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Pain management in hepatic patients following abdominal surgery

"Essay "

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Abbreviations

ADAMTS 13	:	ADintegrin-like And Metalloprotease with ThromboSpondin type 13
AMHs	:	A-Mechano-Heat Receptors
ASIA	:	American Spinal Injury Association
CNS	:	Central nervous system
C-PMRs	:	C-polymodal receptors
CYP450	:	Cytochrome P450
FDA	:	Food and drug administration
IVPCA	:	Intravenous patient-controlled analgesia
LA	:	Local anesthetic
LT	:	Low-threshold
M3G	:	Morphine-3-glucuronide
M6G	:	Morphine-6-glucuronide
NAPQI	:	N-acetyl-benzoquinone imine
NS	:	Nociceptive specific
NSAIDs	:	Non-steroidal anti-inflammatory drugs
PAG	:	Periaqueductal gray
PCA	:	Patient controlled analgesia
PNB	:	Peripheral nerve block
SAB	:	Subarachnoid block
SRT	:	Spinoreticular track

TCAs	:	Tricyclic antidepressants
UGT	:	Uridinediphosphate glucuronosyl transferase
VPL	:	Ventral posterolateral
VPLN	:	Ventral posterolateral nucleus
WDR	:	Wide dynamic range

Introduction

Pain management in patients with cirrhosis is a difficult clinical challenge for health care professionals, and few prospective studies have offered an evidence-based approach. In patients with end stage liver disease, adverse events from analgesics are frequent, potentially fatal, and often avoidable. Severe complications from analgesia in these patients include hepatic encephalopathy, hepatorenal syndrome, and gastrointestinal bleeding, which can result in substantial morbidity and even death. ***(Chandok&Watt2010)*.**

The effects of liver disease on pharmacokinetics and pharmacodynamics are highly variable, and difficult to predict as the mechanisms of these effects are not well understood.

Four different theories have been proposed to account for the effects of chronic liver disease with cirrhosis on hepatic drug elimination: the sick cell theory; the intact hepatocyte theory; the impaired drug uptake theory; and the oxygen limitation theory.

In cirrhosis, drug glucuronidation is spared relative to oxidative drug metabolism; however, in advanced cirrhosis this pathway may also be impaired substantially. There is evidence that in cirrhosis other conjugation pathways may also be impaired to variable degrees. Growing evidence suggests that biliary drug excretion is impaired in cirrhosis.

A major finding which has emerged in recent years is that, even with moderate degrees of hepatic impairment, there is a decrease in clearance of drugs or active metabolites normally cleared by the kidney. Neither serum creatinine levels nor creatinine clearance are useful markers of the renal dysfunction associated with cirrhosis. Both may greatly overestimate renal function in patients with cirrhosis due to increased fractional renal tubular secretion of creatinine.

Pharmacokinetic investigations in a variety of chronic liver diseases without cirrhosis (e.g. carcinoma, schistosomiasis and viral hepatitis) suggest that in the absence of cirrhosis, impairment of drug elimination is not sufficient to warrant reduction of drug dosage. However, if cirrhosis is present, 'safe' drug use requires an awareness of the possibility of multiple interactions between changes in hepatic and renal disposition and pharmacodynamics. ***(Morgan &McLean 1995)*.**

Like anti-inflammatory medications, opioids can have deleterious effects in patients with cirrhosis. If opiates are required for pain control, lower doses and/or longer intervals between doses are needed to minimize risks. Hydromorphone and fentanyl may be the better choices.

In general, recommendation (expert opinion) for long-term acetaminophen use in cirrhotic patients (not actively drinking alcohol) is for reduced dosing at 2 to 3 g/d. For short-term use or 1-time dosing, 3 to 4 g/d appears to be safe; however, with the new FDA recommendations, a maximum dosage of 2 to 3 g/d is recommended. NSAIDs and opioids may be used at reduced doses in patients with chronic liver disease without cirrhosis. Patients with cirrhosis have fewer analgesic options. NSAIDs should be avoided in those with both compensated and decompensated cirrhosis, primarily because of the risk of acute renal failure due to prostaglandin inhibition. Opiates should be avoided or used sparingly at low and infrequent doses because of the risk of precipitating hepatic encephalopathy. Patients with a history of encephalopathy or substance abuse should not take opioids. When appropriate, anticonvulsants and antidepressants are options worthy of exploration in chronic neuropathic pain management in patients with advanced liver disease. Diligent follow-up for toxicity, adverse effects, and complications is necessary.***(Lancaster & Chadwick 2010)***

Whether or not neuraxial anesthesia should be performed in hepatic patients is a matter of considerable debate. The hypothesis that epidural analgesia would improve liver blood flow, thus leading to better outcome has been supported by many studies using animal models.

