iv, r, im	55–75%	5.1–5.5 h		216 L	[74–76]

$t_{\frac{1}{2}}\beta$ = elimination half-life iv = intravenous sl = sublingual po = peroral td = transdermal r = rectally IR = immediate release CR = controlled release h = hour(s) min = minute(s) L = litre(s) kg = kilogramme(s)

In the presence of severe liver insufficiency, tramadol should be carefully administered: only 50 mg immediate release formulation should be used and dosage intervals should be extended [5].

3.2.2 Strong Opioids

Alfentanil

Alfentanil is a short-acting synthetic opioid [81] with an initial plasma elimination rate of 90% within the first 30 minutes after intravenous application [48]. Its potency is 30–40-times that of morphine and 0.2-times that of fentanyl [53]. The distribution of alfentanil is very rapid and the terminal half-life is between 70 min [49] and 94 [48]. The plasma protein binding of alfentanil is 92%, the volume of distribution is 0.86 L/kg [48, 49]. Alfentanil is mainly bound to human α_1-acid glycoprotein (AAG).

Alfentanil undergoes hepatic metabolism and is a substrate of different cytochrome P4503A enymes [81, 82]. The two major pathways via CYP3A4 form noralfentanil and N-phenyl-propionamide [81]. None of those are significantly active metabolites [5]. In addition to CYP3A4, alfentanil is a substrate for CYP3A5 and CYP3A7 (CYP3A4 $\geqslant$ CYP3A5 $\gg$ CYP3A7) [81]. Alfentanil is a poorly to intermediately extracted drug [83].

Ferrier et al. [84] investigated alfentanil pharmacokinetics in 11 patients with cirrhosis. It turned out that the clearance of alfentanil was significantly reduced in patients with cirrhosis (1.6 ± 1.0 mL/min/kg) compared to the control group (3.1 ± 1.6 mL/min/kg). The elimination half-life was prolonged from 90 ± 18 minutes in the control group to 219 ± 128 minutes in patients with cirrhosis. The total apparent volume of distribution was similar in both groups. Although the AAG-concentration in the plasma did not differ in the two groups, patients with cirrhosis had a higher plasma-free-concentration than the control group. Ferrier et al. assume that a change in the binding sites of the protein occurs in patients with cirrhosis, impairing plasma protein binding. They concluded that the administration of alfentanil in cirrhotic patients would result in a prolonged and pronounced effect of the drug.

In contrast, Belpaire et al. found that, in patients with cirrhosis, AAG- and albumin concentrations were decreased, thus increasing plasma concentration of alfentanil [85].

Nevertheless, the use of alfentanil is generally considered be safe in the presence of liver insufficiency [5].

Buprenorphine

Buprenorphine is a partial μ-receptor agonist with antagonistic effects on κ-receptors [3]. Given orally, buprenorphine is highly metabolised in the liver and the bioavailibility is too little [3]. Given sublingually, it has a bioavailability of 50–55% [3]. Approximately two-thirds of buprenorphine are not metabolised and eliminated directly by the biliary system via the feces. The remaining third is metabolised via CYP3A4 [86]. Norbuprenorphine, buprenorphine-3-glucuronide and norbuprenorphine-glucuronide are the major metabolites of buprenorphine and are eliminated via the biliary system and the kidneys [86]. Norbuprenorphine is an active metabolite (about 1/40 potency of the parent drug) [3]. Buprenorphine binds in 96% to α- and β-globulins [3, 86]. The half-life of buprenorphine is about 4–7 hours, the volume of distribution is about 100–300 L [3].

In hepatic impairment, the half-life of buprenorphine is prolonged, which is of low clinical relevance [86].

In 2009, Zuin et al. [87] described a case report of acute liver and kidney failure in a patient with previously latent hepatitis C chronic infection following a recommended doses of buprenorphine. Both organs recovered after the suspension of the treatment with buprenorphine. Zuin et al. connected the liver and kidney impairment to the drug treatment.

Murphy [5] found no evidence to guide treatment in the presence of liver failure. Pergolizzi et al. [86] identified buprenorphine as *top-line choice for opioid treatment in the eldery*.

