REVIEW

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Navigating the 'Pits and Perils' of Analgesic Therapy in Advanced Liver Disease and Cirrhosis

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ABSTRACT

The role of the liver in drug metabolism makes individuals with hepatic dysfunction more susceptible to adverse drug reactions, necessitating careful consideration in analgesic selection and dosing. Acetaminophen, despite being a common cause of liver failure, is considered safe within recommended dosages. Nonsteroidal anti-inflammatory drugs (NSAIDs), while effective, pose risks in cirrhosis due to complications like renal failure and gastrointestinal bleeding. Cyclooxygenase-2 inhibitors have limited data, and their use is discouraged due to cardiovascular concerns. Opiates, though potent, require cautious use in cirrhosis due to altered metabolism, potential adverse effects, and the risk of addiction. Tricyclic antidepressants like nortriptyline and desipramine can be utilized for neuropathic pain, while SSRIs and SNRIs are not recommended. Anticonvulsants such as gabapentin and pregabalin are preferred for neuropathic pain, with gabapentin being the first-line choice. Topical analgesics, including NSAIDs, lidocaine, and rubefacients, are deemed safe for use in cirrhosis, offering localized relief with minimal systemic effects. Nonpharmacological approaches addressing medical, psychological, and socio-economic factors are crucial adjuvants to analgesic therapy in advanced liver diseases. Physiotherapy, psychotherapy, behavioral therapy, relaxation techniques, acupuncture, and traditional practices like yoga and massage, as well as novel modalities, contribute to a holistic pain management strategy. This review provides healthcare professionals with valuable insights into the complex landscape of analgesic therapy in cirrhosis. Meticulous consideration of drug metabolism, hepatic safety, and individual patient factors is paramount in optimizing pain management strategies for this challenging patient population.

Key words: cirrhosis – liver disease – analgesics – pain – NSAIDs – acetaminophen – opiates.

Abbreviations: COX: cyclooxygenase; COXIB: cyclooxygenase-2 inhibitor; CYP460: cytochrome P450; DILI: drug-induced liver injury; NAPQI: N-acetyl-p-benzoquinone imine; NGF: nerve growth factor; NSAID: nonsteroidal anti-inflammatory drug; SNRI: serotonin noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic anti-depressants.

INTRODUCTION

Pain is a ubiquitous symptom encountered in clinical practice. Individuals with cirrhosis are no exception; they do suffer from pain related or unrelated to liver disease. The liver being a crucial site of drug metabolism, hepatic diseases are associated with alterations in the analgesic pharmacokinetics and pharmacodynamics, rendering those with liver diseases more susceptible to adverse drug reactions. Also, analgesics can be hepatotoxic and may contribute to the progression of liver disease or may precipitate complications in those with hepatic dysfunction. It is often a challenge to strike a balance between adequate analgesia and liver safety, and hence, meticulous analgesic selection and dosing is of paramount importance in liver cirrhosis. This review aims to analyze various classes of analgesics, elucidating the impact of liver diseases on their metabolism and the associated implications for hepatic safety. Published data was retrieved using Google Search with a combination of keywords including „pain management", „analgesia", „analgesics", „liver disease" and „cirrhosis", to ensure the identification of relevant articles. This search strategy was designed to capture a comprehensive range of articles addressing the intersection of pain management and liver diseases. Through critically analyzing the available literature and consolidating existing knowledge, this review

seeks to provide healthcare professionals with valuable insights, facilitating decision-making regarding analgesic therapy for patients with cirrhosis.

