REVIEW

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The Safe Use of Analgesics in Patients with Cirrhosis: A Narrative Review

Jiayi Ma, MD,[a] Einar Stefán Björnsson, MD, PhD,[b,c] Naga Chalasani, MD[a]

[a]Indiana University School of Medicine and Indiana University Health, Indianapolis; [b]Department of Gastroenterology, Landspitali University Hospital, Reykjavik, Iceland; [c]Faculty of Medicine, University of Iceland, Reykjavik, Iceland.

ABSTRACT

Pain is prevalent in patients with cirrhosis. Due to potential alterations in drug metabolism, risk for adverse effects, and complications from cirrhosis, physicians are often faced with difficult choices when choosing appropriate analgesics in these patients. Overall, acetaminophen remains the preferred analgesic. Despite its potential for intrinsic liver toxicity, acetaminophen is safe when used at 2 g/d. In contrast, non-selective nonsteroidals should be avoided due to their multiple side effects, including worsening renal function, blunting diuretic response, and increasing risk of portal hypertensive and peptic ulcer bleeding. Celecoxib can be administered for short term (≤5 days) in patients with Child's A and Child's B cirrhosis (50% dose reduction). Opioids carry the risk of precipitating hepatic encephalopathy and should generally be avoided, when possible. If clinical situation demands their use, opioid use should be limited to short-acting agents for short duration. Gabapentin and pregabalin are generally safe. Duloxetine should be avoided in hepatic impairment. Topical diclofenac and lidocaine seem to be safe in patients with cirrhosis.
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Pain is common and affects 30%-79%[1] of patients with cirrhosis. Due to potential changes in drug metabolism, risk for adverse effects, and complications of cirrhosis, physicians are often faced with difficult choices when choosing appropriate analgesics to prescribe in these patients. Acetaminophen (APAP), despite its intrinsic hepatotoxicity, is generally considered safe when used in moderation. Available data related to using nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant agents such as antiepileptics, antidepressants, and topical agents are discussed as well.

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Requests for reprints should be addressed to Naga Chalasani, MD, Indiana University School of Medicine and Indiana University Health, Fairbanks Hall Suite 1600, 340 West 10th Street, Indianapolis, IN 46202.

E-mail address: nchalasa@iu.edu

ACETAMINOPHEN (APAP)

Many clinicians consider APAP risky to use in patients with cirrhosis due to its well-known intrinsic liver injury. Nevertheless, the amount of APAP required to cause acute liver failure has been shown to be >10-15 g,[2] which is far beyond the recommended daily limit of 4 g in the general population.

APAP Use By Individuals with Heavy Alcohol Consumption

Patients at increased risk of APAP hepatotoxicity are those who drink alcohol excessively and chronically, including patients with alcohol-associated liver disease. Alcohol has been shown to induce hepatic cytochrome P450 2E1,[3] and chronic alcohol overconsumption can be associated with glutathione deficiency,[4] both of which increase levels of N-acetyl-p-benzoquinone imine, the hepatotoxic intermediate of APAP. In a seminal paper, Zimmerman and Maddrey[5]

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recognized APAP-induced hepatotoxicity in association with excessive alcohol intake. The authors identified patients using alcohol regularly who developed severe acute liver injury or liver failure with concurrent APAP use, and some patients developed acute liver failure while taking doses within the recommended ≤4 g daily. They recommended that chronic and heavy alcohol drinkers (>60 g/d) take ≤2 g of APAP per day.[5]

Two additional studies investigated APAP use in chronic drinkers. Dart et al[6] randomized patients with active alcohol use to APAP 4 g per day or placebo for 5 days. In patients with chronic hepatitis C or alcoholic liver disease, there was no evidence of liver injury due to APAP.[6] In another study, patients with alcohol use were randomized to APAP 4 g per day or placebo for 3 days.[7] Patients with underlying alcoholic liver disease did not show a significant difference in the pre- and post-treatment alanine aminotransferase values.[7]