Fentanyl

Fentanyl, a strong synthetic opioid, is 70- to 100-times as potent as morphine [53]. It is very popular and can be administered intravenously, orally and transdermally [88]. About 84% of fentanyl is bound to plasma proteins [48, 50], its half-life is 219–495 minutes [48], and the volume of distribution is 4 L/kg [48]. Fentanyl is subject to high hepatic extraction [5]. CYP3A4 is responsible for the metabolism of fentanyl, the main inactive metabolite is norfentanyl [5, 89].

Haberer et al. [52] compared fentanyl pharmacokinetics in anaesthetized patients with cirrhosis and patients without cirrhosis. In patients without cirrhosis, the average elimination half-life was 263 minutes, the total plasma clearance was 10.8 mL/min/kg and the total apparent volume of distribution was 3.81 L/kg. No significant change was observed in patients with cirrhosis: $t_{\frac{1}{2}}\beta$ was 304 minutes, clearance was 11.3 mL/min/kg and the volume of distribution was 4.41 L/kg. They concluded that the elimination half-life of fentanyl is not primarily influenced by the hepatic metabolism. McClain and Hug suggested earlier [90], that this effect is better reflected by its slow release from tissue depots than its hepatic elimination.

Murphy [5] found that fentanyl clearance is likely impaired by hepatic failure and would require dosage reduction, but I did not find any conclusive data or specified dosage guidelines.

Hydromorphone

Hydromorphone is a semi-synthetic μ- and δ-opioid-receptor agonist, and a derivate of morphine [5, 54]. After oral administration, hydromorphone is absorbed in the upper small intestine and extensively metabolised in the liver [54]. The two major metabolites are hydromorphone-3-glucuronide and dihydroisomorphine glucuronide [54].

Liver insufficiency leads to higher plasma concentrations of hydromorphone after oral administration due to a reduced first-pass effect [5, 91]. However, no dosage guidelines for hydromorphone administration in the presence of liver insufficiency have been identified.

Methadone

Methadone is an oral synthetic opiate agonist [92] with a high oral bioavailability (about 80%) and a long half-life [5, 55]. Methadone is highly bound to AAC [55]. The drug is metabolised in the liver and undergoes N-demethylation [92]. Methadone metabolism underlies significant interindividual variation and therefore, plasma elimination half-life varies from 4.2–130 hours [55].

Novick et al. [93] examined 14 patients with liver disease and five healthy subjects. The authors separated them into four groups: control group, mild liver disease, moderate liver disease and severe liver disease (viral hepatitis, cholestasis,

alcoholic hepatitis, fatty infiltration). Patients with cirrhosis too severe to permit liver biopsy, acute severe hepatitis and fulminant hepatic failure were not part of the study. The authors found a prolonged half-life after oral methadone administration in patients with severe chronic liver disease only. All other kinetic indices remained similar to the control group. The authors concluded that the maintenance dosage of methadone in patients with mild or moderately severity does not need to be changed in stable chronic liver disease, but modest decrease in the methadone maintenance dose may be indicated for patients with severe liver disease.

Kanchana et al. [92] investigated orthotopic liver transplantation (OLT) in patients with methadone maintenance treatment (MMT) with end stage liver disease (ESLD). They suggest that it is not necessary to wean off methadone before OLT. Liu et al. [94] found, that following OLT treatment the same dosage of methadone should be used as before the treatment. However, Murphy [5] said that methadone is contraindicated in the presence of severe liver disease.

These data show that dosage adjustments are not precise and need further investigations.

Morphine

Morphine was first isolated from opium in 1806 by Sertürner [95]. It is a strong agonist at the μ-receptor.

The drug is hydrophilic and is subject to phase-II-reaction (glucuronidation) without oxidation [4]. Its major metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is analgetic as well [4]. M3G and M6G are excreted via the kidneys [58]. Oral morphine is known to undergo clinically important first-pass metabolism in the liver and is bound to plasma proteins, mainly albumin and to a lesser extent to γ-globulin [96].

Table 4 on page 14 gives an overview of the most important pharmacokinetics in patients with normal liver function.

