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Analgesics in Patients with Hepatic Impairment

Pharmacology and Clinical Implications

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Abstract

The physiological changes that accompany hepatic impairment alter drug disposition. Porto-systemic shunting might decrease the first-pass metabolism of a drug and lead to increased oral bioavailability of highly extracted drugs. Distribution can also be altered as a result of impaired production of drug-binding proteins or changes in body composition. Furthermore, the activity and capacity of hepatic drug metabolizing enzymes might be affected to various degrees in patients with chronic liver disease. These changes would result in increased concentrations and reduced plasma clearance of drugs, which is often difficult to predict.

The pharmacology of analgesics is also altered in liver disease. Pain management in hepatically impaired patients is challenging owing to a lack of evidence-based guidelines for the use of analgesics in this population. Complications such as bleeding due to antiplatelet activity, gastrointestinal irritation, and renal failure are more likely to occur with nonsteroidal anti-inflammatory drugs in patients with severe hepatic impairment. Thus, this analgesic class should be avoided in this population.

The pharmacokinetic parameters of paracetamol (acetaminophen) are altered in patients with severe liver disease, but the short-term use of this drug at reduced doses (2 grams daily) appears to be safe in patients with non-alcoholic liver disease.

The disposition of a large number of opioid drugs is affected in the presence of hepatic impairment. Certain opioids such as codeine or tramadol, for instance, rely on hepatic biotransformation to active metabolites. A possible reduction of their analgesic effect would be the expected pharmacodynamic consequence of hepatic impairment. Some opioids, such as pethidine (meperidine), have toxic metabolites. The slower elimination of these metabolites can result in an increased risk of toxicity in patients with liver disease, and these drugs should be avoided in this population.

The drug clearance of a number of opioids, such as morphine, oxycodone, tramadol and alfentanil, might be decreased in moderate or severe hepatic impairment. For the highly excreted morphine, hydromorphone and oxycodone, an important increase in bioavailability occurs after oral administration in patients with hepatic impairment. Lower doses and/or longer administration intervals should be used when these opioids are administered to patients with liver disease to avoid the risk of accumulation and the potential increase of adverse effects. Finally, the pharmacokinetics of phenylpiperidine opioids such as fentanyl, sufentanil and remifentanil appear to be unaffected in hepatic disease. All opioid drugs can precipitate or aggravate hepatic encephalopathy in patients with severe liver disease, thus requiring cautious use and careful monitoring.

1. Introduction

The liver has a predominant role in the pharmacokinetics of most drugs. Therefore, drug disposition may be altered in patients with hepatic impairment. Liver dysfunction is often progressive, and drug elimination impairment increases along with the increase in liver dysfunction. In patients with certain types of hepatic dysfunction, such as chronic active hepatitis or liver cancer without cirrhosis, drug elimination is altered only to a small extent.[1,2]

Unlike estimates of glomerular filtration rate (GFR; creatinine or inulin clearance), which are

useful for determining the pharmacokinetic parameters of drug elimination in renal impairment, no adequate biomarkers relating to hepatic function and drug elimination capacity are available. Various classification schemes and dynamic liver function tests have been developed to predict drug handling in patients with liver disease. The most commonly used systems to scale the severity of hepatic impairment are the Child-Pugh classification and the Model for End-Stage Liver Disease (MELD) system.[3] The Child-Pugh system incorporates three measurable laboratory variables (serum bilirubin, albumin and prothrombin time) and two clinical variables (the presence of ascites and encephalopathy). Disease severity is classified as mild, moderate or severe (Child-Pugh classes A, B and C, respectively). The MELD system is based on serum bilirubin and creatinine concentrations, the international normalized ratio of prothrombin time, and the underlying cause of liver disease.[3]

The US Food and Drug Administration and the European Medicines Agency have issued directives encouraging industries to conduct pharmacokinetic studies in patients with hepatic impairment for drugs likely to be used in these patients or for drugs for which hepatic impairment might significantly affect pharmacokinetics.[4,5] Despite these directives, dosage adjustment recommendations in patients with hepatic impairment are often lacking for older drugs, which is the case for most of the commonly used analgesics.

Pain relief is central to improving the quality of life of every patient, including patients with liver disease. Thus, analgesics are likely to be used frequently in patients with hepatic impairment. The metabolism and elimination of the majority of analgesics, including paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, can be impaired in patients with liver disease. Drug accumulation and increased side effects might occur as a consequence of this impairment. In addition to modifying pharmacokinetics, liver disease can also substantially alter pharmacodynamic effects. An example detailed later in this review is increased sensitivity to opioids, which can cause cerebral dysfunction or aggravate pre-existing hepatic encephalopathy.[6]

Liver disease alters pharmacokinetics, but drugs themselves can also impair liver function. Drug-induced liver injury is a potential complication of most drugs, including analgesics.[7] Acute liver failure is a well known adverse effect of high-doses of paracetamol, one of the most widely used analgesics.[8] Hepatotoxicity has also been described in patients using acetylsalicylic acid or NSAIDs.[9] Some drugs in this class, such as nimesulide or diclofenac, are more likely to provoke hepatic injury than others.[10,11] The new more selective cyclooxygenase (COX)-2 inhibitors, such as lumiracoxib, were also associated with hepatotoxicity.[12] Although rare, NSAID-induced liver injury should not be underestimated owing to the common and widespread use of these drugs in the population.

A paucity of evidence exists regarding the safety and efficacy of pharmacological pain therapies in patients with hepatic impairment.[13] Physicians display significant variability in their recommendations for the use of analgesics in this population. Healthcare providers often consider the use of analgesics in patients with cirrhosis as unsafe, leading to under-treatment of pain in this population.[14] The aim of this review is to resume and analyse the published data on various analgesics in patients with hepatic impairment and provide evidence for the safe use of these drugs in this population.

2. Hepatic Dysfunction and Drug Pharmacokinetics

2.1 Hepatic Clearance

Hepatic metabolism is the main elimination pathway for most lipophilic drugs. The efficiency of drug removal by the liver, so-called hepatic clearance, is determined by hepatic blood flow, plasma protein binding and intrinsic clearance, which represent the metabolic activity of hepatic enzymes. Hepatic clearance may be described with equation 1:

$$CL_H = Q_H \times E_H \quad \text{(Eq. 1)}$$

where Q_H is the hepatic blood flow and E_H is the hepatic extraction ratio, which depends on liver blood flow (Q_H), intrinsic clearance (CL_{int}) and

unbound drug fraction (f_u). Thus, equation 1 can be presented as equation 2:

$$CL_H = Q_H \times \frac{f_u \times CL_{int}}{Q_H + f_u \times CL_{int}} \quad \text{(Eq. 2)}$$

The hepatic clearance of drugs with high extraction ratios ($E_H > 0.7$) depends largely on liver blood flow. A decrease in liver blood flow or the presence of intra- and extrahepatic porto-systemic shunting may strongly affect the clearance of these drugs. In contrast to that of highly extracted drugs, the hepatic clearance of poorly extracted drugs ($E_H < 0.3$) is mainly influenced by changes in the plasma protein binding and intrinsic metabolic clearance, as shown in equation 2. The effect of liver disease on these parameters is discussed below. Hepatic clearance for drugs with an intermediate extraction ratio may be affected by liver blood flow, plasma protein binding and metabolic activity.[3,15]

2.2 Pharmacokinetic Changes in Liver Disease

Orally administered drugs absorbed from the gastrointestinal tract pass into the portal vein and can undergo substantial metabolism in the liver before reaching the systemic circulation, a phenomenon known as the first-pass effect. Cirrhosis may lead to porto-systemic shunts and development of collateral circulation. A substantial fraction of the blood, which should normally reach the portal vein, may flow through this collateral circulation, reducing mesenteric blood flow through the liver. Drugs with intermediate or high hepatic extraction ratios have increased oral bioavailability in patients with cirrhosis as a result of reduced first-pass metabolism.[16,17] Increased bioavailability combined with the decreased hepatic clearance discussed below can cause an important increase in the area under the plasma concentration-time curve (AUC).[18]