Short-Term (<14 Days) Use of APAP

Multiple studies (Table 1[8-10]) have demonstrated the safety of acute APAP use in patients with cirrhosis. Benson[8] performed an early trial of APAP in which 6 patients with cirrhosis were given APAP 4 g daily for 5 days and levels measured. APAP plasma concentrations did not reach potentially toxic levels during the trial.[8] Furthermore, no patients had changes in clinical status or laboratory tests. Subsequently, a larger study was undertaken in 20 subjects, 8 with cirrhosis. After 13 days of APAP 4 g or placebo daily, there were no differences in aminotransferase levels between patients. There was no change in the clinical status of any subject. The author concluded that there was no contraindication in using APAP at 4 g/d for short periods of time in stable chronic liver disease.[8]

In another study, 13 patients (4 cirrhosis, 9 controls) were given APAP 1 g, 3 times daily for 5 days.[9] Despite significantly higher APAP plasma concentrations in cirrhotics vs controls, there were no signs of hepatotoxicity or significant changes in alanine aminotransferase. More recently, McGill et al[10] evaluated using lower-dosage APAP in patients with compensated cirrhosis. In this study, 12 patients with cirrhosis and 12 noncirrhotic healthy volunteers received 1.3 g of APAP daily for 4 days and 650 mg on day 5. There was no evidence of liver injury through either traditional biochemistries or novel markers. Interestingly, APAP adduct clearance was significantly delayed in cirrhosis, but the clinical significance of this is unclear. Thus, short-term use of APAP in doses of 3-4 grams per day appears to be safe in patients with cirrhosis.

CLINICAL SIGNIFICANCE

In patients with cirrhosis:

- Acetaminophen is preferred.
  - Acute pain: 3-4 g/d.
  - Chronic (>14 days) pain: 2g/d.
  - Avoid alcohol.
- Nonsteroidal anti-inflammatory drugs are contraindicated.
- Celecoxib (<5 days) can be used in Child's A and B (with dose reduction) cirrhosis.
- Avoid long-term opioids. For short-term use, give immediate-acting formulations.
- Gabapentin and pregabalin are safe; use cautiously in patients with hepatic encephalopathy.
- Topical lidocaine and diclofenac are safe.

Long-Term (>14 Days) Use of APAP

To date, there are few data about the safety of long-term use of APAP in patients with cirrhosis. However, due to changes in APAP pharmacokinetics leading to longer half-life and higher plasma concentrations in patients with cirrhosis, it seems reasonable to recommend a reduced daily dose for chronic use. Furthermore, 2 case-control studies[11,12] offer real-life safety data on long-term APAP use (Table 2).

Khalid et al[11] investigated the effects of analgesics on hepatic decompensation requiring hospitalization in 244 patients. When the authors compared the rates of APAP use between cases (n = 91) admitted to the hospital vs controls (n = 153) not hospitalized, they found no significant difference between the groups. The median dose of APAP in the last 30 days prior to hospitalization in cases and controls were comparable at 2 and 2.3 g, respectively. Even after matching by Child-Pugh score, the subgroup analysis yielded the same results.[11] Similarly, Fenkel et al[12] performed a similar study in 213 patients. Cases (n = 89) and controls (n = 124) had the same definitions as the study by Khalid et al.[11] Similar findings were reported as the proportion of patients using APAP within the last 30 days prior to admission did not differ significantly between cases and controls.[12]

Combining pharmacokinetic parameters, safety data from short-term trials, and real-life experience, APAP can be taken chronically at a dose of 2 g/d in patients with cirrhosis who abstain from alcohol. Furthermore, because APAP lacks side effects such as nephrotoxicity and gastrointestinal bleeding, and does not trigger hepatic decompensation when used appropriately, it is the preferred analgesic.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Non-Selective NSAIDs

The NSAIDs are another class of analgesic medications available over the counter. However, unlike APAP, NSAIDs should be avoided in patients with cirrhosis, due to side effects and serious adverse events. NSAIDs inhibit prostaglandin synthesis, which may decrease glomerular filtration rate (GFR) and renal blood flow in patients with