Literature investigating the effect of liver insufficiency and morphine metabolism is not clear. Patwardhan et al. [97] found that the systemic clearance and elimination half-life were similar in cirrhotic patients and in a group of healthy volunteers. In contrast, Mazoit et al. [98], Crotty et al. [99], Hasselstrom et al. [56] and Kotb et al. [57] proved decreased systemic clearance and impaired extraction in patients

Table 5: *Studies that Investigated the Effects of Liver Insufficiency to Morphine Pharmacokinetics.*

	normal		**impaired**		
Study	$t_{\frac{1}{2}}\beta$	bioavailability	$t_{\frac{1}{2}}\beta$	bioavailability	**Reference**
Patwardhan et al.	*no differences* of systemic clearance and elimination half-life in cirrhotic patients and healthy volunteers; disposition and elimination of morphine were unaffected by moderate to severe cirrhosis				[97]
Mazoit et al.	111 min		201 min		[98]
	6 normal and 8 cirrhotic subjects; volume of distribution did not differ; cirrhotic patients had a prolonged terminal half-life of unchanged morphine and a decrease in total body clearance				
Crotty et al.	decreased systemic clearance and impaired extraction were found; reduction of 25% of extraction ratio compared with healthy subjects				[99]
Hasselstrom et al.	3.3 h	47%	5.5 h	101%	[56]
	8 patients with alcoholic cirrhosis, 6 male patients with cancer and normal liver and renal function; elimination half-life increased in cirrhotic patients, mean oral bioavailability in cirrhotic patients increased				
Kotb et al.	4.01 h	18%	7.36 h	27.7%	[57]

$t_{\frac{1}{2}}\beta$ = elimination half-life h = hour(s) min = minute(s)

with liver impairment. Table 5 summarises the outcomes of these studies.

In his review, Morphy concluded that *morphine use in hepatic failure does not appear to have been usefully studied* [5].

Nalbuphine

Nalbuphine is a semi-synthetic opioid that undergoes extensive hepatic first-pass metabolism [60]. Bioavailability after oral administration is 11.8%, elimination half-life after intravenous application is 3.7 hours [60].

No publications for nalbuphine administration in the presence of liver insufficiency have been identified.

Oxycodone

Oxycodone is a semi-synthetic opioid μ- and κ-receptor-agonist [62, 63]. Oral bioavailability is 60–87% [61], the volume of distribution 2–3 L/kg [63]. The elimination half-life depends on the application route and is 2–3 hours after intravenous, 3 hours after immediate release (IR) oral and 8 hours after controlled-release (CR) oral administration [63]. The drug binds mainly to albumin (45%) [62, 63].

Oxycodone undergoes hepatic metabolism mainly via two pathways: CYP3A4 catalyses the formation of the main metabolite noroxycodone, CYP2A6 the formation of oxymorphone. Noroxycodone is further metabolised via CYP2D6 to noroxymorphone, and oxymorphone is further metabolised via CYP3A4 to noroxymorphone [12, 62, 63, 100, 101].

Tallgren et al. [12] examined six volunteer patients with end stage liver disease before and after liver transplantation. They found an altered mean elimination half-life of oxycodone before (13.9 hours) and after transplantation (3.4 hours). They concluded that the elimination of oxycodone is severely impaired in patients with cirrhosis.

Kaiko [102] found a prolongation of 2 hours of the elimination half-life of oxycodone. He recommends to start oral oxycodone therapy with the usual dose [102].

Oxymorphone

Oxymorphone is a semi-synthetic opioid receptor agonist. It has an oral bioavailability of about 10%. Oxymorphone is subject of liver metabolism. Its main metabolites are oxymorphone-3-glucuronide and the active 6-hydroxyoxymorphone [64].

No dosage guidelines for oxymorphone administration in the presence of liver insufficiency have been identified.

Pethidine/Merperidine

Pethidine is a synthetic opioid agonist that is highly metabolised by the liver. Bioavailability after oral administration is 50%, elimination half-life is 3.5 hours and volume of distribution is 3–5 L/kg [65]. About 60–80% of the drug is bound to plasma proteins, mainly AAG [65]. Pethidine is metabolised to meperidinic acid and the active metabolite norpethidine [5, 65]. Elimination half-life of norpethidine is longer than that of pethidine (12–24 hours) [65].