One characteristic of liver disease, especially cirrhosis, is impaired production of drug-binding proteins such as albumin and α_1-acid glycoprotein. Decreased levels of these proteins cause an increase in the free fraction of drugs, which is particularly important for highly bound drugs ($f_u < 0.1$). Because only the unbound fraction of a drug can enter or leave tissue compartments, decreases in plasma protein binding influence drug distribution, increasing the distribution volume (V_d) of certain drugs.[3,15] The difference between total plasma clearance and plasma clearance of the unbound fraction is crucial in interpretations of pharmacokinetic data for highly bound drugs in patients with liver disease. In some cases, total drug clearance may appear to be unimpaired in these patients even though clearance of the unbound fraction is markedly reduced. In fact, the decrease in metabolic capacity present in liver disease is counterbalanced by the increase of free drug fraction, leading to the false conclusion that drug metabolism is unaffected. The values for total drug plasma concentrations and clearance are normal, but the clearance of the unbound fraction is reduced because more of the free drug enters the tissues (increased distribution).[3,19,20] With the progression of liver disease, changes in body composition such as increased extracellular fluid (ascites, oedema) and decreased muscle mass occur, altering the V_d.[6]

The hepatic metabolism of drugs is divided into two types and steps of biotransformations: phase I and phase II. Phase I reactions are oxido-reductive processes mainly catalysed by monooxygenases such as cytochrome P450 (CYP) enzymes, whereas phase II reactions are catalysed by conjugating enzymes. The function and expression of these enzymes can be altered in patients with liver disease. Phase I enzymes are generally considered to be more affected in liver disease than are phase II enzymes, likely owing to the higher sensitivity of phase I enzymes to hypoxia caused by shunting, sinusoidal capillarisation and reduced perfusion.[21,22] Isoforms of CYP are affected to variable degrees depending on the severity of liver disease. Frye et al.[23] have found a strong decrease in the metabolic activity of CYP2C19 in patients with mild liver disease, whereas CYP1A2, CYP2D6 and CYP2E1 activity in these patients seemed relatively preserved. However, patients with moderate to severe liver disease displayed decreased metabolic activity for all of the CYP isoforms studied. The type of liver disease (cholestatic, hepatocellular or metastatic) also influences the degree of CYP metabolic activity impairment.[19]

As previously mentioned, phase II reactions, especially glucuronidation, are affected by liver impairment to a lesser extent. Possible explanations for this difference may be the up-regulation of uridine 5′-diphosphate glucuronosyltransferase (UGT) activity in the remaining hepatocytes,[24] a favourable localization of the glucuronyltransferases in the microsomes,[20] or increased extrahepatic metabolism.[25] With some drugs, however, glucuroconjugation can be preserved in the presence of mild or moderate liver disease but altered in patients with severe disease.[20] The biliary clearance of some drugs or metabolites eliminated by biliary excretion can be reduced in patients with liver disease, requiring dose reduction or avoidance of these drugs. However, studies of this effect are rather limited.[1,3]

Renal function often becomes impaired in patients with severe liver disease. The renal impairment that occurs in severe liver disease without any laboratory, anatomical or clinical evidence of another cause is called hepatorenal syndrome.[26] Patients with this syndrome can display significantly diminished renal drug clearance. Impaired renal function and drug clearance can also occur in patients with mild to moderate liver disease and is often underestimated because serum creatinine levels in these patients do not rise even when the GFR is very low.[27] This phenomenon might occur due to the underproduction of creatinine when muscular mass is diminished or as a result of decreased hepatic production of creatine, the substrate for creatinine production.[28] Besides the serum creatinine level, both the measured and the calculated creatinine clearance (using the Cockcroft and Gault method[29]) predict GFR adequately in cirrhotic patients with normal renal function but overestimate GFR in cirrhotic patients with renal impairment.[30] This information must be considered when assessing renal function and prescribing drugs with predominantly renal elimination in hepatically impaired patients.

The pharmacokinetic changes described above are mostly observed in cirrhotic patients. In patients with chronic liver disease, but without significant fibrosis, drug pharmacokinetics are unchanged or modified only to a small extent.[2]

3. Analgesics in Patients with Hepatic Impairment

Pain management in hepatically impaired patients is challenging because evidence-based guidelines for the use of analgesics in this population are lacking. Table I summarizes the findings on the disposition of analgesics in hepatic impairment and provides practical recommendations on the use of these drugs in this population.

3.1 Paracetamol (Acetaminophen)

3.1.1 Hepatotoxicity and Safety Issues

Paracetamol is commonly recommended as a first-choice analgesic for various nociceptive acute or chronic pain conditions and remains one of the safest accessible analgesics for multimorbid patients. However, the use of paracetamol in patients with hepatic disease is often avoided, probably owing to the well known association between paracetamol overdose and hepatotoxicity. Paracetamol is mainly metabolized to glucuronide and sulphate conjugates, and a small proportion (<5%) is oxidized via CYP, mostly CYP2E1, to a hepatotoxic intermediate, N-acetyl-p-benzoquinone imine (NAPQI). This metabolite is rendered nontoxic by conjugation to glutathione (figure 1).[62] Some studies have shown that patients with alcoholic or non-alcoholic liver disease have lower levels of glutathione.[63,64] However, in a review of the literature, Lauterburg[65] stated that, with the exception of findings in chronic alcoholic patients, no evidence exists of a higher risk for adverse effects from paracetamol in patients in which low glutathione has been observed, for example, patients with chronic hepatitis C or non-alcoholic cirrhosis.

Retrospective studies analysing hospital admissions for paracetamol overdose found an increased risk of acute liver injury in patients with pre-existing liver disease. Alcoholic liver disease, non-alcoholic fatty liver disease and hepatitis C virus infection were detected as risk factors for the development of acute liver injury, severe liver failure or increased mortality following paracetamol overdose.[66,67] These studies render attentive to the higher vulnerability of this population in case of paracetamol overdose but state that it

Table I. Pharmacokinetic alterations and recommendations for the use of analgesics in hepatic impairment

Analgesic	Pharmacokinetics changes in patients with liver disease	Recommendations and dose adjustments[a]
Paracetamol (acetaminophen)[b]	50–100% ↑ $t_{½}$; ↑ AUC; ↓ CL[31-34]	Reduce doses to 2 g/daily
Nonsteroidal anti-inflammatory drugs[c]		
Aspirin (acetylsalicylic acid)	2-fold ↑ AUC of salicylic acid f_u; higher risk of salicylate toxicity[35]	
Naproxen	↓ CL_U by 60%[36]	Reduce doses by 50%
Ibuprofen	No significant changes[37]	No adjustment
Etodolac	No significant changes[38]	No adjustment
Sulindac	3-fold ↑ AUC for sulindac and 4-fold ↑ AUC for sulindac sulfide (active metabolite)[37]	Reduce doses
Diclofenac	No changes or possible ↑ AUC in alcoholic cirrhosis	No adjustment
Celecoxib	40% ↑ AUC in mild and 140% ↑ AUC in moderate liver disease[39]	Moderate liver disease: reduce doses by 50%
Opioids		
Codeine	Reduced transformation to morphine	Avoid use, possible lack of analgesic effects
Tramadol	3.2-fold ↑ AUC and 2.6-fold ↑ $t_{½}$, lack of transformation to O-demethyl tramadol[40]	Prolong dosage intervals or reduce doses. Analgesic effects not evaluated in this population
Tapentadol[b]	1.7- and 4.2- fold ↑ AUC and 1.2- and 1.4-fold ↑ $t_{½}$ in mild and moderate liver disease, respectively[41]	Moderate liver disease: low doses and prolonged dosing interval Severe liver disease: no data available
Morphine[b]	↑ Oral bioavailability; ↑ $t_{½}$; ↓ CL[42-45]	2-fold prolongation in dosage intervals. If administered orally also reduce doses
Oxycodone	↑ AUC; ↑ $t_{½}$; ↓ CL[46,47]	Use lower doses with prolonged dosage intervals
Hydromorphone[b]	↑ Oral bioavailability; no changes in $t_{½}$ in moderate liver disease[48]	Reduce doses, consider dosage interval prolongation only in severe liver disease
Pethidine	↑ oral bioavailability; 2-fold ↑ $t_{½}$; 2-fold ↓ CL[49-52]	Avoid repeated use, risk of neurotoxic metabolite accumulation
Methadone	↑ $t_{½}$; possible risk of accumulation[53,54]	No changes needed in mild and moderate liver disease Careful titration in severe liver disease
Buprenorphine	No data. Possible ↓ of its metabolism	No recommendations
Fentanyl	No changes after single IV dose in moderate liver disease[55]	Dose adjustment usually not needed, might be necessary if continuous infusion or transdermal patches are used
Sufentanil	No changes after single IV dose in moderate liver disease[56]	Dose adjustment usually not needed, might be necessary in continuous infusion
Alfentanil	↓ Protein binding; ↑ $t_{½}$; ↓ CL even in patients with mild liver disease[57-59]	Reduce dose and prolong dosing interval Prefer another phenylpiperidine opioid
Remifentanil	No changes[60,61]	No adjustment

a Refers to dose adjustment in severe liver disease unless indicated otherwise.

b Analgesics metabolized by conjugation.

c Dose adjustments refer to patients with mild to moderate liver disease. In patients with severe liver disease NSAIDs should be avoided due to their antiplatelet activity, gastrointestinal irritation and increased renal toxicity.