Table 1 Safety of Short-Term Use of Acetaminophen

Study Publication Year	Patient Population	Liver Disease Severity	APAP n	Safety
McGill et al (2022)[10]	12 patients	11/12 CP A	12/12 with cirrhosis 12/12 without cirrhosis	No significant change in ALT over study period in either group
Benson (1983)[8]	26 patients	CP not available	6/6 in pilot study 20 in follow-up study	Pilot: APAP for 5 days: no changes in clinical status or laboratory tests Follow up: APAP for 13 days: no changes in clinical status or liver tests
Andreasen and Hutters (1979)[9]	13 patients, 4 with cirrhosis	CP not available	4/4 with cirrhosis 9/9 without cirrhosis	Participants with cirrhosis had significantly higher APAP plasma concentration on days 2 and 5. No signs of hepatotoxicity or significant changes in ALT between groups

ALT = alanine aminotransferase; APAP = acetaminophen; CP = Child-Pugh.

advanced cirrhosis, with risk of acute kidney injury.[13] Furthermore, NSAIDs can blunt response to diuretics and decrease natriuresis, leading to ascites.[13] Ibuprofen has been shown to decrease urinary output and sodium excretion in patients with decompensated cirrhosis.[14] Naproxen has been shown to reduce renal blood flow, natriuresis, response to furosemide, and inhibit platelet aggregation in patients with cirrhosis and ascites.[15]

Five studies[11,12,16-18] (Table 3) have analyzed the adverse clinical impact of NSAIDs in patients with cirrhosis. De Lédinghen et al[16] examined 200 patients with cirrhosis and portal hypertensive bleeding. Patients (n = 125) with cirrhosis-related portal hypertensive bleeding were more likely to have used NSAIDs during the week prior to their admission than controls (n = 75) with cirrhosis and non-bleeding esophageal varices (25% vs 11%, $P = .016$). After adjusting for confounders, NSAID use significantly increased the odds of portal hypertensive bleeding by 2.9 times.[16]

Two other studies assessed the effect of NSAIDs on hospitalization.[11,12] Khalid et al[11] found a significantly lower proportion of admitted patients with cirrhosis and hepatic decompensation reported using NSAIDS, compared with control patients not admitted. However, cases used larger doses of NSAIDs and for more days than control subjects, suggesting that NSAIDs may have contributed to their hepatic decompensation and hospitalization.[11] Fenkel et al[12] conducted a similar study but found no significant association between non-excessive NSAID use and risk of liver-associated hospitalization.

Lee et al[17] investigated the effect of NSAIDs on the risk of upper gastrointestinal bleeding in a national cohort. After adjusting for confounding medications, both oral and parenteral non-selective NSAIDs were associated with increased risk of variceal and non-variceal upper gastrointestinal bleeding. Celecoxib was not associated with an increased risk of upper gastrointestinal bleeding.[17] Luo et al[18] examined 4000 patients with cirrhosis and peptic ulcer bleed with NSAID use. The authors found that oral NSAIDs were associated with a significantly increased risk of developing peptic ulcer bleeding by 94%.[18]

Selective Nonsteroidal Anti-Inflammatory Drugs

Cyclooxygenase-2 (COX-2) inhibitors are selective NSAIDs with better gastrointestinal tolerability and potential for less

Table 2 Acetaminophen Use in Cirrhosis and Rate of Hospitalization

Study Publication Year	Patient Population	Liver Disease Severity	APAP n	Safety
Fenkel et al (2010)[12]	213 patients	CP not available	Cases 17/89 Controls 32/124	APAP use did not affect hospitalization
Khalid et al (2009)[11]	244 patients	CP A/B/C Cases 7/41/43* Controls 107/40/5*	Cases 17/91 Controls 38/153	APAP use did not differ significantly between cirrhotic cases and controls 30 days prior to hospitalization

ALT = alanine aminotransferase; APAP = acetaminophen; CP = Child-Pugh.
*Statistically significant ($P < .05$).