The usage of pethidine in the presence of liver insufficiency is not well studied. Pond et al. [66] investigated patients with alcoholic cirrhosis and age-matched healthy subjects treated with oral and parenteral pethidine. The mean bioavailability in the healthy subjects was 57%, in the patients with cirrhosis 80%. Terminal half-life was 6.4 hours in healthy subjects, and 10.9 hours in the presence of cirrhosis. The volume of distribution remained similar. The authors recommend to use 50–75% of the normal oral dose only in the presence of liver insufficiency. In intravenous treatment, they recommend no dosage adjustments in single application. In multiple doses they recommended to prolong the dosage interval by factor two or reduce the dose by 50%.

Danziger et al. [103] described a case report of meperidine-associated central nervous system excitatory toxicities in a patient with alcoholic hepatitis and normal renal function. The authors recommended avoiding the administration of multiple doses of meperidine in patients with hepatic disease.

Piritramide

Piritramide is a synthetic μ-receptor opioid agonist and is eliminated from the body via hepatic metabolism [67]. The substance is lipophilic [68].

The elimination half-life of piritramide is 1–8 hours [67, 68], and the volume of distribution is 4.7 L/kg [67].

No data was found concerning the usage of this drug in the presence of liver insufficiency.

Remifentanil

Remifentanil, a relatively new synthetic opioid, is a potent selective μ-opioid receptor agonist [69, 82]. It is approximately 20–30 times more potent than alfentanil [53, 104, 105].

After intravenous application, it is bound to plasma proteins by 92% [3]. In contrast to fentanyl, alfentanil or sufentanil, remifentanil does not undergo hepatic metabolism. It is metabolised by nonspecific circulating and tissue esterases, resulting in very rapid elimination of the drug [3, 69, 82].

The major metabolic product of remifentanil is GR90291. Its analgesic potency is only 1/300 to 1/1,400 of the activity of remifentanil [3, 104]. The half-life of remifentanil is 10–20 min, the half-life of GR90291 is 88–137 min [3].

Dershwitz et al. [104] found no differences of pharmacokinetics of remifentanil and GR90291 in patients with severe, chronic liver disease. Navapurkar et al. [70] investigated the pharmacokinetics of both remifentanil and GR90291 in six adult patients undergoing orthotopic liver transplantation and also recognised a significant extrahepatic metabolism of remifentanil.

Therefore remifentanil may be an appropriate opioid in the therapy of patients with severe hepatic failure, with no need for dosage adjustments.

Remifentanil seems to be an ideal opioid in the presence of liver insufficiency, although its usage requires a clinical setting [5].

Sufentanil

Sufentanil is a very strong lipophilic analgesic (μ- and κ-receptor agonist), and has 5- to 10-times the potency of fentanyl [53].

Examinations in 10 surgical patients showed an average elimination half-life of 164 ± 22 minutes [71]. The volume of distribution is 2.86 L/kg [71].

92.5% of sufentanil is bound to plasma proteins, mainly α_1-glycoprotein [50, 72].

Sufentanil undergoes hepatic metabolism. CYP3A4 was identified to be responsible for N-dealkylation of the drug. The main metabolites are norsufentanil and SM6 [89]. None of the two is active [5]. Sufentanil has a high plasma clearance, the elimination is mainly limited by the hepatic blood flow [72, 89].

Continuous infusion of sufentanil can lead to accumulation [82], however, uncomplicated cirrhosis does not affect the metabolism of the drug [5, 72].

Tilidine/Naloxon

Tilidine is a prodrug. Its active metabolite is nortilidine, which is formed in the liver by demethylation [73]. The second active metabolite is bisnortilidine. Tilidine and nortilidine are mainly eliminated by the liver [73].

Tilidine is administered orally in combination with naloxone to avoid intravenous abuse. In the presence of liver insufficiency, the conversion of tilidine to nortilidine, and the elimination of naloxone are reduced [3]. Therefore, the use of another opioid might be indicated [3].

3.3 Co-Analgesics

3.3.1 Antidepressants

Amitriptyline

Amitriptyline, a tricyclic antidepressant, is N-demethylated in the liver to the active metabolite nortriptyline [106]. Both substances are further metabolised by CYP2D6 [106].

No dosage guidelines in the presence of liver insufficiency have been identified, however, there is one report associated with liver failure and the administration of amitriptyline [107].