AUC = area under the plasma concentration-time curve; **CL** = total plasma clearance; **CL_U** = clearance of the unbound drug fraction; **f_u** = unbound drug fraction; **IV** = intravenous; **$t_{½}$** = elimination half-life; ↑ indicates increase; ↓ indicates decrease.

remains unclear whether therapeutic doses of paracetamol would be more toxic in patients with chronic liver disease or cirrhosis.[66,68]

A double-blind, two-period, crossover study was conducted in 20 patients with chronic liver disease to analyse the development of adverse

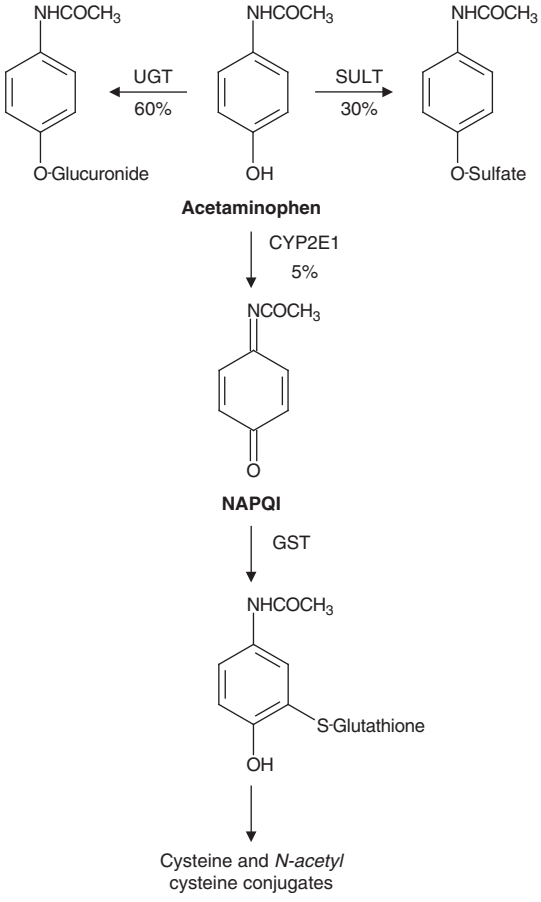

Fig. 1. Simplified presentation of paracetamol (acetaminophen) major metabolic pathways. **CYP** = cytochrome P450; **GST** = glutathione S-transferase; **NAPQI** = N-acetyl-p-benzoquinone imine, toxic intermediate metabolite; **SULT** = sulfotransferase; **UGT** = uridine 5′-diphosphate glucuronosyltransferase.

reactions and the deterioration of liver-related laboratory tests (e.g. levels of bilirubin, alkaline phosphatase, serum bile acids, creatinine, albumin and prothrombin time). Patients were randomly assigned to either paracetamol 4 g or placebo daily for 13 days, after which they were crossed over to the alternate treatment for 13 days. Compared with placebo, the use of paracetamol during this period appeared to have no significant effect on clinical features or laboratory tests.[69] The findings of a case-control study evaluating the implication of over-the-counter analgesics in acute decompensation in patients with cirrhosis suggested no association between the occasional use of low-dose paracetamol (2–3 g/day) and the decompensation of cirrhosis.[70] The number of studies evaluating the safety of paracetamol in patients with liver disease without cirrhosis is rather limited. In a randomized controlled trial, Dargere et al.[71] found no difference in the variation of serum levels of alanine transaminase (ALT) between patients with non-cirrhotic chronic hepatitis C receiving paracetamol 3 g/day or placebo for 7 days.

An especially delicate and often controversial question is the use and hepatotoxicity of therapeutic doses of paracetamol in chronic alcohol users. Glutathione levels are known to be reduced in chronic alcohol consumers or fasting subjects.[72,73] It is also known that the CYP2E1 isoenzyme responsible for the metabolism of paracetamol to the toxic intermediate NAPQI is induced by chronic alcohol consumption.[74] It is therefore not surprising that the production of NAPQI, estimated from the urinary concentration of cysteine and N-acetylcysteine conjugates, is higher in non-cirrhotic chronic alcohol users than in subjects who do not consume alcohol.[75] This makes chronic alcohol users (cirrhotic or not) more vulnerable to elevated doses of paracetamol. Many reports, mostly retrospective studies or case reports, have found an association between alcohol use and enhanced paracetamol toxicity in cases of overdose but also when paracetamol was used at therapeutic doses.[76-79] A randomized placebo-controlled study demonstrated no increase in serum aminotransferases or international normalized ratio in alcoholic subjects receiving therapeutic doses of paracetamol (4 g/day) for 48 hours.[80] Nevertheless, a more recent randomized placebo-controlled study has shown a small but significant increase in ALT at the end of treatment in moderate alcohol consumers taking paracetamol 4 g daily for 10 days. Serum ALT levels increased from 21.3 ± 7.6 IU/L before treatment to 30.0 ± 19.6 IU/L at the end of the 10-day treatment period.[81] Although the clinical implications of this elevation are unclear, precautions should be taken if paracetamol is used in alcoholic patients, especially long term. The US Food and Drug Administration requires a warning

label for paracetamol-containing products stating that individuals who consume three or more alcoholic beverages per day should consult their physician before using paracetamol.

3.1.2 Pharmacokinetic Changes

Pharmacokinetic studies in patients with liver cirrhosis have shown an increase in the elimination half-life ($t_{½}$) of paracetamol ranging from 50% to 100% compared with that in control subjects. The AUC was significantly higher and plasma clearance of the drug was reduced, whereas the mean values for maximum plasma drug concentration (C_{max}) and the time to C_{max} (t_{max}) did not differ.[31-34] In two of these studies, a correlation was found between the $t_{½}$ of the drug[34] or plasma clearance[31] and prothrombin time as well as the plasma albumin levels. In one of these studies, the $t_{½}$ was doubled in patients with both low albumin levels (<35 g/L) and high prothrombin time ratios (>1.4).[34] The other study showed that a 10% decrease in prothrombin level decreased plasma clearance by 10%.[31] The correlation with albumin levels was statistically less important. None of the studies showed correlation between drug $t_{½}$ or plasma clearance and plasma bilirubin levels.

The possible accumulation of repeatedly administered paracetamol in subjects with chronic liver disease has been evaluated in two studies.[31,69] In both studies, six subjects received paracetamol 1 g four times per day over 5 days. No progressive accumulation of paracetamol was apparent in the plasma of cirrhotic patients, despite a slight prolongation of its $t_{½}$.

The production of the reactive hepatotoxic intermediate NAPQI, estimated from the urinary concentration of cysteine and N-acetylcysteine conjugates, is enhanced in alcoholic subjects without cirrhosis but unaffected in cirrhotic subjects abstaining from alcohol.[75] Another study confirmed that the metabolic pattern in blood and urinary excretion did not differ between cirrhotic and healthy subjects after administration of a single dose of paracetamol 1 g.[82]

In a study evaluating the pharmacokinetics of paracetamol in children with non-alcoholic fatty liver disease, higher concentrations of paracetamol glucuronide were observed, although they did not seem to affect the rate of paracetamol elimination because no difference in the pharmacokinetic parameters for paracetamol itself was observed between children with non-alcoholic fatty liver disease and healthy children. The cysteine and mercapturic acid conjugate concentrations were not determined; therefore, it is difficult to evaluate whether the use of paracetamol in this population increases the risk of hepatic injury.[83]

The pharmacokinetics of paracetamol in patients with acute viral hepatitis without cirrhosis were not significantly altered compared with that in control subjects. However, the $t_{½}$ and the AUC increased, and the plasma clearance decreased, in subjects during the acute hepatitis phase compared with that during convalescence. The authors suggest that patients with hepatitis can take conventional doses of paracetamol, and prolonged dosage intervals are necessary only in serious cases in which prothrombin time is prolonged.[84]

3.1.3 Summary

In summary, the few available studies suggest that the use of short-term therapeutic doses of paracetamol in patients with non-alcoholic cirrhotic liver disease cause no accumulation or deterioration of liver-related laboratory tests, indicating that this drug can be used in these patients at normal doses. However, owing to the changes in the pharmacokinetics and the vulnerability of this population, it seems reasonable to limit the adult daily dose to 2 g, half the suggested therapeutic dose. Physicians should remain attentive to any symptoms indicating a possible aggravation of the hepatic function. Doses should be reduced to 2 g/day, or paracetamol should be avoided as much as possible in chronic alcohol users.