PHARMACOTHERAPY OF PAIN

The pain-relieving medications or the analgesics are broadly classified as systemic and topical. Systemic agents include oral or parenteral acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors (COXIBs), opiates, tricyclic anti-depressants (TCA), selective serotonin reuptake inhibitors (SSRIs), gabapentin, pregabalin, and serotonin noradrenaline reuptake inhibitors (SNRIs) [1]. The topical pharmacotherapeutic options include local anesthetics, rubefacients, and topical non-steroidal anti-inflammatory drugs [2]. Pain management in patients with advanced liver disease is a real challenge. Liver disease is associated with altered first-pass metabolism, proper drug metabolism, and biliary excretion. In addition, the low levels of carrier proteins like albumin, sarcopenia, and edema alter the drug distribution, further complicating analgesic management. About a third to half of patients with advanced liver disease develop concomitant renal dysfunction, which adds to this quagmire. The intrinsic risks of renal dysfunction, coagulopathy, thrombocytopenia, and hepatic encephalopathy in patients with cirrhosis also need to be considered in selecting analgesic choices. The risk of opiate drug abuse and overuse is yet another area of concern, especially in patients with alcohol-related liver diseases. Also, there is a scarcity of large-scale, well-conducted trials on analgesic therapy in patients with advanced liver disease.

Acetaminophen

Acetaminophen, also known as paracetamol, is one of the most widely utilized analgesic and antipyretic medications, as well as one of the most common causes of liver failure worldwide. It is metabolized in the liver by glucuronidation or sulfation into inactive agents and subsequently excreted through the kidneys. A small fraction undergoes cytochrome P450-mediated conversion N-acetyl-p-benzoquinone imine (NAPQI), an active metabolite efficiently conjugated with glutathione and excreted (Fig. 1). However, in acetaminophen overdose or when the glutathione supply is depleted, NAPQI can overwhelm the detoxification pathways, leading to hepatotoxicity. Concomitant use of cytochrome P450 enzyme inducers like rifampicin, phenobarbital, phenytoin, and St. John's wort enhances NAPQI synthesis and hepatic toxicity [3, 4].

Acetaminophen hepatotoxicity is dose-dependent and typically develops with doses exceeding 4 grams per day, though this threshold may be reduced by concomitant alcohol or enzyme-inducing drug use. Acetaminophen overdosage is one of the most common causes of liver failure worldwide and can be intentional or accidental. Despite this risk, multiple trials have evaluated its safety in liver diseases, including cirrhosis, and deemed acetaminophen safe for use at a dose of up to 2 to 3 grams a day [5, 6]. Also, multiple societal recommendations support the safe use of acetaminophen in individuals with liver disease [7, 8]. The recommended dose varies between experts. Still, it is up to 500-1000 mg every 4-6 hours as needed, not exceeding 4,000 mg a day in mild liver disease and 2000-3000 mg, or a lower effective dose, for the shortest period in those with cirrhosis [4, 9].