Duloxetine

Duloxetine is a potent serotonin and norepinephrine reuptake inhibitor with a half-life of about 12.5 hours [108]. The drug is rapidly metabolised in the liver; its major

metabolite is 4-hydroxy duloxetine, followed by 5-hydroxy-6-methoxy duloxetine and four other metabolites with less plasma concentration [108].

No dosage guidelines in the presence of liver insufficiency have been identified, however, there is one report associated with liver failure and the administration of duloxetine [109].

3.3.2 Anticonvulsants

Carbamazepine

65–85% of carbamazepine is bound to plasma albumin and AAG [110]. It undergoes hepatic metabolism via the cytochrome P450 system [111] and has a single active metabolite – carbamazepine-10,11-epoxide [110–112].

Carbamazepine administration is associated with asymptomatic elevations of liver enzymes in 5–10% [113]. Furthermore, carbamazepine is associated with idiosyncratic drug induced liver injury (DILI) [113]. Bjornsson et al. [113] recommended discontinuation of the drug immediately when abnormal elevations of liver enzymes occur.

Carbamazepine is contraindicated in the presence of severe hepatic impairment [5].

Gabapentin

Gabapentin has a dose dependent bioavailability of about 60%, a volume of distribution of about 0.8 L/kg and an elimination half-life of about 5–7 hours [114]. The mechanism of action is unknown [114]. The drug does not undergo hepatic metabolism [114]; therefore, dosage adjustments in the presence of liver insufficiency may not be necessary.

Murphy concluded that gabapentin is probably the safest choice in the group of anti-convulsants when liver insufficiency is present [5].

Lamotrigine

Lamotrigine has 98% bioavailability, 0.9–1.3 L/kg volume of distribution, 12–59 hours elimination half-life [114]. Although the precise mechanism of action is unknown,

a direct inhibition of voltage-sensitive sodium channels is proposed [114]. Lamotrigine is metabolised into 2-N-glucuronide conjugate mainly by glucuronic acid conjugation [114].

The effects of liver insufficiency on lamotrigine metabolism have not been studied sufficiently. However, several cases of lamotrigine related liver insufficiency have been reported [115–121].

Pregabalin

Pregabalin is a potent ligand for the α-2-δ subunit of voltage-gated calcium channels [122]. It has a high bioavailability, a half-life of about 6.3 hours and does not bind to plasma proteins [122]. Pregabalin is not metabolised in the liver; therefore, no adjustments in dosage are necessary in the presence of liver insufficiency [122].

Topiramate

After oral administration, topiramate is rapidly absorbed, its bioavailability is about 80% [123]. The drug is 13–17% bound to plasma proteins, the apparent volume of distribution is 0.6–0.8 L/kg [123]. Topiramate is not metabolised extensively, 70% of the drug is eliminated unchanged via the kidneys [123]. No active metabolites have been identified.

Liver insufficiency does not extensively affect the metabolism of topiramate. Plasma concentrations are increased by 29% in patients with moderate to severe liver disease [123].

Valproic Acid (VPA)

VPA is rapidly absorbed in the gastrointestinal tract and highly bound to plasma proteins [124, 125]. The volume of distribution is 0.1 to 0.4 L/kg [124], the elimination half-life is 10–16 hours [124]. VPA underlies excessive hepatic metabolism via glucuronidation, β-oxidation and ω-oxidation. Its main metabolite is 3-oxo-valproic acid [124].

VPA administration is associated with liver injury for which several case reports and reviews have been published [126–131]. Elevated liver tests occur in 44% of

the subjects [113], however, hepatic fatalities associated with VPA therapy occur only in 1/49,000 cases [128].

Murphy recommended avoiding VPA in patients with known liver disease [5].

3.3.3 Corticosteroids

Tanner and Powell [132] reviewed the use of corticosteroids, especially prednisone, in the presence of liver disease: prednisone is metabolised in the liver to its active metabolite prednisolone. Patients with impaired liver function showed lower prednisolone serum levels than controls, increased unbound drug in the serum and decreased elimination of the active metabolite [132]. The authors assume that the impaired conversion of prednisone in severe liver insufficiency may be compensated by the decreased protein binding and the decreased elimination of the drug [132]. These findings suggest that the therapeutic efficacy of prednisone may not be influenced in the presence of severe liver insufficiency [132].

