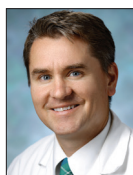


ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Pain Management in Liver Disease



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G&H How prevalent are acute and chronic pain in patients with liver disease, and what are the most common sources of pain in this setting?

JH Pain is very common in patients with liver disease, much like it is in the general population. Patients with liver disease can have pain that any person may have (eg, chronic back or knee pain) and are not immune to having other general conditions that cause pain, such as migraine headaches. Some liver conditions, especially cirrhosis and advanced liver disease, can exacerbate that pain.

In addition, patients with liver disease may have worsening ascites, or accumulation of fluid in the abdomen, which stretches the abdomen forward and puts stress on the back. Acute flares of a chronic liver injury, particularly with certain autoimmune liver diseases, can cause right-sided abdominal pain that can be both acute and chronic. Patients with alcohol-related liver disease often have peripheral neuropathy, which can be a severe nerve-mediated pain that occurs in the lower extremities or hands and is described as burning or occasionally as pins and needles because of alcohol-induced toxicity to nerves. Primary sclerosing cholangitis and primary biliary cholangitis are autoimmune-mediated conditions of the liver that affect the bile ducts and cause acute and chronic abdominal pain. Severe acute hepatitis of any type (ie, drug-, viral-, or autoimmune-related) can also cause pain in the abdomen.

Finally, conditions in which the liver is enlarged for any reason (eg, because of a glycogen storage disease or iron overload) can hurt and cause a dull abdominal pain. Acute fatty liver disease can also sometimes cause

abdominal pain because the liver becomes engorged with fat and inflammation; this can also be seen with severe alcohol-induced hepatitis and chronic nonalcoholic fatty liver disease.

G&H How can pain be best evaluated in the setting of liver disease?

JH Clinicians should query patients for subjective measures of the quality of their pain. Patients should be asked to rate their pain on a scale of 0 to 10 and asked about triggers that make their pain worse (or, conversely, better), the duration of the pain, and how often it occurs during a week or month. More objective measures, such as imaging of the liver, may also be used to identify possible triggers of pain, for example, an enlarged liver or a dilated or strictured bile duct. Liver enzymes are a marker of liver inflammation; it is not unusual for a patient with very high liver enzyme levels to have abdominal pain because of the inflamed liver.

G&H How can clinicians separate pain from other symptoms that patients may perceive as pain (eg, constipation or bloating)?

JH As part of the evaluation process, it is important to ask specific questions so that patients can provide detailed answers that enable clinicians to understand the quality of the pain. For example, if a patient says that he or she has abdominal pain and bloating that gets much better after having a bowel movement, the pain is probably not related to the liver but to a side effect of a medicine (eg, lactulose). It can sometimes be difficult to differentiate,

for example, the pain of acute hepatitis vs acute cholecystitis, so imaging and laboratory tests can help determine the source. It can also be hard to distinguish between pain caused by liver disease and pain caused by pancreatitis, which can cause similar pain. Differentiating between similar pain requires a careful process of elimination using a thorough patient history and physical examination as well as laboratory tests, imaging, and occasionally even procedures such as endoscopies.

G&H What are the biggest challenges of managing pain in patients with liver disease?

JH One challenge is that many commonly used pain medicines, including some over-the-counter medicines, are not safe at standard doses in patients with liver disease. There are many misconceptions both within the public as well as within the medical community regarding which medicines are safe and which are not in this patient population. In addition, some of the stronger pain medicines, such as narcotics, may be problematic

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because they can cause confusion and mental status changes in patients who have abnormal liver function and therefore have abnormal clearance of those medications from the bloodstream. Thus, the toxicity of those medicines can be enhanced in patients with chronic liver disease. Some patients with chronic liver disease may also have had substance abuse problems in the past, so giving them an addictive substance may lead to new addictive behavior.

G&H How safe is acetaminophen use in patients with liver disease?

JH Acetaminophen is the most common cause of acute liver failure and drug-induced liver injury in the United States. It is well known that acetaminophen use beyond

8 g per day is toxic to the liver, but it is quite safe at low doses. That is often misunderstood. Patients with liver disease are frequently told that they can never take acetaminophen, but what they should be told is that they cannot take acetaminophen in high doses. High-dose acetaminophen should be avoided in patients with cirrhosis and impaired liver function or acute liver injury. Typically, 2 g per day of acetaminophen is quite safe in patients with any form of liver disease, even cirrhosis, and is commonly used in liver transplant populations without any toxicity issues.

It should be noted that patients who chronically overuse alcohol are more susceptible to acetaminophen-induced injury because of changes in the metabolism of acetaminophen that are induced by heavy alcohol use. Therefore, patients who use alcohol heavily should stay at a very low dose of acetaminophen (eg, only 1 g per day or less).

G&H Are there any safety concerns with liver disease patients taking nonsteroidal anti-inflammatory drugs?

JH Nonsteroidal anti-inflammatory drugs (NSAIDs) are very effective for all types of pain but can cause two issues in patients with cirrhosis and portal hypertension. One is that NSAIDs inhibit prostaglandin synthesis in the stomach, so they restrain the natural healing of the stomach and intestine that occurs on a daily basis. Thus, patients with cirrhosis who take these medications are at risk for developing NSAID-induced ulcers or ulcerations. The other issue is that NSAIDs interfere with the way sodium is handled in the kidneys. Patients who are already prone to volume overload from cirrhosis and portal hypertension will experience impaired sodium excretion and become more volume-overloaded. As patients retain sodium, they also retain water, which can contribute to increasing edema, ascites, and even varices filling up with blood and therefore increasing the risk of bleeding. Thus, NSAIDs should be avoided in patients with cirrhosis and portal hypertension because of the risk of gastrointestinal bleeding, volume overload, and kidney damage.