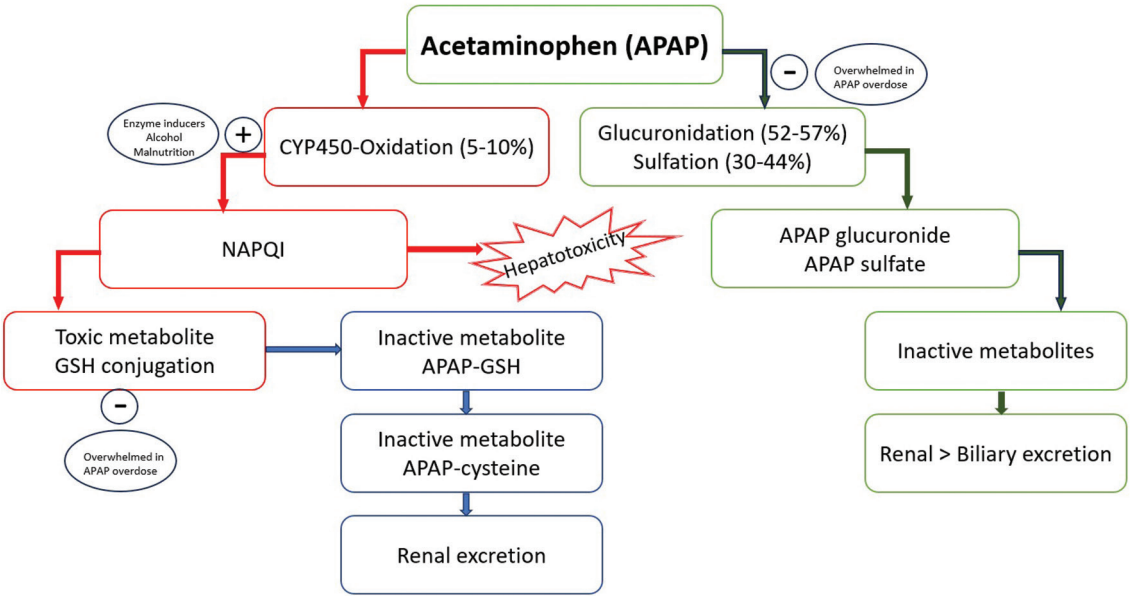

Fig. 1. Metabolism of acetaminophen (APAP). Under normal conditions, APAP is conjugated, and the kidneys excrete the metabolites. APAP overdosage overwhelms this conjugating pathway, leading to higher levels of hepatotoxic N-acetyl-p-benzoquinone imine (NAPQI). Enzyme inducers, including ethanol, enhance NAPQI synthesis. NAPQI, though scavenged by glutathione (GSH), accumulates to cause hepatotoxicity, with GSH depletion, which is common in APAP overdoses. N-acetyl cysteine (NAC) repletes the GSH stores and alleviates hepatotoxicity.

In summary, despite the concerns of hepatotoxicity, acetaminophen, at recommended dosages, is considered one of the safest analgesics for use in patients with liver diseases, including cirrhosis of the liver. The safe dosage would be up to 500 mg every 6 hours, with a maximum daily dose of 2 grams.

Non-steroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs are the backbone of pain management and are amongst the most effective and widely used analgesics. They are competitive, non-selective inhibitors of cyclo-oxygenase isoenzymes, COX-1 and COX-2, the enzyme that catalyses the conversion of arachidonic acid to prostaglandin H2, thereby reducing prostaglandin biosynthesis. Prostaglandins evoke an inflammatory response owing to vasodilatation, increased vascular permeability, and chemotaxis. Prostaglandins increase the nociceptor sensitivity and lower the pain threshold. Also, they act in the hypothalamus, resulting in fever. Hence, by reducing the prostaglandin levels, NSAIDs yield anti-inflammatory, analgesic, and antipyretic actions [10]. Orally administered NSAIDs are well absorbed; however, the bioavailability depends on the degree of hepatic first-pass metabolism as well. Diclofenac undergoes significant hepatic first-pass metabolism and has a lower oral bioavailability. On the other hand, Sulindac is a prodrug metabolized in the liver to an active metabolite [11]. Nonsteroidal anti-inflammatory drugs are highly protein-bound. Most are eliminated after hepatic biotransformation by phase I and II reactions, and only minimal drug is eliminated from the body unchanged. The cytochrome P450 (CYP450) enzymes, especially CYP2C9, play a crucial role in the metabolism of most NSAIDs. The resultant metabolites or conjugates are excreted chiefly through urine and, to a lesser extent, feces [12].

Clinically significant NSAID-induced hepatotoxicity is rare, with about 1-10 cases per 100,000 prescriptions. Asymptomatic transaminase elevation is reported in as high as 18% of NSAID users; most of them are mild, transient, self-limited, reverting to normal even if the medications are continued and clinically insignificant. Reports of significant drug-induced liver injury (DILI) do exist in the literature, mostly idiosyncratic, and follow a hepatocellular pattern of injury. Virtually all NSAIDs have been linked with hepatotoxicity in literature. Diclofenac, being the most prescribed NSAID, obviously has the largest reported incidence of hepatotoxicity. Sulindac has the highest risk, about 5-10 times the risk in comparison to other currently marketed NSAIDs [13, 14]. Nimesulide, a relatively COX-2-specific NSAID, has been withdrawn from most markets following reports of hepatotoxicity [15]. Bromfenac was also withdrawn from clinical use following high post-marketing rates of liver failure [16]. Clinically significant hepatotoxicity is more frequently reported in the elderly, women, and those with underlying viral hepatitis C. Concomitant use of other drugs with hepatotoxic potential increases the risk of NSAID-associated DILI [13]. Ibuprofen has the best hepatic safety profile, with exceedingly rare reports of DILI despite being one of the most utilized NSAIDs. Oxicams also have a well-documented hepatic safety profile [13].