Table 3 Safety of Nonsteroidal Anti-inflammatory Drug Use in Cirrhosis

Study Publication Year	Patient Population	Liver Disease Severity	NSAID n	Safety
Khalid et al (2009)[11]	244 patients	CP A/B/C Cases 7/41/43* Controls 107/40/5*	Cases 15/91* Controls 48/153*	Doses and days of NSAID use were higher among cirrhosis cases
Fenkel et al (2010)[12]	213 patients	CP not available	Cases 9/89 Controls 17/124	NSAID use and hospitalization 0.77 (0.30-1.99) p=0.587
De Ledinghen et al (1999)[16]	200 patients	CP A/B/C Cases 24/49/52 Controls 9/31/35	Cases: 31/125* Controls 8/75*	NSAID use and first portal hypertensive bleed OR 2.9 (1.8-4.7) $P = .022$
Lee et al (2012)[17]	4876 patients	CP not available	2494/4876	Risk of upper gastrointestinal bleeding and NSAID use Celecoxib aOR: 1.44 (0.89-2.31) Oral Non-selective NSAIDs aOR: 1.87 (1.66-2.11) Parental Non-selective NSAIDs aOR: 1.90 (1.55-2.32)
Luo et al (2012)[18]	4013 patients	CP not available	475/4013	Risk of peptic ulcer bleeding with NSAID use Oral NSAIDs HR 1.94 (1.37-2.75) $P < .001$

aOR = adjusted odds ratio; CP = Child Pugh; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio.
*Statistically significant ($P < .05$).

nephrotoxicity.[15,19,20] Celecoxib is the only COX-2 inhibitor currently marketed in the United States, but other COX-2 inhibitors, such as parecoxib and etoricoxib, are available outside the United States. According to the US Food and Drug Administration package insert, celecoxib dose should be reduced by 50% in patients with Child's B cirrhosis, whereas it should be avoided in Child's C cirrhosis.[21] Two studies evaluated the effect of very short-term celecoxib on renal physiology in patients with cirrhosis. One trial did not find significant changes in renal function or diuretic response after 5 doses of 200 mg celecoxib administered every 12 hours.[15] In another study,[20] celecoxib 200 mg daily for 5 days did not worsen serum creatinine or diuretic response to water load, but 4 of 9 patients had >20% reduction in their GFR. Because this study did not have a control group it is difficult to attribute this decrease in GFR to celecoxib. Long-term studies evaluating efficacy and safety in patients with cirrhosis are lacking. Long-term use of COX-2 inhibitors in patients with cirrhosis should be avoided regardless of their Child's class, whereas short-term (<5 days) celecoxib might be tried and administered cautiously in patients with Child's A and B cirrhosis.

Topical Diclofenac

Diclofenac is available in topical form as an over-the-counter analgesic. Compared with its oral formulation, the rate of hepatotoxicity with topical formulation is rare (<1%), which is comparable with vehicle applications.[22] This might be due to the limited bioavailability of topical vs oral diclofenac.[23] There are no published reports evaluating the safety and efficacy of topical diclofenac in patients with cirrhosis and hepatic impairment. However, it is expected to be safe in patients with cirrhosis due to its very low bioavailability (<10% of systemic administration).

OPIOIDS

Opioid Use in Patients with Cirrhosis

Opioids are another class of medications commonly prescribed for pain. Interestingly, when taken at analgesic doses, opioids have not been shown to cause drug-induced liver injury or acute liver failure.[24] However, the liver is the main site of metabolism for most opioids. Patients with cirrhosis have decreased drug clearance and increased bioavailability of opioids, which can lead to prolonged half-life and accumulation of drug metabolites.[25] There are several studies that characterized opioid use in patients with cirrhosis[26-32] (Table 4).

Tapper et al[26] followed a cohort of 300 patients with cirrhosis and found that opioid use was significantly and negatively associated with health-related quality of life and sleep. In another study of 144 hospitalized patients with cirrhosis, opioid use was independently associated with hospital admission.[27] Other studies show that regular opioid use is common among inpatients with cirrhosis and is independently associated with excessive length of stay.[28,29] Additionally, 2 studies found opioid use to increase the risk of hepatic encephalopathy.[30,31] Finally, one study found chronic opioid use was independently associated with prolonged mechanical ventilation.[32]

Tramadol

Tramadol is a partial opioid agonist and serotonin and norepinephrine reuptake inhibitor. Due to its partial agonism, it does not induce maximal activation of the opioid receptor. As a result, studies have shown tramadol to cause less respiratory depression[33] and to have low abuse potential.[34] Nevertheless, hepatic impairment significantly alters the pharmacokinetics of tramadol, with cirrhotic patients