G&H How should narcotics be used in patients with liver disease?

JH Narcotics, including oxycodone and fentanyl, can certainly be used in patients with liver disease. Although these commonly prescribed agents are very effective for pain management, their metabolism is affected by advanced liver disease and liver dysfunction. Therefore, if narcotics are required for patients with liver disease, clinicians typically alter the usual dose and frequency of administration.

For example, a clinician may typically prescribe oxycodone 10 mg every 6 hours for an acute injury. However, in a patient with liver disease, the clinician might prescribe half that dose and slow down the frequency to every 8 to 10 hours; this gives the patient's body time to clear the narcotic and helps avoid an overdose effect. Thus, narcotics are safe if they are used judiciously in patients with liver disease. High-dose narcotics should be avoided

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in any patient with cirrhosis and abnormal liver function. In fact, high doses and chronic use of narcotics should never be recommended because of their addictive qualities, potential for abuse, and potential to induce mental status changes, confusion, and hepatic encephalopathy. If a patient with a chronic pain condition has a narcotic or opiate addiction, methadone is a very safe alternative to short-acting opiates to treat chronic pain and opiate addiction without causing serious medical problems.

G&H What other classes of pain medicines may be used in patients with liver disease?

JH Other medicines to treat chronic abdominal pain and neuropathic pain include gabapentin and pregabalin as well as selective serotonin reuptake inhibitors and other medicines used to treat depression. These agents are quite safe to use in patients with liver disease, are without many toxic side effects, and are often preferred in patients with chronic pain.

G&H Is there a role for cannabis or cannabinoids in the management of pain in liver disease?

JH Cannabis is increasingly being used by patients with chronic liver disease as an adjunct to other pain medications. However, the safety of cannabinoids in liver disease is not well studied. There is some concern that they may

increase liver fibrosis. However, they are thought to be quite safe in general in patients with liver disease, especially cirrhosis, because of their effects on pain control, stimulation of appetite (which can help the patient's nutritional status), and euphoric effects (which can help the patient deal with the mental burden of having a chronic liver condition).

G&H Are there any other potential concerns with the use of pain medicine in liver disease?

JH It is important to emphasize that the main concern with narcotics, cannabinoids, and neuropathic agents is that they increase the risk of hepatic encephalopathy and mental status changes. Hepatic encephalopathy is treated with drugs that induce bowel movements, but narcotics inhibit bowel movements by causing chronic constipation. This can exacerbate the risk of hepatic encephalopathy. In addition, the mind-altering effect of these medications can increase the confusion, lethargy, and mental status changes typically associated with hepatic encephalopathy, leading to serious problems. Driving is always an issue in patients with hepatic encephalopathy, so there is also concern about the risk of motor vehicle accidents in patients with chronic liver disease who are taking chronic pain medicines that might affect the mind.

G&H When should pain be comanaged by liver disease specialists and pain management specialists?

JH Liver disease specialists have an important role in the treatment of pain in patients with liver disease because we understand liver physiology and function well. It is our job to educate patients about which medicines and doses are safe. Over-the-counter medications in particular should be scrutinized carefully because they may contain either NSAIDs or acetaminophen without patients' knowledge.

Pain management specialists are also typically very well aware of the safety, efficacy, and risks of medicines in patients with chronic liver disease. In patients who have severe or chronic pain and require narcotics (eg, with sickle-cell anemia, which causes chronic liver disease and is associated with chronic pain), management is quite complicated and often best done with the partnership of a pain management specialist. Consultation with a pain management specialist is also recommended with acute musculoskeletal pain that is not necessarily specific to liver disease. For example, back or hip pain that requires nonsystemic pain management, such as a joint injection with a corticosteroid, can be managed with either orthopedic surgery or pain management specialists. Such

treatment can be very efficacious because there is no need for a systemic medication that might cause complications in patients with liver disease. Milder pain that does not require narcotics does not necessarily need a pain management specialist.

G&H Which nonpharmacologic approaches may help in the management of pain in the setting of liver disease?

JH Although there have been no randomized controlled trials, acupuncture and acupressure have been used over several centuries, especially in the eastern part of the world. Such nonpharmacologic approaches have been shown to help modify pain in patients with all types of chronic medical conditions, in particular liver disease. The side effects are certainly minimal or none.

G&H What are the priorities of research for pain management in liver disease?

JH Unfortunately, this is an understudied field of research. There is a wealth of research in the investigation of chronic abdominal pain in the various medical conditions that affect the gastrointestinal tract, such as chronic

pancreatitis or irritable bowel syndrome. However, to my knowledge, there is not very much research in the etiology and management of pain in patients with chronic liver disease. Most studies designed to examine the efficacy of new pain medicines exclude patients with liver disease to prevent unnecessary side effects. Thus, the efficacy and safety of new medications are often unknown in patients with liver disease.

Disclosures

Dr Hamilton has no relevant conflicts of interest to disclose.

Suggested Reading

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