These findings are similar to the data of Uribe et al. [133]: the authors identified alterations in elimination half-life and serum protein binding of corticosteroids in the presence of chronic and acute liver disease and examined the correlation between the albumin concentration and the concentration of unbound prednisolone in patients with liver disease and in healthy subjects. Based on the significant correlation of increased free prednisolone and reduced albumin plasma levels, the authors suggest dosage adjustments according to serum albumin concentrations [133].

3.3.4 Ketamine

Ketamine is a NMDA receptor antagonist, that is administered orally, rectally or intravenously [134, 135]. It is subject of hepatic first-pass metabolism. Multiple metabolites have been identified [135]. The most important active metabolite is norketamine, which is one third as potent as ketamine [135]. Elimination half-life of ketamine is 2.17 hours [135].

No data on dosage adjustments in the presence of liver insufficiency have been identified.

3.3.5 Cannabinoids

Cannabinoids are a heterogeneous group of substances. The most commonly abused drug worldwide is *Cannabis sativa*, which contains over 60 cannabinoids [136]. Its primary psychoactive component is $\triangle^9$-tetrahydrocannabinol (THC) [136]. The main metabolites of THC are 11-hydroxytetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy- tetrahydrocannabinol (THC-COOH), both of them are psychoactive; cannabidilol (CBD) is a non-psychoactive agent [136].

Cannabinoids are acting primarily via CB1 and CB2 receptors, which are found mainly in the brain (CB1) and cells of the immune system (CB2) [137]. Interestingly, both CB1 and CB2 receptors are upregulated in the early stages of liver injury; their role as possible tool for treatment is subject of current research [137].

THC is metabolised in the liver as well as in other tissues (brain, intestine and lung) [136].

No data on dosage adjustments in the presence of liver insufficiency have been identified.

4 Discussion

Pain management in the presence of liver insufficiency remains a clinical challenge. Although most substances described in this review have been examined in the presence of liver disease, there is a lack of evidence based dosage guidelines according to the severity of liver insufficiency.

Comparing the effects of liver insufficiency on drug metabolism is very difficult. Large variations in study design, definition of liver impairment, disease aetiology and co-medication result in incomparableness of the studies.

Non-Opioids

Table 6 on page 30 gives an overview on the use of non-opioid-analgesics in the presence of liver insufficiency.

NSAIDs are known to cause liver injury and liver failure [5, 18, 20–23], therefore the liver function of subjects with liver disease should be close meshed monitored. Prescription of the drug should be stopped immediately when liver function gets worse.

Diclofenac has the greatest risk to cause liver injury [21], but may be prescribed carefully in the presence of liver insufficiency. Ibuprofen, meloxicam, nimesolide and etericoxib can be used with care. Nimesolide should be administered only for a short period of time [138]. Paracetamol should be avoided in the presence of moderate to severe liver failure [5].

Opioids

Table 7 on page 31 gives an overview on the use of opioids in the presence of liver insufficiency.

The use of alfentanil, dihydrocodeine, fentanyl, pethidine, remifentanil, sufentanil and tramadol is relatively safe. Remifentanil seems to be the best choice, how-

ever its fast metabolism requires clinical settings.

Codeine, methadone, oxycodone and tilidine should be avoided.

Co-Analgesics

Table 8 on page 32 gives an overview on the use of co-analgesics in the presence of liver insufficiency.

Pregabalin and gabapentin are not metabolised in the liver, and are therefore safe in the presence of liver insufficiency. Carbamazepine and VPA are contraindicated and should not be used in subjects suffering of liver insufficiency. There is no adequate data available to give recommendations for amitriptyline, duloxetine, lamotrigine, topiramate, corticosteroids or ketamine.

Perspective

In order to evaluate the effects of liver insufficiency on drug metabolism, further investigation in this field is necessary. Therefore, a standardised definition and evaluation of liver insufficiency is essential. The Child-Pugh-Classification might be a proper tool to grade the severity of the disease.

Since the available literature is hardly comparable, pain treatment in patients suffering liver insufficiency remains highly dependent on the physician's clinical experience.

