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Review Article

Pain Management in Patients with Cirrhosis; A Mini Narrative Literature Review with Evidence-Based Recommendations

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ABSTRACT

Cirrhosis is a significant public health concern, causing approximately 790,000 deaths annually. Despite the possibility of adverse effects from analgesics, which can be fatal and preventable, guidelines for their use in this setting do not exist, and there is a lack of research in this field. Thus, this review aims to summarize and analyze published data on different opioids in patients with liver cirrhosis to provide possible evidence-based guidelines for the safe use of opioids. Both compensated and decompensated patients should avoid NSAIDs. Because of the risk of hepatic encephalopathy, opioids must be avoided or used sparingly at low and infrequent doses. A long-term follow-up is required for toxicity, adverse effects, and complications of all pain relievers.

Keywords: cirrhosis, pain management, opioid, analgesia, NSAIDs

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INTRODUCTION

Cirrhosis is a significant public health concern, causing approximately 790,000 deaths annually (1). According to autopsy studies, hundreds of millions of people are affected worldwide (1). In addition to long-term alcohol abuse(2,3), hepatitis B (4) and C infection(5), autoimmune hepatitis (6), and fatty liver (7) are the most common causes of cirrhosis. The liver's role is notable in the metabolism and pharmacokinetics of most drugs. Therefore, the use of medications in patients with cirrhosis often raises several concerns, especially for gastroenterologists and hepatologists, who are frequently asked for their opinions about the safety of drugs in this setting. Healthcare professionals usually struggle to manage pain in people with cirrhosis due to the difficulty of the disease.

Although pain relief is essential for improving the quality of life of all patients, healthcare providers often regard the use of analgesics in patients with cirrhosis as unsafe. This results in the undertreatment of pain in this population. A significant concern with prescribing analgesics to patients with cirrhosis is the possibility of precipitating or worsening renal failure (8), provoking hepatic encephalopathy (9), and causing portal hypertension (8). As a result of the altered metabolic processes and pharmacokinetics associated with opioids in these patients, there is also an increased risk for oversedation, undersedation (10), and constipation (11).

Despite the possibility of adverse effects from analgesics, which can be fatal and preventable, guidelines for their use in this setting do not exist, and there is a lack of research in this field. Thus, this review aimed to summarize and analyze published data on different analgesics in patients with liver cirrhosis to provide possible evidence-based guidelines for their safe use.

Hepatic drug metabolism in patients with cirrhosis

In cirrhosis, the activity of cytochrome enzymes 1A2 and 3A4, which are crucial for drug metabolism, is reduced by at least 50% (12). This reduction in enzyme activity has a significant impact on drug clearance, leading to increased serum drug concentrations. Medications with a low extraction ratio, which rely heavily on the liver's metabolic capacity for intrinsic clearance through these enzymes, are therefore more affected than medications with a high extraction ratio (like morphine) (12). Albumin, a liver-produced protein, plays a crucial role in medication binding (13). In patients with cirrhosis, albumin production is significantly decreased (12). This condition, combined with water and salt retention, can unbind the medications in the serum, increasing the risk of toxicity (12). Besides these, cirrhosis causes the formation of portosystemic shunts (14). It impairs the first liver passage, resulting in a decrease in liver drug clearance and necessitating a reduction in the initial dose. Additionally, portosystemic shunting may reduce sinusoidal permeability to oxygen, which is necessary for liver oxidative cytochrome P450 enzymes to function, impairing oxygen access to hepatocytes and thereby reducing the liver's ability to oxidize drugs (12).

It has been found that patients with well-compensated cirrhosis with near-normal liver function experience the same or only minor changes in drug pharmacokinetics (15). In contrast, patients with severe cirrhosis have significant trouble with drug synthesis (15). The figure below summarizes the effects of cirrhosis on drug metabolism. A summary of the above paragraphs is shown in the chart below.

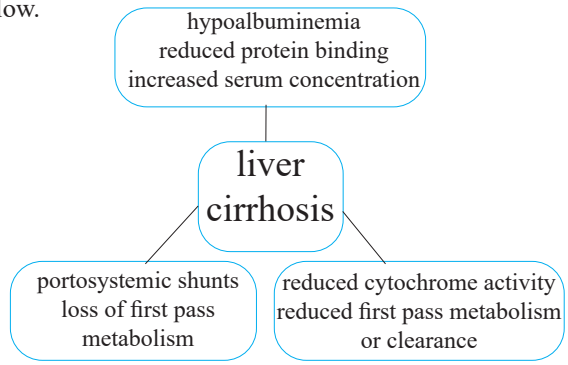

Figure 1. Effects of liver cirrhosis on drug metabolism.

Use of analgesics in patients with cirrhosis

The liver is responsible for the metabolism of many commonly used analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids (12). Those suffering from chronic liver disease, especially cirrhosis, are more likely to experience adverse effects from these pain relievers, many of which are potentially fatal (15). Often, prescribing analgesics to these patients raises the risk of precipitating or worsening renal failure (16), causing hepatic encephalopathy (9), portal hypertension (8), and gastrointestinal bleeding (17). In this patient population, pain management is challenging because there are no evidence-based guidelines for the use of analgesics.