Though it sounds like NSAIDs have a relatively safe liver toxicity profile, they are not preferred as analgesics or anti-inflammatory agents in cirrhosis of the liver. This is, however, not due to the direct hepatoxic effects of this class of drugs but rather due to their non-hepatic adverse effects, which consequently decompensate the underlying liver disease and tilt the balance against their use. As mentioned, NSAIDs are highly protein-bound and mostly metabolized in the liver; cirrhosis hence impairs the drug pharmacokinetics and consequently elevated serum drug levels. Cirrhosis is associated with complex hemodynamic changes resulting in altered plasma volume, vascular tone, and volume redistribution, culminating in renal hypoperfusion. Through afferent arteriolar dilatation, prostaglandins maintain the glomerular perfusion and filtration pressures. NSAIDs, by blocking prostaglandin synthesis, result in this mechanism failing, contributing to a heightened risk of renal failure in cirrhosis [11, 17, 18].

Portal hypertension, accompanying cirrhosis, is associated with gastrointestinal varices and mucosal vasculopathy and an increased risk of gastrointestinal bleeding. An insult on the gastrointestinal mucosal barrier in this setting can culminate in massive and even life-threatening luminal bleeds. Prostaglandins are pivotal in maintaining the gastrointestinal mucosal barrier: increasing mucus and bicarbonate secretion, improving microcirculation, and via epithelial cytoprotective effects [11, 17, 19, 20]. Nonsteroidal antiinflammatory drugs damage the mucosa through direct local effects and systemic effects mediated by reduced prostaglandin synthesis, leading to dreadful bleeds in individuals with cirrhosis and portal hypertension.

Cirrhosis is associated with thrombocytopenia due to increased platelet loss, splenic sequestration, and decreased synthesis due to thrombopoietin deficiency. Concurrent immune thrombocytopenia related to autoimmune hepatitis, viral hepatitis, or drugs, as well as bone marrow suppression by alcohol, drugs, or viral hepatitis, can contribute to low platelet counts [21]. Hepatic synthesis of coagulation factors is attenuated in cirrhosis, resulting in coagulopathies. Qualitative platelet dysfunction is also well-documented in chronic liver disease. Overall, cirrhosis, in many ways, qualifies itself as an acquired bleeding diathesis. Thromboxane A2, a COX-mediated arachidonic acid derivative, is essential for platelet aggregation [22]. Nonsteroidal antiinflammatory drugs, by inhibiting COX, reduce thromboxane levels and platelet aggregation and aggravate the risk of bleeding, adding to already existing hemostatic defects in cirrhosis.

In summary, NSAIDs, despite exhibiting low direct hepatotoxic potential, are not preferred in cirrhosis due to an elevated risk of complications, including renal failure, gastrointestinal bleeding, and exacerbation of hemostatic defects.

Cyclooxygenase-2 Inhibitors

Cyclooxygenase-2 inhibitors are selective COX-2 inhibitors. COX-2 is an inducible enzyme, typically lacking in most tissues under normal physiological state but induced by various pathological states. COX-1, on the other hand, is the constitutive isoform expressed in most tissues and plays a vital protective role in basal physiological states [23]. Both isoforms contribute, but COX-2 is the principal isoenzyme contributing to inflammation. Introduced in 1998-1999 as gastro-safe

analgesics, with great interest amongst patients and clinicians, most molecules of this class were found to be linked with high cardiovascular events and hence withdrawn from the market. Currently, celecoxib is the only COXIB available in the United States for human use.