3.2 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

3.2.1 Pharmacodynamic Complications

Patients with severe liver disease, especially those with cirrhosis and ascites, display unstable renal haemodynamics. Even with normal GFR and renal blood flow, renal perfusion in these patients is sensitive to modest reductions in plas-

ma volume. The impairment of renal function and the effects of vasoconstrictive hormones are countered by the increased production of vasodilatory renal prostaglandins in these patients.[85] NSAIDs inhibit the compensatory actions of prostaglandins by inhibiting their synthesis. This inhibition decreases GFR and renal blood flow. These agents also reduce the capability of the kidneys to excrete sodium and water and can thus be responsible for the formation of ascites.[86-88] Renal impairment with reduced GFR, renal blood flow, and sodium and water excretion occurs in patients with liver disease when ibuprofen,[89,90] indomethacin,[91] aspirin (acetylsalicylic acid),[92] naproxen[93] and sulindac are administered.[94] The subjects most sensitive to acute renal impairment after NSAID use were those with ascites and significant sodium retention. An important reduction in natriuresis after the administration of diuretics was observed in patients with ascites who received two doses (with a 6-hour interval) of indomethacin 50 mg, naproxen 250 mg or aspirin 900 mg. Urine sodium levels were 78% lower in cirrhotic patients receiving furosemide (frusemide) and indomethacin than those in patients receiving only furosemide. The reduction in urine sodium levels was 49% for those receiving naproxen and 17% for patients who took aspirin. This reduction did not occur or occurred to a very small extent in healthy subjects, confirming the increased vulnerability of cirrhotic patients to the adverse effects of NSAIDs.[95] In the previous studies, the decrease in natriuresis was reversed by drug cessation. However, in these studies, NSAIDs were usually administered for a very short time. Whether renal impairment is also reversible in cirrhotic patients treated with NSAIDs for longer periods is unknown.

Limited information is available on the use and effect of COX-2 selective inhibitors on renal function in cirrhotic patients. A double-blind, randomized, controlled study showed no apparent impairment in the renal function of patients with cirrhosis and ascites when celecoxib was administered for 2.5 days. Neither the mean values of GFR, renal plasma flow, and prostaglandin E2 excretion nor the response to furosemide were reduced.[93] In a pilot study in nine cirrhotic patients who received celecoxib for 4 days, no significant changes were observed in the mean values for serum creatinine, GFR, prostaglandin E2, urinary volume or sodium excretion before or after drug administration. However, four patients displayed a decrease in GFR greater than 20%.[96] Experimental evidence of the expression of COX-2 in the kidney and their importance in renal homeostasis were clearly established.[97] Therefore, it is difficult to imagine that COX-2 inhibitors would present fewer renal problems than non-selective NSAIDs in cirrhotic patients. These findings, together with the decrease of GFR in several patients and the lack of studies of long-term use, lead to the conclusion that the prescription of COX-2 inhibitors should be particularly restrictive in patients with hepatic disease.

The haemostatic abnormalities and coagulation disorders present in liver disease increase the risk of bleeding in these patients.[98] One of the mechanisms leading to this coagulopathy is the reduced platelet synthesis of proaggregatory thromboxane A2. NSAIDs inhibit the platelet production of thromboxane A2, thus increasing the risk of bleeding.[99]

Acute bleeding from oesophageal varices is a major complication of hepatic cirrhosis. A case-control study found significant association between the use of anti-inflammatory drugs and the first bleeding episodes associated with oesophageal or cardiac varices in cirrhotic patients. The study suggested that cirrhotic patients using NSAIDs are approximately three times more likely to present with this complication than are cirrhotic patients who do not use these drugs.[100] Owing to selective COX inhibition, the risk of acute bleeding from oesophageal varices might be lower if COX-2 inhibitors are used. However, the effect of these drugs on the first bleeding episodes associated with oesophageal or cardiac varices in cirrhotic patients has not been investigated yet.

3.2.2 NSAID-Induced Liver Injury

Hepatotoxicity is considered a class characteristic of NSAIDs. Approximately 10% of all drug-induced liver injuries are NSAID related.[101] With most NSAIDs, the mechanism of hepatic injury is considered idiosyncratic, dose independent and

dependent on individual susceptibility. An exception is aspirin, which has intrinsic dose-dependent hepatotoxicity.[9] Although hepatotoxicity is listed as a class warning for NSAIDs, the risk of liver injury differs among substances. NSAIDs such as bromfenac, ibufenac and benoxaprofen have been withdrawn from the market due to their hepatotoxicity. This serious adverse effect was also the reason for the withdrawal or lack of approval of nimesulide and lumiracoxib in several countries.[101,102] Higher drug-related hepatotoxicity has also been observed with aspirin, diclofenac and sulindac.[103] Although the risk of hepatotoxicity has not been evaluated in patients with underlying liver disease, the use of these NSAIDs should be avoided in this population.

3.2.3 Pharmacokinetics of Specific NSAIDs in Hepatic Impairment

Most NSAIDs are eliminated via hepatic metabolism involving oxidative (predominantly CYP2C9-catalysed) and conjugation reactions. The decreased enzymatic activity in liver disease might result in modification of the disposition of these drugs. Pharmacokinetic studies for several NSAIDs in hepatic impairment have been conducted in the past decades.

Aspirin

The pharmacokinetic properties of aspirin are unaffected in alcoholic patients with liver disease. However, the unbound fraction of its hydrolysed metabolite, salicylic acid, is increased owing to decreased plasma protein binding. This decrease results in doubled AUC values of the free salicylate, indicating a higher risk for salicylate toxicity in these patients.[35]

Naproxen

Similarly, no differences in the total plasma clearance of naproxen have been observed between individuals with alcoholic cirrhosis and healthy controls after single or multiple dose administration. The plasma protein binding of the drug has been significantly reduced in cirrhotic subjects, resulting in a 2- to 4-fold increase of plasma free drug concentration. A reduction of approximately 60% has been observed for the unbound drug clearance. Assuming that unbound drug concentration determines pharmacological effect, naproxen doses in alcoholic cirrhotic patients should be reduced by at least 50%.[36]

Ibuprofen

Pharmacokinetic studies with ibuprofen have suggested that hepatic impairment has only a minimal effect on the disposition of the drug. Alcoholic liver disease had a small but not statistically significant influence on the $t_{½}$ and the AUC of ibuprofen.[37] Another study has demonstrated that the $t_{½}$ is nearly doubled after the administration of a single oral dose of ibuprofen racemate.[104]

Etodolac

Despite the high protein binding and extensive hepatic metabolism of etodolac, no significant differences in the pharmacokinetics of this drug have been found in patients with stable cirrhosis and healthy volunteers after administration of a single oral dose.[38]

Sulindac

Sulindac is a pro-drug, the bioactivation of which leads to the active metabolite sulindac sulfide. One study showed that absorption was delayed in patients with poor hepatic function. The patients in the study displayed 3- and 4-fold increases in the AUC for sulindac and sulindac sulfide, respectively, indicating the necessity for dose reduction of this drug in patients with hepatic impairment.[37]

Diclofenac

Diclofenac undergoes significant hepatic metabolism and is highly protein bound. Thus, a modification in its pharmacokinetics might be expected in the context of hepatic impairment. However, the pharmacokinetics of diclofenac were unaffected after a single oral dose of diclofenac 100 mg in ten patients with chronic hepatitis or compensated hepatic cirrhosis.[105] A more recent study has demonstrated a 3-fold increase in the AUC in alcoholic cirrhotic patients but no change in patients with chronic hepatitis compared with healthy subjects.[106] Because pharmacodynamic measurements were not made and no increase in side effects was observed in the study, the authors suggested that doses should be

titrated to patient response instead of according to the severity of hepatic impairment.