Table 4 Safety of Opioid Use in Patients with Cirrhosis

Study Publication Year	Patient Population	Liver Disease Severity	Opioid n	Safety
Rubin et al (2021)[28]	116,146 patients	CP and MELD not available	62% any opioid use 34% regular opioid use	Rate of serious opioid-related adverse events With cirrhosis: 1.6% Without cirrhosis: 1.9% aOR 0.96 (0.81-1.13)
Moon et al (2020)[31]	6451 patients	CP and MELD not available	1806/6451	Opioid use and developing hepatic encephalopathy Short term aHR: 1.44 (1.07-1.94) Chronic opioids aHR 1.84 (1.07-3.12)
Moon et al (2020)[29]	217 patients	Median MELD Opioids 13.9 No opioids 15.0	118/217	Inpatient opioid use associated with 1.52 times longer length of stay versus non opioid users
Glick et al (2020)[32]	144 patients	Mean MELD-Na 25	45/144	Chronic opioid use independently predicts prolonged mechanical ventilation OR 2.67 (1.10-6.55)
Tapper et al (2019)[30]	166,192 patients	CP and MELD not available	↑ from 9% to 20% opiate use in patients developing hepatic encephalopathy during study period	Impact of opioid use on newly diagnosed hepatic encephalopathy aHR 1.24 (1.21-1.27)
Tapper et al (2019)[26]	300 patients	CP A 70%	67/300	Opioid use significantly negatively affected HRQOL Opiate use associated with increased odds of poor sleep OR 2.85 (1.11-7.29)
Acharya et al (2017)[27]	144 patients	On opioids: mean MELD 20.2 Not on opioids: mean MELD 20.17	62/144	Opioid use independently predictive of readmissions OR 2.7 (1.3-6.1)

aHR = adjusted hazard ratio; aOR = adjusted odds ratio; CP = Child Pugh; HRQOL = health-related quality of life; MELD = model for end-stage liver disease; OR = odds ratio.

showing significant increases in plasma drug concentration and elimination half-life.[35] Expectedly, drug labeling for the immediate-release formulation recommends 50 mg every 12 hours in severe hepatic impairment,[36] while the extended-release formulation is contraindicated in severe hepatic impairment.[37]

Hydrocodone

Hydrocodone as a single drug is only available in the extended-release formulation. Immediate-release hydrocodone is a combination product, most often combined with APAP. For the immediate-release formulation, the manufacturer's label states that patients with hepatic impairment may have higher plasma concentrations of drug than those with normal liver function, and recommends a low initial dose.[38] Importantly, patients must also be counseled to not exceed 2 g daily of APAP from all sources. The extended-release formulation is available as a tablet or capsule. The tablet formulation shows increased maximum concentration and total drug concentration in moderate and severe hepatic impairment,[39] while the capsule formulation shows increased maximum concentration and total drug concentration in mild and moderate hepatic impairment, and was not studied in severe hepatic impairment.[40] The manufacturers recommend no dose adjustments in mild or moderate hepatic impairment for either formulation, and 50% initial dose reduction for the tablet form vs 10 mg every 12 hours for the capsule formulation in severe hepatic impairment.[39,40] However, due to primary hepatic metabolism and increased maximum and total drug concentrations, it is likely the safest practice to avoid long-acting formulations all together.

Oxycodone

Oxycodone is available as a single drug in both immediate and extended-release formulations and in combination with APAP. Oxycodone undergoes extensive hepatic metabolism. However, too few patients with hepatic impairment were evaluated in clinical trials for immediate release oxycodone.[41] In a study of hepatically impaired vs healthy volunteers, oxycodone peak concentration, total drug concentration, and half-life were all increased in hepatically impaired participants.[42] The manufacturer's label

recommends starting oxycodone at a reduced dose due to potentially lower hepatic clearance.[41] Similar pharmacokinetic changes are reported for extended-release oxycodone.[43] The manufacturer recommends starting extended-release oxycodone at one-third to one-half the usual dosage.[43] Overall, immediate-release oxycodone should be started at the lowest effective dose with increased dosing intervals. Avoid extended-release formulations.