Animal model studies have reported that COXIBs are more renal safe than NSAIDs in cirrhosis [24]. The CLASS study reported a lesser incidence of gastrointestinal, renal, and hepatic toxicity with celecoxib compared with NSAIDs [25]. A trial evaluating placebo, celecoxib, and naproxen concluded that celecoxib does not impair the renal and platelet functions in decompensated cirrhosis, while naproxen did [26]. However, this study was limited by its sample size of a mere 28 patients and needs further confirmation. In a pooled data analysis from randomized trials, Soni et al. [27] concluded that celecoxib hepatoxicity is comparable to placebo and lesser than diclofenac. Idiosyncratic, immunologic variant hepatotoxicity is reported with celecoxib, especially in patients with sulfonamide allergy [28]. Lumaricoxib is associated with severe hepatitis and is genetically linked to specific HLA subtypes [29]. Overall, the published literature regarding the hepatic effects of COXIBs is sparse, which may be linked to multiple post-marketing withdrawals of this class of drugs.

In summary, COXIBs have scant data regarding safety as well as toxicity in liver diseases and are associated with major cardiovascular events. Considering the lack of data, these molecules cannot be recommended for use in liver diseases.

Opiates

Opiates, by binding to specific receptors, mu-opioid receptors, in the central nervous system, inhibit the release of neurotransmitters involved in modulating neuronal excitability and pain transmission, leading to analgesic effects. Opiates are potent analgesics and are associated with risks of tolerance, dependence, and potential side effects, including but not limited to respiratory depression, sedation, as well as anticholinergic effects. Opiates are subjected to high hepatic first-pass metabolism, resulting in reduced bioavailability. Most opiates are lipophilic and are to be metabolized or conjugated to generate hydrophilic molecules to be excreted (Fig. 2). Morphine, hydromorphone, and oxymorphone are metabolized exclusively by glucuronidation to inactive 3-glucuronides in the liver. Metabolism of fentanyl, oxymorphone, and methadone yields inactive metabolites. Phase 1 reactions by CYP450 enzymes metabolize the rest of the opiates. Some of these metabolites are active and will undergo further conjugation. For example, codeine and hydrocodone are metabolized to morphine and hydromorphone, respectively, which are subsequently conjugated by glucuronidation.

Liver diseases affect both phase 1, CYP450-mediated, and phase 2, glucuronidation reactions, but more so, the CYP450. The impact of advanced liver disease on metabolism and safety varies from opiate to opiate. Hepatic dysfunction increases the bioavailability of opiates, as a functional liver should have resulted in significant first-pass metabolism. The bioavailability of morphine is almost doubled in patients with advanced cirrhosis [30]. As the liver is the primary site of opiate metabolism, the peak plasma drug concentrations and half-lives are increased. Studies reveal that the hepatic clearance of morphine is about 25% decreased in cirrhosis, with a resultant high ratio of morphine to its inactive glucuronide metabolite [31]. The peak concentration of oxycodone is reported to be increased by 50% in patients with moderate to severe liver disease [32]. Hypoalbuminemia related to advanced liver diseases alters the opiate protein binding and alters pharmacokinetics. Also, the analgesic effects of codeine, hydrocodone, and oxycodone are reduced in cirrhosis as they fail to convert to their active metabolites [17]. Concomitant renal dysfunction, hepatorenal syndrome, or otherwise, can further worsen the opiate adverse effects in individuals with cirrhosis.

Opiate-induced constipation, together with its sedative effects, might precipitate hepatic encephalopathy in advanced cirrhosis. Altered opiate metabolism can contribute to an