Celecoxib

The pharmacokinetic properties of celecoxib are highly influenced by hepatic disease. A 22% increase in C_{max} and a 40% increase in the AUC have been observed in patients with mild hepatic disease. In patients with moderate hepatic disease, the increases were 63% and 140% for C_{max} and AUC, respectively.[39] The metabolism rate is correlated with serum albumin levels. Half the usual dose is recommended in patients with moderate hepatic disease (serum albumin levels between 25 and 35 g/L). Studies in patients with severe liver disease have not been conducted because celecoxib is contraindicated in this population.[107]

Although the pharmacokinetic properties of certain NSAIDs appear to be unaltered in the presence of mild to moderate liver disease, these substances should be avoided in patients with advanced liver disease owing to the increased risk of adverse effects. If used in patients with mild to moderate liver disease, ibuprofen, etodolac and diclofenac can be administered at normal doses, whereas dose reduction is necessary for naproxen, sulindac and celecoxib.

3.3 Opioids

Opioids are largely used in the treatment of moderate to severe pain in a diverse patient population. If used in patients with severe liver disease or history of hepatic encephalopathy, opioids may precipitate or aggravate encephalopathy.[108] This common and serious complication in patients with severe liver disease is characterized by abnormal mental status, ranging from slight cognitive alterations to coma.[109] An increase in GABAergic inhibitory neurotransmission occurs in hepatic encephalopathy. This increase has been found to decrease brain expression of proenkephalin messenger RNA and thus decrease MET-enkephalin release. The decrease in endogenous opioid levels leads to compensatory up-regulation of μ-opioid receptors in the brain and increased sensitivity to exogenous opioid analgesics.[110] In addition to these changes, alterations in the blood-brain barrier in patients with severe liver disease can lead to increased drug concentrations within the central nervous system.[111]

Main metabolic pathway
Minor metabolic pathway
! Metabolic pathway leading to active metabolite formation

Opioid	CYP2B6	CYP2C19	CYP2D6	CYP3A4	UGT	Sulfotransferase	Esterases
Codeine			!	■	■		
Tramadol	■		!	■	▒		
Tapentadol		▒			■	▒	
Oxycodone			!	■			
Morphine					!		
Hydromorphone					■		
Pethidine (meperidine)				▒			■
Methadone	■	▒	▒	■			
Buprenorphine				▒	▒		
Fentanyl				■			
Sufentanil				■			
Alfentanil				■			
Remifentanil							■

Fig. 2. Major enzymes involved in opioid drug metabolism. **CYP** = cytochrome P450; **UGT** = uridine 5′-diphosphate glucuronosyltransferase.

Although the risk of precipitating encephalopathy cannot be neglected, suitable pain management is important in patients with liver disease. When alternative analgesia is unavailable or insufficient, cautious use of opioids should be considered in these patients.[112,113] The pharmacokinetics of these drugs in patients with hepatic impairment are presented below to guide the choice of suitable opioids. The major pathways and enzymes involved in the metabolism of each opioid are shown in figure 2.

3.3.1 Codeine

Codeine is a weak opioid analgesic chemically related to morphine. It is metabolized by the liver

mainly to codeine-6-glucuronide and norcodeine, and a small fraction (approximately 10%) is *O*-demethylated to morphine.[114] Codeine itself has a very weak affinity for μ-opioid receptors.[115] Its analgesic activity is mainly due to the conversion to morphine, as several studies have demonstrated.[116-118] CYP2D6 is the enzyme implicated in the biotransformation of codeine to morphine. As previously described, oxidative enzyme capacity is reduced in patients with hepatic impairment. In this case, the result will be a reduced production of morphine and, in turn, a decrease or lack of analgesia after codeine administration. Although a relative preservation of CYP2D6 activity may occur in mild liver disease, this preservation diminishes as impairment progresses.[23] For instance, diminution of approximately 80% of the CYP2D6 metabolic activity is observed in chronic hepatitis C patients with liver kidney microsomal type 1 antibodies.[119]

Currently, no clinical studies demonstrate the analgesic effect or the metabolism of codeine in patients with hepatic impairment. Due to the lack of studies and the possible lack of analgesic effects, codeine appears to be a sub-optimal pain treatment choice in patients with liver disease.

3.3.2 Tramadol

More than 80% of tramadol is metabolized by the liver.[120] The biotransformation of tramadol to its main metabolite, *O*-demethyl tramadol, is catalysed by CYP2D6. Tramadol is characterized by a bimodal mechanism of action: modulation of the central monoaminergic pathways and activation of μ-opioid receptors. Tramadol itself has higher monoaminergic activity, whereas its metabolite O-demethyl tramadol has higher affinity and activates μ-opioid receptors more potently.[121-123] In patients with liver disease and, hence, lowered CYP2D6 activity, tramadol is expected to act more as a monoaminergic modulator than as an opioid agonist. One prospective randomized controlled study has shown that, compared with extensive CYP2D6 metabolisers, poor metabolisers consume more tramadol and experience less postoperative pain relief.[124] Because metabolizing capacity is reduced in patients with liver disease, the analgesic effects of tramadol might be lower than expected in this group of patients. However, this theory has not been demonstrated in liver disease so far. Moreover, the monoaminergic effect of tramadol itself seems to have analgesic effects because the pain tolerance thresholds to sural nerve stimulation in poor metabolizers were significantly increased after tramadol injection.[125] Significant differences were observed between healthy subjects and patients with hepatic impairment in a study comparing the pharmacokinetics of tramadol.[40] In patients with liver cirrhosis, the AUC was increased by a factor of 3.2 and the $t_{½}$ by a factor of 2.6, on average. These changes are principally due to reduced hepatic clearance. Similar changes in the pharmacokinetics of tramadol were observed in patients with primary liver carcinoma on top of chronic hepatitis C. The bioavailability and AUC of tramadol were also increased but to a lesser extent in patients with secondary metastatic liver malignancy.[126] Owing to these metabolic changes and in order to prevent potential drug accumulation, prolonging the dosing intervals in patients with hepatic impairment is recommended.

3.3.3 Tapentadol

Tapentadol is a new centrally acting analgesic, the mechanism of action of which is a combination of μ-opioid receptor agonism and inhibition of noradrenaline (norepinephrine) reuptake.[127] It undergoes important first-pass metabolism, explaining the bioavailability of only 32%. This analgesic is extensively metabolized, mainly by conjugation to tapentadol-O-glucuronide (55%) and tapentadol sulphate (15%).[41] Phase I enzymes CYP2C9, CYP2C19 and CYP2D6 are responsible for 15% of the metabolism of tapentadol.

In a study conducted by the manufacturer, higher serum concentrations of tapentadol were observed in subjects with mild and moderate liver disease than in subjects with normal hepatic function. AUC was increased by a factor of 1.7 and 4.2 and $t_{½}$ was increased by a factor of 1.2 and 1.4 in subjects with mild and moderate liver disease, respectively. These changes are probably due to an increase in the bioavailability of the drug. Although glucuronidation is somewhat preserved in liver disease, the rate of formation of

tapentadol-O-glucuronide was lower in subjects with increased liver impairment. It was suggested that no dose adjustment was necessary in patients with mild liver disease. For patients with moderate liver disease, it was recommended that the treatment should be initiated with the lowest available dose (50 mg) and increased dosing intervals (maximum of three doses in 24 hours). No studies were conducted in subjects with severe hepatic impairment and therefore the use of tapentadol is not recommended in this population.[41,128]

Currently, there are no recommendations on the use of this substance in patients with hepatorenal syndrome. More investigation and experience in the use of this drug is needed in order to confirm its safety in this population.

3.3.4 Oxycodone

Oxycodone is a semi-synthetic μ-opioid agonist that has pharmacodynamic potency similar to that of morphine. Compared with morphine, oxycodone displays similar protein binding capacity but a higher oral bioavailability (60–87%). The metabolism of oxycodone depends on oxidative enzymes – notably CYP3A4 and CYP2D6 – which transform oxycodone to noroxycodone and the active metabolite oxymorphone, respectively.[129] An impairment in oxycodone metabolism in liver disease might occur as a result of decreased hepatic blood flow and/or decreased intrinsic clearance, since the metabolising activity of oxidative enzymes is reduced in chronic liver disease. In this case, the formation of the active metabolite oxymorphone would be reduced, leading to potentially lower analgesic effects as observed in poor CYP2D6 metabolizers.[130,131]

In patients with hepatic impairment, the C_{max} of oxycodone was increased by 40% and the AUC by 90% after administration of a 20 mg controlled-release oxycodone tablet. Reductions of 15% of the C_{max} and 50% of the AUC of the active metabolite oxymorphone also occurred. The $t_{½}$ of oxycodone was prolonged by 2 hours.[46] These data suggest that oral oxycodone should be initiated at lower doses in patients with hepatic impairment.