Table 6: *Recommendations for the Usage of Non-Opioids in the Presence of Liver Insufficiency.*

Substance	In LI	Comment	Ref.
Diclofenac	✓	No dosage adjustments necessary. Be aware of potential liver injury.	[21, 24]
Ibuprofen	✓	Relatively safe. No data on dosage adjustments. Avoid in severe liver disease.	[6, 20, 28, 139]
Meloxicam	✓	No need for dosage adjustments in Child-Pugh A and B, no data in Child-Pugh C.	[31]
Metamizole	∅	No data has been identified.	
Nimesolide	▽	Administration possible, 4–5-times dosage reduction necessary. Be aware of for the risk of liver injury, regular liver blood tests recommended. Avoid prolonged use.	[32, 138]
Etoricoxib	▽	In Child-Pugh A: 60 mg once-daily. In Child-Pugh B: 60 mg every other day. No data in Child-Pugh C.	[41]
Celecoxib	▽	Decreased metabolism in LI. Reduce dose by 50% in Child-Pugh B, avoid in Child-Pugh C.	[6, 39]
Rofecoxib	∅	Drug metabolism may be altered. No data on dosage adjustments.	
Paracetamol	▽	Reduce dosage in cirrhosis. No changes necessary in mild liver failure. Avoid in moderate to severe liver failure.	[5, 6]

✓ = recommended ▽ = adjustments recommended × = not recommended ∅ = no data available LI = Liver Insufficiency IR = Immediate Release

Table 7: *Recommendations for the Usage of Opioids in the Presence of Liver Insufficiency.*

Substance	In LI	Comment	Ref.
Alfentanil	▽	Reduce dosage, use with care.	[3–5]
Buprenorphine	∅	Little data available. Top line medication in the elderly.	[86]
Codeine	×	Avoid in the presence of LI.	[3, 5, 140]
Dihydrocodeine	▽	Use with caution.	[65]
Fentanyl	✓	No significant change in metabolism. Use carefully in continuous infusion.	[3–6, 139, 140]
Hydromorphone	▽	Decrease initial dose by 50%.	[140]
Methadone	▽	No changes in metabolism in mild liver disease. Do not use in severe liver disease. Data not precise.	[3, 5, 6, 140]
Morphine	▽	Double dosing interval. Reduce dose in cirrhosis. Use with care.	[3, 4, 6, 139, 140]
Nalbuphine	∅	No data available.	
Oxycodone	▽	Impaired metabolism in cirrhosis. Use $\frac{1}{2}$–$\frac{1}{3}$ of normal initial dose, reduce dosing interval.	[3, 6, 140]
Oxymorphone	∅	No data available.	
Pethidine	▽	50–75% of normal dose, avoid multiple dosing. Use with care (neurotoxic metabolite).	[3, 6, 66, 141]
Piritramide	▽	Dose reduction necessary.	[4]
Remifentanil	✓	Not dependent on hepatic metabolism. Normal dose. Clinical setting necessary.	[3–6, 70, 104]
Sufentanil	✓	Safe with single dosing. Avoid continuous infusion.	[3–5, 72, 82]
Tilidine	×	Avoid the drug.	[3]
Tramadol	▽	Use carefully. Only 50 mg IR and extension of dosage intervals.	[5, 6]

✓ = recommended ▽ = adjustments recommended × = not recommended ∅ = no data available LI = Liver Insufficiency IR = Immediate Release

Table 8: *Recommendations for the Usage of Co-Analgetics in the Presence of Liver Insufficiency.*

Substance	In LI	Comment	Ref.
Amitriptyline	∅	No data on dosage adjustments available.	
Duloxetine	∅	No data on dosage adjustments available.	
Pregabalin	✓	Not metabolised in the liver.	[122]
Gabapentin	✓	Not metabolised in the liver.	[114]
Lamotrigine	∅	Not well studied in the presence of LI.	
Carbamazepine	×	Contraindicated in the presence of LI.	[5, 6]
Topiramate	∅	LI alters plasma concentrations. No dosage guidelines available.	[123]
VPA	×	Known to cause liver injury. Avoid in patients with LI.	[5]
Corticosteroids	∅	Not well studied in the presence of LI.	
Ketamine	∅	Not well studied in the presence of LI.	
Cannabinoids	∅	Not well studied in the presence of LI.	

✓ = recommended ▽ = adjustments recommended × = not recommended ∅ = no data available LI = Liver Insufficiency IR = Immediate Release

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