Opiate	Metabolism	Metabolite(s)
Codeine	Glucuronidation (>50%), CYP3A4 (<15%), CYP2D6 (<15%)	Codeine glucuronide > Norcodeine > Morphine*
Oxycodone	CYP3A4/5 (45%), CYP2D6 (20%)	Noroxycodone > Oxymorphone*
Hydrocodone	CYP2D6, CYP3A4	Hydromorphone*, Norhydrocodone
Morphine	Glucuronidation - 3 (60%) or 6 (<10%)	Morphine-3-glucuronide, Morphine-6-glucuronide*
Oxymorphone	Glucuronidation	Oxymorphone-3-glucuronide, Oxymorphone-6-glucuronide*
Hydromorphone	Glucuronidation	Hydromorphone-3-glucuronide
Fentanyl	CYP3A4	Norfentanyl
Meperidine	CYP3A4, CYP2B6, CYP2C19	Normeperidine‡
Tramadol	CYP2D6, CYP3A4	O-desmethyltramadol*, N-desmethyltramadol
Methadone	CYP3A4 > CYP2D6, CYP1A2	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
*Pharmacologically active metabolites with analgesic activity.		‡ Neurotoxic, but no analgesic properties

Fig. 2. Opiate metabolism involves phase 1 and phase 2 reactions and mostly occurs in the liver. Glucuronidation is the predominant phase 2 reaction and is the primary metabolic pathway for the biotransformation of morphine, hydromorphone, and oxymorphone. Phase 1 reactions, mediated by CYP450 enzymes, are responsible for the metabolism of most other opiates. Metabolism of some opiates yields active metabolites with analgesic activity (e.g., codeine, tramadol). Hepatic dysfunction alters the opiate metabolism, metabolites, and the volume of distribution.

increased risk of respiratory depression if not appropriately dosed. The increased bioavailability of meperidine and, consequently, its metabolite normeperidine increases the risk of seizures; hence, it is to be avoided in cirrhosis [33]. Healthcare providers might also consider the likelihood of the development of opiate addiction in patients with cirrhosis [17]. Tramadol is less sedating and has a lower risk of respiratory depression and addiction but may precipitate seizures and serotonin syndrome [34, 35]. Opiate use disorders, in many countries, are considered a relative contraindication to liver transplantation, as they may predict alcohol recidivism [17].

Considering the hepatic metabolism of opiates and the potentially severe adverse effects, no opiate is a perfect analgesic in cirrhosis. Expectedly, most opiate drug package inserts recommend dose adjustments in cirrhosis. Most experts opine that, when required, opiates may be used in cirrhosis at lower dosages and or with longer intervals between dosing with close monitoring for potential adverse effects, including hepatic encephalopathy [1, 9, 17, 36-42]. Most experts recommend cautious use of oxycodone, hydromorphone, fentanyl, or tramadol in patients with liver diseases or cirrhosis [1, 40, 42-44]. On the contrary, Klinge et al. [45] consider oxycodone not the drug of choice in patients with cirrhosis. Wilcock et al. [38] recommend fentanyl, the safer opiate, morphine with caution, and avoid methadone, hydromorphone, oxycodone, and tramadol. Hydromorphone is the opiate of first choice in patients with concurrent hepatic and renal diseases [40]. Codeine and meperidine are not recommended as analgesics in cirrhosis [38-40, 43]. Individuals with mild to moderate liver disease who are on methadone maintenance dosages might continue the same; the adverse effects of withdrawal might outweigh the risk of methadone [37, 40]. The pharmacokinetics of fentanyl and sufentanil are little affected by hepatic dysfunction [38, 41]. Remifentanil is metabolized into inactive metabolites by plasma and tissue esterase, and its pharmacokinetics are unaffected by hepatic or renal dysfunction; it is considered the ideal opioid for hepatic failure [46].

In summary, opiates may be used, if indicated, in patients with cirrhosis at a lower dose and with longer intervals between dosing. Most experts prefer hydromorphone, oxycodone, fentanyl, or tramadol. When deemed essential, the safe dose would be hydromorphone, up to 1 mg, every 6 hours, or oxycodone, up to 2.5 mg, every 6 to 8 hours. They should be used with caution in advanced liver diseases due to the marked alterations in pharmacokinetics and the potential to precipitate encephalopathy. Extended-release preparations are not recommended, as drug half-lives are already prolonged due to aberrant metabolism.