Obviously, lumbar epidural blocks have either no influence or a negative effect on liver perfusion. A recent study reported augmented liver perfusion under a thoracic epidural regimen. In two other papers, thoracic epidural analgesia lead to reduced hepatic blood flow that was further decreased when catecholamines were administered to increase blood pressure. With respect to the postoperative course, epidural analgesia seems favorable because of the reduction in pain, morphine consumption, and the fact that it may allow earlier extubation even after liver transplantation. It is well known that epidural anesthesia leads to vasodilatation and increased fluid application in hepatic surgery. Even if epidural anesthesia in patients with CLD undergoing minor abdominal surgery might exert beneficial effects on the haemostatic system, care should be taken with postoperative liver dysfunction after hepatic resection. First, local anesthetics are metabolized hepatically and plasma concentrations might increase significantly in these patients. Second, a high prevalence of haemostatic abnormalities is found in patients undergoing major liver resection while receiving epidural analgesia.

The same is true for subcostal transversusabdominis plane blocks or the installation of a catheter into the musculo-fascial layer before skin closure. ***(Friedman, 2010)*.**

The actual incidence of neurological dysfunction resulting from hemorrhagic complications associated with neuraxial block is unknown.

Although the incidence cited in the literature is estimated to be 1 in 150 000 epidural and 1 in 220 000 spinal anesthetics, recent surveys

suggest that the frequency is increasing and may be as high as 1 in 3000 in some patient populations. Overall, the risk of clinically significant bleeding increases with age, associated abnormalities of the spinal cord or vertebral column, the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling neuraxial catheter during sustained anticoagulation (particularly with standard unfractionated heparin or low molecular weight heparin). ***(Horlocker, 2011).***

Physiology of pain

Pain:

The international association of pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. There is an inherent concept in all definitions of pain, which is that the pain always has a major subjective component and it includes both a physiologic sensation and an emotional reaction to that sensation. In some cases, there may be no tissue injury; but the pain is no less "real" ***(Kanner 2003)***.

Terms used in pain:

Allodynia:

Pain due to a stimulus which does not normally provoke pain.

Analgesia:

Absence of pain in response to stimulation which would normally be painful ***(Kanner 2003)***

Central pain:

Pain initiated or caused by a primary lesion or dysfunction in the central nervous system ***(Kanner 2003)***

Dysaesthesia:

An unpleasant abnormal sensation, whether spontaneous or evoked ***(Kanner 2003)***

Hyperalgesia:

Increased(exaggerated) response to a stimulus which is normally painful**.** ***(Kanner 2003)***

Hyperesthesia:

Increased sensitivity to stimulation, excluding special senses ***(Kanner 2003)*****.**

Hyperpathia:

A painful condition characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold ***(Kanner 2003)***.

hypoalgesia:

Diminished pain in response to a normally painful stimulus.

hypoesthesia:

Decreased sensitivity to stimulation, excluding the special senses ***(Kanner 2003).***

Neuralgia:

Pain in the distribution of a nerve or nerves.

Neuritis:

Inflammation of a nerve or nerves ***(Kanner 2003)***.

Neuropathic pain:

pain initiated or caused by a primary lesion or dysfunction in the nervous system.

Neuropathy:

A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, and polyneuropathy ***(Kanner 2003).***

Nociceptor:

A receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged.

Noxious stimulus:

A noxious stimulus is one which is damaging to normal tissue and maybe chemical, thermal or mechanical ***(Kanner 2003)***.

Pain threshold:

The least experience of pain which a subject can recognize ***(Kanner 2003)***

Pain tolerance level:

The greatest level of pain which a subject is prepared to tolerate.***(Kanner 2003)***

Parasethesia:

An abnormal sensation, whether spontaneous or evoked. ***(Kanner 2003)***

Peripheral neuropathic pain:

Pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system ***(Kanner 2003)***.