Important differences in pharmacokinetic parameters have been observed before and after liver transplantation in end-stage cirrhotic patients when oxycodone was administered intravenously. The median $t_{½}$ was 13.9 hours (range 4.6–24.4 hours) before transplantation and 3.4 hours (range 2.6–5.1 hours) after transplantation, and the clearance increased from 0.26 L/min before to 1.13 L/min after transplantation. In these patients, higher ventilatory depression was observed before transplantation, which was believed to be the result of the increased sensitivity to the adverse effects of opioids in cirrhotic patients.[47] Because of the important increase in median $t_{½}$ and AUC, the dosage interval of oxycodone should be increased and/or doses should be reduced in patients with severe liver cirrhosis.

3.3.5 Morphine

Morphine undergoes significant first-pass metabolism after oral administration, and its average bioavailability is 30–40%. The drug is weakly bound to plasma proteins (20–40%).[132] Metabolism of morphine to the active morphine-6-glucuronide and the inactive but neurotoxic morphine-3-glucuronide occurs mainly in the liver.[132] Morphine is an intermediately to highly extracted drug with a hepatic extraction ratio of approximately 0.7.[133] Hence, the possible decreased clearance of morphine in cirrhotic patients should be mostly due to a decrease in hepatic blood flow and, to a smaller extent, a decrease in intrinsic metabolizing capacity. Although the plasma protein binding of morphine is decreased in hepatic disease,[134] the higher amount of the free fraction is expected to have no significant impact on the V_d because morphine is only weakly protein bound.

Several studies have investigated the disposition of morphine in patients with hepatic impairment. Patwardhan et al.[135] found no significant alteration in morphine elimination and plasma clearance in cirrhotic patients (Child-Pugh A or B) after intravenous administration. In contrast, few other studies have shown impairment in the metabolism of intravenous morphine in patients with liver disease.[42-44] In a study by Mazoit et al.,[44] the terminal $t_{½}$ in cirrhotic patients was 2-fold greater and the clearance decreased by 37% compared with that in normal subjects. The authors suggest that the dosing interval of morphine

should be increased 1.5- to 2-fold in cirrhotic patients in order to avoid accumulation of the drug. The change in these pharmacokinetic parameters was even more pronounced in a study by Hasselström et al.[43] that included patients with Child-Pugh B or C hepatic impairment. Crotty at al.[42] have reported a reduction of 25% in the extraction ratio of morphine in cirrhotic patients. They conclude that this reduction is due to diminished intrinsic hepatic clearance (reduction in the enzyme activity or intrahepatic shunting) because no differences in hepatic blood flow were observed. Their study also demonstrated that systemic clearance was significantly higher than hepatic clearance, furnishing some indirect support for the possible extra-hepatic metabolism of morphine. The extrahepatic conjugases found in the kidneys or intestines might assume a greater role in morphine elimination in liver failure.[19]

The differences in morphine elimination values in the study by Patwardhan et al.[135] compared with those in other studies[42-44] are principally due to differences in the severity of the liver disease of the subjects studied. As mentioned in section 2.2, glucuronidation, which is relatively preserved in mild to moderate liver disease, might be impaired in severe liver disease.[20]

As a result of decreased first-pass metabolism, the oral bioavailability of morphine in patients with hepatic impairment is likely to be increased. This has been demonstrated in a study by Hasselström et al.[43] in which the oral bioavailability of morphine in cirrhotic patients was 100% compared with 47% in control subjects after a single oral dose. In another study, the bioavailability after administration of controlled-release morphine tablets to cirrhotic patients was 27.7%, whereas that in controls was 16%.[45] These studies also showed prolongation of the $t_{½}$ and a decrease in morphine clearance in cirrhotic patients.

An important increase in the bioavailability of controlled-release morphine was also noted in a study of patients with liver carcinoma. Bioavailability was 64.8% in patients with primary liver carcinoma, 62.1% in patients with secondary metastatic carcinoma, and 16.8% in controls. Consequently, the AUC was increased 4-fold in primary carcinoma and 3-fold in metastatic carcinoma.[136]

The data presented above indicate that if morphine is given intravenously to patients with severe liver disease, the dosage interval should be increased. In the case of oral administration, not only should the administration interval be prolonged but the dose should also be reduced. Morphine should be avoided in patients with hepatorenal syndrome because of the increased risk of neurotoxicity resulting from morphine-3-glucuronide and morphine 6-glucuronide accumulation in severe renal impairment.

3.3.6 Hydromorphone

Hydromorphone is a semi-synthetic opioid that undergoes important first-pass metabolism, resulting in low oral bioavailability.[137] It is predominantly metabolized by glucuroconjugation to hydromorphone-3-glucuronide. Several other metabolites are formed in smaller amounts: hydromorphone-3-glucoside, dihydromorphine, and unconjugated and conjugated dihydroisomorphine.

In patients with moderate hepatic impairment, C_{max} and AUC were increased 4-fold after single-dose administration of oral immediate-release hydromorphone. This increase was probably a consequence of reduced first-pass metabolism. The $t_{½}$ of the drug in patients with hepatic impairment was the same as that in controls.[48] According to the results, a reduction of hydromorphone dose with maintenance of the standard dosing interval is necessary in patients with moderate liver disease. Possible decreases in the metabolizing capacity of conjugating enzymes with the advancement of liver disease may lead to an increase in the $t_{½}$ in patients with severe liver disease. However, no studies investigating the pharmacokinetics of hydromorphone in patients with severe liver disease are currently being undertaken. In the presence of renal impairment, an accumulation of the neuroexcitatory metabolite hydromorphone-3-glucuronide has been observed.[138,139] Therefore, hydromorphone should be avoided in patients with hepatorenal syndrome.

3.3.7 Pethidine (Meperidine)

Pethidine (meperidine) was the first synthetic opioid analgesic.[140] It is predominantly metabolized by hydrolysis to meperidinic acid, which

is conjugated and excreted, but it is also N-demethylated by CYP3A4 to normeperidine (norpethidine). This metabolite has neurotoxic effects and has been implicated in the development of neuromuscular irritability and seizures.[141,142] The oral bioavailability of pethidine is approximately 50%.[49,50] Thus, to obtain equianalgesia, oral doses should be twice as high as intravenous doses, generating plasma concentrations of normeperidine that are higher after oral than those after intravenous administration.

In cirrhotic patients, a 60–80% increase in bioavailability was observed after oral administration.[49,50] Significant impairment in pethidine disposition also occurred after intravenous administration, with a decrease of approximately 50% in the plasma clearance and a 2-fold increase in the $t_{½}$.[50,51] The decreased formation of norpethidine in cirrhotic patients might lead to the conclusion that these patients are relatively protected from its toxicity. However, the slower elimination of the metabolite might lead to an increased risk of cumulative toxicity if repeated doses are administered.[50,52] In conclusion, if administered to patients with hepatic impairment, oral doses of pethidine should be reduced. Repeated doses of pethidine should be avoided because of the risk of norpethidine accumulation and neurotoxicity. Further accumulation of norpethidine occurs in patients with renal impairment; thus, this analgesic should be avoided in patients with hepatorenal syndrome.[142]

3.3.8 Methadone

Methadone is a synthetic opioid predominantly used as maintenance treatment in individuals with opioid dependence. It has high average bioavailability of approximately 70–80%, but large variability has been reported (36–100%).[143] The protein binding of methadone is high (60–90%). It is mainly bound to α_1-acid glycoprotein, and its distribution is not significantly altered by hypoalbuminaemia.[143] Methadone is metabolized by oxidation, with principal involvement of CYP3A4 and CYP2B6. The elimination of methadone and its metabolites is urinary and faecal.[144]

As previously mentioned, methadone is largely used as maintenance treatment in patients with chronic opioid addiction. A significant proportion of these patients have chronic hepatitis C that can progress to cirrhosis. The prevalence of hepatitis C virus antibodies in patients enrolled in methadone maintenance programmes is very high, ranging from 67% to 96%.[145,146] In a study of 14 methadone-maintenance patients, the disposition of methadone was unaltered in subjects with mild to moderate chronic liver disease. In patients with more severe liver disease, the $t_{½}$ was prolonged from 19 to 35 hours, but drug clearance and AUC were not significantly altered.[53] Similar results have been observed in patients with severe alcoholic cirrhosis,[54] leading to the suggestion that no dose adjustment is necessary in these patients. Moreover, a CYP3A4 induction has been suggested as an explanation for the requirement of higher doses of methadone in patients with hepatitis C.[147] The use of methadone for analgesia and not as maintenance treatment in patients with hepatic impairment has not been investigated. Methadone disposition seems to be relatively unaffected in renal impairment;[148] thus, its clearance should not be decreased further in the presence of hepatorenal syndrome. However, due to the important interindividual variability in the pharmacokinetics of methadone as well as its long $t_{½}$, this drug should not be used as a first-line analgesic treatment in patients with liver disease.