Tricyclic Anti-depressants

Neuropathic pain is common in patients with cirrhosis and may be related to diabetes, alcohol, or nutritional deficiencies. Tricyclic anti-depressants has been used conventionally for the management of these symptoms. Biotransformation of TCA mainly occurs in the liver; hence, deranged metabolism may increase the risk of adverse drug reactions. Anticholinergic effects, constipation, ileus, and sedation can precipitate hepatic encephalopathy. Less potent and less sedating agents, nortriptyline and desipramine, may be preferred over the more potent amitriptyline [17, 40, 43]. It is recommended to start TCAs at low doses, titrate for response, and co-administer laxatives if indicated [1, 47].

In summary, nortriptyline or desipramine, started at low doses, can be utilized for pain management in cirrhosis or advanced liver diseases. The recommended starting dose would be nortriptyline, 10mg, nightly.

Selective Serotonin Reuptake Inhibitors and Serotonin Noradrenaline Reuptake Inhibitors

Selective serotonin reuptake inhibitors and SNRIs are increasingly evaluated and utilized in the management of pain. SSRIs are less efficacious than TCA for neuropathic pain and are reportedly associated with increased gastrointestinal bleeding [48]. Duloxetine, an SNRI, has been linked with drug-induced liver injury [40, 49]. Venlafaxine is metabolized extensively in the liver, necessitating significant dose alterations.

In summary, SSRIs and SNRIs are not recommended for analgesia in individuals with cirrhosis.

Anticonvulsants

Gabapentin and pregabalin are used in the management of neuropathic pain or as adjuvant to conventional analgesics. They interact with the presynaptic alpha 2-delta subunits of voltage-gated calcium channels and interfere with the excitatory neurotransmitter release. Gabapentin neither has significant hepatic biotransformation nor has significant hepatotoxicity; hence, it is considered the first-line agent for the treatment of neuropathic pain in cirrhosis [40, 45, 46]. Pregabalin is not metabolized in the liver but has been implicated in rare cases of liver failure, so it is considered a second choice in neuropathic pain [1, 40, 50, 51].

Carbamazepine, oxcarbazepine, valproate, lamotrigine, and topiramate are the other anticonvulsants that might benefit in neuropathic pain. Carbamazepine is metabolized in the liver and is a potential hepatotoxin and, hence, not recommended in patients with advanced liver diseases [43, 45, 52]. Oxcarbazepine, valproate, and lamotrigine are predominantly metabolized in the liver, while partially so for topiramate. Oxcarbazepine has been linked with elevated liver enzymes but not to severe hepatotoxicity except for anecdotal case reports. Life-threatening hepatotoxicity has been reported with both valproate and lamotrigine, and hence, they are preferably avoided in patients with advanced liver diseases [53].

In summary, gabapentin and pregabalin lack significant hepatic biotransformation and are the preferred anticonvulsants for pain management in cirrhosis. The starting dose would be, gabapentin 300 mg a day or pregabalin 50 mg twice daily.

Cannabinoid based Medications

Cannabinoids have been in the limelight as analgesics for more than a decade; however, due to ethical and legal issues, they are not approved for use in most countries. The Canadian guidelines recommend the use of medical cannabinoids as monotherapy or adjunct therapy in individuals with chronic pain, including peripheral or central neuropathic pain [54]. Cannabinoids are metabolized in the liver; hence, hepatic diseases might affect their clearance. The data regarding the safety of cannabinoids in the setting of liver diseases is

limited and contradictory, and hence, further validation is required to make recommendations for or against the use of cannabinoids in advanced liver diseases [55]. Also, there should be reservations regarding the use of cannabinoids in patients with a history of substance use disorders, which happens to be frequent in patients with cirrhosis.

Novel Analgesics

Nerve growth factor (NGF) inhibitors include antibodies to NGF, tanezumab, and fasinumab, and inhibitors of NGF receptors, which interfere with pain signalling. Early-phase trials have reported promising results in the treatment of chronic pain disorders, including osteoarthritis and neuropathic pains. The efficacy and safety of the medications still need to be validated, and as of now there, no recommendations can be made on their use in advanced liver disease or cirrhosis [56]. Other analgesics in the pipeline include TRPV1 inhibitors, voltage-dependent sodium, calcium, or potassium channel inhibitors, and inhibitors of enzymes involved in nociception. However, none of these are currently approved for human use [57].