NSAIDs

It is generally recommended to avoid NSAIDs in patients with advanced chronic liver disease or cirrhosis due to the increased risk of variceal bleeding (15), impaired renal function (16), and ascites (18). It has been shown, however, that various types of NSAIDs work differently in cases of cirrhosis. It has been reported that naproxen, metabolized by the P450 system, can cause hepatic damage (19), especially in people with liver disease. One of the most likely NSAIDs to cause liver damage is diclofenac (20). Damage can result in elevated liver function tests (LFTs) but not symptoms in many cases (20). Etoricoxib, however, is reported to be unaffected by hepatic impairment during absorption (21). In addition,

etoricoxib's binding to plasma proteins was not affected by hepatic disease (21). Mild and moderate hepatic insufficiencies tolerated etoricoxib well. It has been shown that long-term aspirin use does not increase the risk of bleeding in patients with cirrhosis, reduces the risk of hepatocellular carcinoma (HCC), and may be beneficial if used in an appropriate dosage for these patients (22).

Opioids

Those with advanced liver disease or cirrhosis should use opioids with caution. Reduced doses and prolonged intervals of administration should be used with morphine, oxycodone, and hydromorphone (23). The use of tramadol in patients with decompensated cirrhosis should be avoided due to the possibility of severe side effects, including respiratory depression (24). It has been reported that buprenorphine treatment causes mild to moderate liver injury and a mild to transient elevation of serum enzyme levels (25). Since codeine's effects are difficult to predict, alternative therapies should be considered (12). Hepatic encephalopathy can be caused by chronic opioid administration because tolerance results in escalating doses (15). Even though methadone and fentanyl are heavily protein-bound, their metabolism does not produce toxic products in patients with cirrhosis (8). Consequently, these compounds may be better tolerated. Table 1 shows a summary of the suitability of opiate types for patients with cirrhosis.

Table 1. A summary of opioids' effects when used in liver diseases.

	Recommendation	
	Class A/B cirrhosis	**Class C cirrhosis**
Codeine	Use it with caution; use lowest available dose (15mg) and titrate up slowly; Avoid in renal insufficiency.	Should be avoided
Tramadol	Safe to use; No need for dose adjustment	An immediate-release form dose (50mg every 12h) can be used; avoid extended-release formulation.
Hydromorphone	Safe to use (preferred opiate); No need for dose adjustment	Use with caution; administered at reduced doses and prolonged dosing intervals
Morphine	Use it with caution; administer at the minimum effective dose; avoid in renal insufficiency	Use it with caution; administer at the minimum effective dose and prolonged dosing intervals; avoid in renal insufficiency
Buprenorphine	Use it with caution; use only the lowest dose	Should be avoided
Methadone	Safe to use; no need for dose adjustment	Use it with caution; administered at reduced doses and prolonged dosing intervals.
Fentanyl (patch)	Use it with caution; reduce dose by 50%	Use it with caution; administered at reduced doses and prolonged dosing intervals (12.5 µg Q72h)
Fentanyl (intravenous)	Safe to use	Safe to use; first opiate choice in hepatorenal syndrome

A longer interval between doses and possibly lower doses of opioids is generally recommended for patients with cirrhosis when opioids are required to achieve optimal pain relief without adverse effects. The patient must be closely controlled for signs of sedation, constipation due to opioids, and early encephalopathy. The opioids should be discontinued immediately if any of these complications are observed.

Acetaminophen (Paracetamol)

Acetaminophen is a safe and effective analgesic for patients with chronic liver disease (15).

As a result of concerns regarding acetaminophen's altered metabolism in patients with chronic liver disease, acetaminophen is often restricted to 2 grams per day for those with cirrhosis or advanced chronic liver disease (26). It causes acute liver failure and severe hepatic necrosis when consumed at doses greater than 10 grams (26).

CONCLUSION:

When it comes to analgesia, patients with cirrhosis often encounter challenges. Unfortunately, evidence-based guidelines do not provide clear instructions on the use of analgesics in these patients.

The general recommendation is to administer lower doses or reduce the dosing frequency when treating cirrhosis, even with drugs that may be hepatotoxic. For long-term use, it is advised to limit paracetamol dosage in patients with cirrhosis to two grams per day. Despite the slower elimination of paracetamol in these patients, repeated administration does not lead to hepatotoxic intermediates. Both compensated and decompensated patients with cirrhosis should avoid NSAIDs. Opioids, due to the risk of precipitating hepatic encephalopathy, should be avoided or used sparingly at low and infrequent doses. A comprehensive long-term follow-up is necessary to monitor for toxicity, adverse effects, and complications.

CONFLICT OF INTEREST:
The authors declare no conflict of interest related to this work.

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