3.3.9 Buprenorphine

Buprenorphine is a partial agonist at the μ-opioid receptors. It has very high first-pass clearance and is therefore not administered orally but only using sublingual, parenteral or transdermal routes. The bioavailability of sublingually administered buprenorphine is 50–55%, with important interindividual variability.[149,150] This drug is highly protein bound (96%), primarily to α- and β-globulin.[151] Buprenorphine is partially metabolized by the liver, with the main metabolic pathway being oxidation to norbuprenorphine by CYP3A4.[152] Both buprenorphine and norbuprenorphine are further glucuronidated.[153] The elimination is mainly through the faeces (80–90%), mostly as free buprenorphine and norbuprenorphine. The remaining 10–20% is eliminated in the urine as

metabolites.[154,155] Enterohepatic recirculation probably occurs, resulting in an apparent prolongation of the $t_{1/2}$.[151]

Buprenorphine pharmacokinetics were not studied in patients with hepatic impairment. Sublingually administered buprenorphine theoretically bypasses the liver; however, the drug might be partially swallowed and thus subjected to hepatic first-pass metabolism, which might explain the average bioavailability (50–55%) and large variability. Decreased CYP3A4 enzymatic activity in liver disease might result in an increase of the bioavailability and decrease of the clearance of buprenorphine. However, owing to the partial buprenorphine metabolism and the partial bypass of the liver with the sublingual administration, these changes might be of low clinical relevance.

Several cases of buprenorphine hepatic toxicity have been described, most frequently after intravenous use of the drug.[156-158] Contradictory results exist regarding the hepatotoxicity of buprenorphine in patients already presenting liver disease, particularly hepatitis C. One study demonstrated elevated transaminases in patients with a history of hepatitis who were treated with therapeutic doses of sublingual buprenorphine. The increase in aspartate aminotransferase (AST) was dependent on buprenorphine dose.[159] No evidence of buprenorphine hepatotoxicity was found in another study that included adolescents and young adults, among whom 19% were hepatitis C positive.[160] Safe use of buprenorphine in patients with active hepatitis C has been suggested in a case series study in which no increase was observed in the transaminases of four patients treated with buprenorphine.[161] The authors of this study have suggested that patients with hepatitis C should not be excluded from treatment with buprenorphine. A more prudent course, however, would be to monitor liver enzyme levels carefully if buprenorphine is administered to this group of patients. Buprenorphine appears to be a safe option for pain treatment in patients with renal disease.[162,163] Although the pharmacokinetics of the drug might be relatively unchanged in liver disease, no studies confirming this hypothesis are currently available.

3.3.10 Fentanyl

Fentanyl is a synthetic opioid from the phenylpiperidine class. Similar to the other drugs of this class, it exhibits multiple-compartment pharmacokinetics. It is highly protein bound (85%), mainly to albumin. Fentanyl is largely metabolized in the liver by CYP3A4. Its $t_{1/2}$ is approximately 3.6 hours, with large interindividual variability. Important prolongation of the $t_{1/2}$ was observed in patients receiving continuous infusion of fentanyl.[164] Since the hepatic extraction ratio of fentanyl is high (0.8), its clearance would mainly be affected by changes in hepatic blood flow, not by a reduction in intrinsic enzyme activity or protein binding.[165]

The pharmacokinetics of fentanyl were unaltered in patients with biopsy-confirmed cirrhosis after a single intravenous dose of fentanyl.[55] However, none of these patients had profound hepatic insufficiency, and their hepatic blood flow was not markedly diminished compared with that in healthy subjects. These results should be interpreted with caution if fentanyl is administered to patients with hepatic shunting or reduced hepatic blood flow.

The pharmacokinetics of transdermal fentanyl matrix patches in cirrhotic patients have been studied by their manufacturer. The C_{max} and AUC were increased by 35% and 73%, respectively, and the $t_{1/2}$ remained unchanged after application of a fentanyl matrix patch (50 μg/hour).[166]

The pharmacokinetics of continuously infused fentanyl in cirrhotic patients have not been established, and whether the accumulation of fentanyl is more pronounced in these patients than in patients with normal liver function is unknown. Fentanyl has often been reported as a first-choice opioid in renal impairment,[167-169] although its clearance might be reduced in the presence of high blood urea nitrogen levels.[170] This opioid appears to be a good choice in patients with hepatorenal syndrome, but dose reduction might be necessary to avoid accumulation, especially with continuous administration.

3.3.11 Sufentanil

Sufentanil is another drug in the piperidine opioid class. Compared with fentanyl, it is more

lipophilic, but has a slightly smaller V_d and shorter $t_{½}$. It is highly protein bound (92%), mainly to α_1-acid glycoprotein. Sufentanil is extensively metabolized by CYP3A4 in the liver and has a hepatic extraction ratio approaching 1.[164]

Similar to that of fentanyl, the pharmacokinetics of sufentanil are not influenced by liver disease after a single intravenous dose.[56] The proposed explanations for the unaffected pharmacokinetics in patients with mild liver disease are a possible sparing of liver blood flow or the incapacity to detect the differences in elimination kinetics owing to the large V_d. A 30% prolongation of the $t_{½}$, slight increase in the V_d, and increase in the clearance in cirrhotic patients have been reported by the manufacturer.[171]

Like that of fentanyl, the $t_{½}$ of continuously infused sufentanil is increased in patients with normal liver function.[164] No studies have been performed to determine the degree of possible accumulation of continuously infused sufentanil in patients with hepatic disease. Sufentanil pharmacokinetics are not significantly altered in renal impairment,[164] and this opioid, like fentanyl, may be used in patients with hepatorenal syndrome.

3.3.12 Alfentanil

Alfentanil is a short-acting opioid that has a rapid onset but an analgesic effect that lasts no longer than 5–10 minutes. It has a significantly smaller V_d and shorter $t_{½}$ than fentanyl and sufentanil. The α_1-acid glycoprotein binding of alfentanil is approximately 92%.[164] It is extensively and almost exclusively metabolized by the CYP3A enzymes.[172] Owing to the intermediate hepatic extraction ratio of alfentanil (0.3–0.6),[57,164] its total hepatic clearance could be influenced by all of the following: hepatic blood flow, intrinsic hepatic enzyme activity and protein binding.

A substantial increase in the $t_{½}$ (219 vs 90 minutes), and a 50% decrease in total clearance have been reported in patients with moderate liver disease. Moreover, protein binding decreased from 88.5% to 81.4%. When corrected to protein binding, a decrease of 70% in the plasma clearance of the unbound fraction has been observed in hepatically impaired patients.[57] Another study has shown similar results for alfentanil disposition in anaesthetised patients with hepatic pathology.[58] The disposition of alfentanil in children with cholestatic hepatic disease was found to be unaltered.[173] The discrepancy between the results of this study in children and those of previous studies might be due to differences in underlying pathology or patient age. Moreover, the length of plasma sampling in this study was only 2 hours, which might explain the lack of detection of the potential pharmacokinetic alterations.

A more recent study, in which a 3-fold increase in AUC in patients with mild liver cirrhosis was observed, confirmed the important alterations of alfentanil disposition even in patients with minor hepatic impairment.[59] Thus, alfentanil seems to be a poor analgesic choice in patients with liver disease because its effects may be both prolonged and enhanced.

3.3.13 Remifentanil

Remifentanil is a phenylpiperidine opioid, which differs considerably from other opioids in its class because of its ester linkages that lead to a specific metabolic pathway. As an ester, remifentanil is predominantly and rapidly hydrolysed by blood and tissue esterases to a carboxylic acid metabolite, which has been found to have only 1/4600 of the parent compound potency in animal models.[174,175] This particular metabolic pathway explains its very short duration of action and rapid elimination.