Morphine

Morphine is available in both immediate and extended-released formulations for multiple routes of administration. In patients with cirrhosis, it has significantly lower plasma clearance, longer elimination half-life, and greater oral bioavailability vs healthy controls for both intravenous and oral administration.[44,45] However, manufacturers' labeling of morphine in hepatic impairment remains vague, with both the oral solution and tablet labeling stating that adequate pharmacokinetic studies of morphine have not been conducted in patients with severe hepatic impairment, and they recommend starting with a lower-than-usual dose.[46,47] Similar recommendations are found for the extended-release formulation.[48]

Hydromorphone

Hydromorphone is available as immediate and extended-release formulations. It mainly undergoes hepatic glucuronidation, which is less affected in cirrhosis.[49] However, a single-dose study of oral hydromorphone in patients with moderate hepatic impairment has shown significantly higher peak and total drug exposures vs normal hepatic function.[50] Similar findings are reported for the extended-release formulation,[51] and neither formulation has been studied in severe hepatic impairment.

Fentanyl

Fentanyl is a synthetic opioid frequently used in intravenous or transdermal form. Manufacturer labeling states that fentanyl should be used with caution in patients with liver dysfunction due to extensive hepatic metabolism, and to reduce dosages as needed.[52] In a single-dose study of intravenous fentanyl in patients with compensated cirrhosis vs controls, the pharmacokinetic parameters were not significantly different between the 2 groups.[53] In contrast, transdermal fentanyl exhibits increased maximum concentration and total drug concentration in patients with cirrhosis vs controls.[54] As a result, the manufacturer recommends against using transdermal fentanyl in severe hepatic impairment, and suggests 50% dose reduction in mild and moderate hepatic impairment.

MISCELLANEOUS ANALGESICS

Antiepileptics

Antiepileptics such as gabapentin and pregabalin are sometimes used to treat neuropathic pain. The LiverTox, an authoritative resource for drug-induced liver injury, classifies these 2 agents as class C, indicating that clinically apparent liver injury is uncommon.[55,56] Mechanistically, both agents are likely safe to use in hepatic impairment, as they are primarily renally eliminated in an unchanged form and undergo negligible hepatic metabolism.[57] However, rare episodes of drug-induced liver injury have been attributed to both agents. Chalasani et al[58] described 66 cases of drug-induced liver injury due to antiepileptics; 4 were due to gabapentin and one to pregabalin. Einarsdottir and Björnsson[59] also reported another case of acute liver failure suspected due to pregabalin, which improved after drug cessation. Nonetheless, due to their minimal hepatic metabolism and rarity of drug-induced liver injury, gabapentin and pregabalin can likely be used safely in patients with cirrhosis.

Antidepressants

Serotonin-norepinephrine reuptake inhibitors have also been used in pain management. Within this class of medications, duloxetine is widely used for pain management.[60] Vuppalanchi et al[61] described a case series of 7 patients with liver injury due to serotonin-norepinephrine reuptake inhibitors. In an analysis of spontaneous reporting of hepatic adverse events for 1.5 million person-years of exposure to duloxetine, there were 26 probable and 127 possible cases of liver injury due to duloxetine, including 37 with severe hepatic injury and 9 with hepatic failure.[62] According to the prescribing information for duloxetine, use in patients with substantial alcohol use or evidence of chronic liver disease is not recommended.[63]

Topical Lidocaine

The bioavailability of lidocaine in gel or patch form is very low at 3% in healthy volunteers.[64] Due to limited systemic absorption, topical lidocaine is unlikely to undergo extensive first-pass metabolism and does not need adjustment for liver dysfunction.[2] Topical lidocaine and lidocaine patches can be used safely in patients with cirrhosis.

CONCLUSION

APAP is the preferred analgesic in patients with cirrhosis. For acute pain, 3-4 g/d is safe. For chronic (>14 days) pain, use 2 g/d. Avoid alcohol use with APAP. NSAIDs, opioids, and duloxetine should be avoided wherever possible. Gabapentin, pregabalin, and topical lidocaine and diclofenac may be safely used in patients with cirrhosis.

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