Topical Analgesia

Topical agents act along the peripheral pain effectors by maintaining higher local concentrations and low serum concentrations. The low systemic levels attenuate the undesirable systemic effects. The frequently utilized local analgesics include,

1. Topical NSAIDs: achieve therapeutic concentrations in skin and subcutaneous tissues, muscles, and joints depending upon the formulation. Diclofenac is the most frequently utilized NSAID for topical use. Bioavailability is low but variable, resulting in low systemic concentrations [2, 58].

2. Local anesthetics: they block the neuronal voltage-gated sodium channels that continue to neuronal excitation and conduction. The available preparations are 5% lidocaine patches and Eutectic Mixture of Local Anesthetics (EMLA) cream with 2.5% prilocaine and 2.5% lidocaine. Studies have shown the efficacy of lidocaine patches in neuropathic pains and postherpetic neuralgia. The systemic concentration of lidocaine following the patch therapy is typically low, found to be 25 times lower than the potentially toxic dose [2, 59].

3. Rubefacient: Also known as counterirritants, include capsaicin, salicylates, and menthol. These agents cause local irritation through type C fiber neuronal excitation and substance P release, followed by the neuronal refractory period and depletion of substance P, providing pain relief. Repeated administration provides a persistent phase of the neuronal refractory period, substance P deficiency, and longer analgesic effects. These agents are poorly absorbed into the systemic circulation, with minimal adverse effects [2, 60].

Topical NSAIDs are considered safe for use in patients with cirrhosis [9]. Topical lignocaine patches and capsaicin are believed to be safe for use in advanced liver diseases and cirrhosis. Adverse effects are mostly limited to local irritation, and there are no recommendations for dose adjustments in liver diseases [2, 36, 61, 62].

In summary, topical analgesics, including NSAIDs, lidocaine, and rubefacients, are considered safe for use in patients with advanced liver disease or cirrhosis.

Nonpharmacological Pain Management

Advanced liver diseases and cirrhosis are often associated with multiple medical, psychological, and socio-economic comorbidities. These factors are probably pivotal in pain perception, tolerance, and modulation. Consequently, addressing these factors is a vital adjuvant to analgesic therapy. Physiotherapy, psychotherapy, behavioral therapy, relaxation therapy, acupuncture, spinal manipulation, and traditional practices like ayurveda, massages, yoga, and qigong might benefit these patients. Novel modalities like electrical nerve stimulation, laser therapy, digital and app-based programs, as well as multimodal pain therapies also need to be exposed in this subset of the patients.

CONCLUSIONS

Pain management in advanced liver diseases and cirrhosis is a challenge due to altered drug metabolism and pharmacokinetics in this subset of patients. Equally is the risk of precipitating complications of cirrhosis by the analgesics. Topical analgesics, including lidocaine patches and rubefacients, are safe options in localized pain syndromes. Acetaminophen, at recommended doses, is a safe analgesic and antipyretic in cirrhosis liver. Systemic use of NSAIDs is not recommended, while topical NSAIDs may be utilized. Opiates may be used with caution, preferably at a lower dose with increased intervals between dosages; hydromorphone, oxycodone, fentanyl, and tramadol are considered safer, while codeine, meperidine, as well as extended-release opiate preparations are to be avoided. Gabapentin and pregabalin are safe for neuropathic pain; when a TCA is deemed necessary, nortriptyline or desipramine are preferred over amitriptyline. Currently, COXIBs, SSRIs, and SNRIs cannot be recommended for pain management in advanced liver disease or cirrhosis. Irrespective of the type of analgesics used, the recipients should be closely monitored clinically for worsening features, especially hepatic encephalopathy.

Conflicts of interest: None to declare.

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