Types of pain:

Two types of pain are usually described:

1. ***Sharp pain:*** it is often described as a pricking sensation, can be accurately localized and rapidly conducted. It is felt mostly in the skin and usually does not outlast the stimulus.
2. ***Dull pain:*** it is usually preceded by sharp pain. It is felt both in skin and deeper tissues; it is diffuse and slowly conducted and outlast the provoking stimulus ***(Kanner 2003).***

Acute pain signifies the presence of a noxious stimulus that produce actual tissue damage or possesses the potential to do so. The presence of acute pain implies a properly working nervous system and is associated with autonomic hyperactivity like hypertension, tachycardia, sweating and vasoconstriction ***(Macintyre et al., 2007).***

On the other hand, chronic pain implies the absence of a threat tissue damage, but the patient describes the experience " in terms of such damage ", Function of the nervous system become reorganized with the potential for spontaneous and atopic nerve excitation. Autonomic hyperactivity is absent. Pain is seemed to be chronic when it persists beyond 3-6 months ***(Macintyre et al., 2007)*****.**

I- Peripheral nervous system

1. Nociceptors

Stimuli generated from thermal, mechanical, or chemical tissue damage activate nociceptors, which are free nerve endings. In contrast to other special somatosensory receptors, nociceptors exhibit high response thresholds and persistent discharge without rapid adaptation and are associated with small receptive fields and small afferent nerve fiber endings ***(Waugh and Grant 2001)*****.**

a) C-Polymodal receptors (C-PMRs):

These are abundant non-myelinated C fibers which respond to all 3 noxious stimuli, i.e., thermal, mechanical and chemical ***(Sharpe et al., 1996)*****.**

b) A-Mechano-Heat Receptors(AMHs):

These respond to mechanical and thermal stimuli, and the afferent stimuli travel in A-delta (Aδ) fibers ***(Waugh and Grant 2001)*****.**

c) High-Threshold mechanoreceptors:

These only respond to intensive mechanical stimuli. The afferent stimuli travel in Aβ fibers ***(Waugh and Grant 2001)*****.**

d) Muscle nociceptors:

These are thought to be the free nerve endings found in the connective tissue between muscle fibers and in tendons and blood vessels ***(Sharpe et al., 1996)*****.**

e) Silent nociceptors:

These C fiber afferent do not fire in response to any noxious stimuli in normal tissue. In the presence of inflammation, they become sensitized, even to the point of being spontaneously active and mechanosensitive. As a consequence, the inflamed tissue becomes very tender and hurts with minimal movement ***(Waugh and Grant 2001)*****.**

Receptor sensitization:

Repeated application of noxious stimuli to nociceptors will usually result in alterations in their thresholds and responses. The nociceptor may become damaged and stop functioning if the stimuli were intense. Sometimes repeated stimulation result in fatigue of the nociceptor. However the most common phenomenon is that of sensitization ***(Guyton 2006)*****.**

With repeated noxious stimulus, most nociceptors start responding to lower intensity stimulus, (decreased threshold) and produce larger response than initially to the same stimulus. This explains at least partially the hyperalgesia apparent after burns and other noxious stimuli ***(Dostrovsky 1990)*****.**

2. Afferent nerve fibers:

After the activation of nociceptors, impulses are conducted along specific nerve fibers. These can be broadly classified into low and high threshold primary afferents. Low threshold afferents are myelinated fibers with specialized nerve endings that convey innocuous sensations such as light touch, vibration, pressure (all Aβ) and proprioception (Aα). High threshold afferents are thinly myelinated (Aγ) or unmyelinated (C) fibers located in the dermis and epidermis, which convey pain and temperature ***(Guyton 2006)*****.**

The Aγ and C fibers have their cell bodies in the dorsal root ganglion. From there, they project to the dorsal horn of the spinal cord.

Because of this double system of pain innervations, a sudden onset of noxious stimulus gives a double pain sensation: a fast sharp pain transmitted by Aγ fibers followed by a second or so later by a slow, chronic burning pain transmitted by C fibers. When type C fibers are blocked without blocking the Aγ fibers by low concentration of local anesthetic, the slow chronic burning type of pain disappear. ***(Guyton 2006)***.

Three specific types of nerve fibers have been identified (A, B and C) as shown in ***(table 1).***

The classification is based on the diameter of the fiber and the speed of conduction of the impulse.

Table (1): Characteristics of nerve fibers ***(Dwarakanath 1991)*****.**

Type	Function	Diameter µm	Conduction velocity (m/s)
C	(dull)Pain, mechanical stimuli	1	0.2-1.5
B	Preganglionic, autonomic	1	3-14
Aδ	Sharp Pain, mechanical and thermal	1	5-15
A	Touch and muscle tone	4	15-40
Aß	Touch, proprioception	8	40-70
Aα	Motor, proprioception	13	70-120