A study of the pharmacokinetic parameters of remifentanil demonstrated no change after a 4-hour infusion in subjects with severe hepatic impairment. Patients with liver disease seemed to be more sensitive to the ventilatory depressant effects of remifentanil. Owing to the short duration of action of this drug, the increased sensitivity in this population is unlikely to have clinical significance.[60]

The clearance of remifentanil in the anhepatic phase of liver transplantation is similar to that of healthy volunteers, confirming the extrahepatic metabolism of the drug and its independence from hepatic function.[61] The pharmacokinetics of remifentanil in patients with renal failure are also unaltered.[176] These results suggest that dose adjustment is unnecessary in patients with liver disease or hepatorenal syndrome.

3.4 Neuropathic Pain Treatment

Neuropathic pain is a medical challenge as it is poorly responsive to classical anti-inflammatory or powerful centrally acting analgesics, such as opioids.[177] Evidence-based guidelines suggest the use of antidepressants and anticonvulsants as first-line neuropathic pain treatment.[178,179] Studies evaluating the disposition, safety and efficacy of neuropathic pain drugs in patients with hepatic impairment are often lacking. In this population, alternative, non-pharmacological interventions should be encouraged whenever possible. However, in some cases when neuropathic pain is not sufficiently relieved by non-pharmacological interventions, drug administration could be considered.

3.4.1 Antidepressants

Tricyclic Antidepressants

Several randomized controlled clinical studies have demonstrated the efficacy of tricyclic antidepressants (TCAs) as neuropathic pain treatment.[180] These drugs are largely metabolized by liver cytochromes, CYP2D6 in particular. In patients with liver disease where a decrease of cytochrome activity is expected, an accumulation of these drugs is possible. In this population, treatment with TCAs should be started at low doses with slow titration. Nortriptyline and desipramine could offer the same efficacy and should be preferred over amitriptyline and imipramine when available since they appear to be less sedating and better tolerated.

Serotonin-Norepinephrine Reuptake Inhibitors

The use of serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine for the treatment of neuropathic pain is increasing. Venlafaxine undergoes significant hepatic biotransformation to several inactive and one active metabolite mediated primarily by CYP2D6 and to a lesser extent by CYP3A4. In patients with moderate hepatic impairment, significant alterations were observed in the $t_{1/2}$ (30% and 60% prolongation) and clearance (50% and 30% decrease) of venlafaxine and its active metabolite, respectively. In patients with severe hepatic impairment, a decrease of up to 90% was observed in venlafaxine clearance. An important inter-individual variability exists, making dosage adjustments difficult in this population.[181] Significant alterations in the disposition of duloxetine (85% clearance decrease) were observed in patients with moderate liver disease.[182] Moreover, duloxetine hepatotoxicity has been evidenced. Patients with pre-existing liver disease appear to be at higher risk of duloxetine-induced liver injury. These findings prompted the manufacturer to include a warning in the product label stating that duloxetine "should ordinarily not be prescribed to a patient with substantial alcohol use or evidence of chronic liver disease."[183]

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) show lower efficacy than TCAs in the treatment of neuropathic pain.[177] Moreover, these drugs might increase the risk of gastrointestinal bleeding from varices in patients with hepatic impairment and thus are not the first-choice treatment for neuropathic pain in this population.[184]

3.4.2 Anticonvulsants

Calcium Channel α2δ Ligands

Anticonvulsants are the second drug class largely used in the treatment of neuropathic pain. Among them, calcium channel α2δ ligands such as gabapentin and pregabalin are currently often used as first-line medications. The disposition of gabapentin and pregabalin is probably unaltered in patients with hepatic impairment since both drugs are excreted renally without previous metabolism and are not bound to plasma proteins.[185] Moreover, gabapentin was not found to be clearly associated with hepatic injury, and thus probably represents the safest choice for the treatment of neuropathic pain in patients with liver disease. Several cases of pregabalin hepatotoxicity have been reported. In one of the reported cases, pregabalin hepatotoxicity occurred in a patient with underlying liver disease.[186] Physicians must be aware of the possible, although rare, occurrence of pregabalin-induced or -aggravated liver injury. As for other patients, in the case of hepatic impairment, these drugs should be started at low doses and titrated cautiously in order

to minimize the dose-dependent dizziness and sedation.[187]

Other Anticonvulsants

Other anticonvulsants used in the treatment of neuropathic pain such as carbamazepine are contraindicated in patients with hepatic impairment due to the important risk of hepatotoxicity.[176]

3.4.3 Opioids

Neuropathic pain states were, for a long time, considered resistant to opioid analgesia. However, some randomized controlled trails have shown a decrease in neuropathic pain after opioid treatment.[188] The use of opioids in patients with hepatic impairment is discussed in section 3.3. Due to the potential risk of development of tolerance or addiction with the long-term use of these drugs and the risk of aggravating hepatic encephalopathy, opioids should be used cautiously and only as second- or third-line neuropathic pain treatment in this population.

4. Conclusion and Clinical Recommendations

The fear of aggravating pre-existing liver disease often leads to undertreatment of pain in patients with hepatic impairment. Ideally, analgesics as well as other hepatically cleared or hepatotoxic drugs, should be avoided in this population and non-pharmacological interventions should be preferred whenever possible. However, in some situations, such as postoperative pain, avoiding the use of analgesics would be unethical. Analgesic drugs can be used in patients with hepatic impairment, but the choice of drug and its dose must be made carefully.

In the limited number of studies existing on this subject, the very young and very elderly populations have often been left out. The selection of suitable drug or dose is even more difficult for this extreme age population or for patients with other co-morbidities.

Drug-drug interactions are another concern in patients with hepatic impairment. For example, the co-administration of NSAIDs with other drugs that could provoke gastrointestinal bleeding, such as low-dose aspirin or SSRIs, or with drugs that could impair glomerular filtration, such as angiotensin-converting enzyme inhibitors, should be avoided in this particularly vulnerable population. Furthermore, opioids should not be combined with any other sedative or anxiolytic drugs to reduce the risk of precipitating hepatic encephalopathy. From a pharmacokinetic point of view, in this population, physicians should avoid the prescription of drugs altering CYP activity which can further modify the metabolism and elimination of other hepatically cleared drugs, analgesics included.

When choosing an analgesic, physicians should follow the guidelines for the type of pain and then select an analgesic within these guidelines that would be suitable and safe in patients with hepatic impairment.

Paracetamol at low doses (maximum 2 g/day) and for a short duration can be used in patients with hepatic impairment for the treatment of weak nociceptive pain. When paracetamol is prescribed, informing the patient about the maximal daily dose and the presence of this drug in many over-the-counter medications is important. NSAIDs should be avoided in patients with liver disease because of their antiplatelet activity, gastrointestinal irritation, the increased risk of acute renal failure, and the potential and unpredictable risk of drug-induced liver injury (e.g. with diclofenac, lumiracoxib and nimesulide).

The disposition of most opioids is affected in severe liver disease. The efficacy of some of them, such as codeine and possibly tramadol and oxycodone, might be compromised because their biotransformation to active opioids is decreased. Other opioids, such as pethidine, should be avoided because of possible accumulation of toxic metabolites.

When using opioids in patients with hepatic impairment, the dosing regimen should be carefully established. For highly extracted drugs, such as morphine or hydromorphone, the initial oral dose must be reduced owing to increased bioavailability. For drugs with decreased clearance, repeated doses should be decreased, or dosing intervals increased in order to avoid drug accumulation. The best approach in hepatically impaired patients is individual titration with short-acting

opioids to achieve optimal doses for pain relief without significant adverse effects.

Glucuroconjugated morphine or hydromorphone at reduced doses, and intravenous fentanyl, sufentanil and remifentanil appear to be the best opioid choices in patients with liver disease.

Opioids such as morphine, pethidine or hydromorphone, which have renally cleared active or toxic metabolites, should be avoided in the presence of hepatorenal syndrome. The dispositions of phenylpiperidine opioids – fentanyl, sufentanil and remifentanil – appear to be unaffected by hepatorenal syndrome. From a theoretical point of view, buprenorphine might be a potential opioid to use in patients with liver disease. However, additional clinical studies are needed to provide evidence of its disposition and safety in this group of patients. Further research is also necessary to determine the disposition of continuously administered fentanyl and sufentanil and the analgesic effects of codeine and tramadol in patients with liver disease.

All patients with hepatic impairment receiving opioids must be carefully monitored for any signs of hepatic encephalopathy, regardless of the medication prescribed.

Gabapentin or low-dose TCAs appear to be the safest options for the management of neuropathic pain in patients with hepatic impairment.

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