Pain Management in Hepatic Patients Following Abdominal Surgery

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Abstract: 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.

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 & Watt 2010).

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).

Over-the-counter analgesics, principally acetaminophen and NSAIDs, are commonly used medications worldwide. Acetaminophen is the most common cause of fulminant hepatic failure in the United States, creating the perception that it may be dangerous in patients with chronic liver disease. In such patients, the half-life of oral acetaminophen is double that in healthy controls, but hepatic injury and renal injury are rare when the dosage is limited to less than 4g/d.

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, our 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

Introduction

Pharmaceuticals such as opioids, anti-inflammatories, and sedatives are used for pain control in patients with chronic liver diseases. However, pain management is difficult, particularly in the setting of end-stage cirrhosis due to the risk of complications such as hepatic encephalopathy, hepatorenal syndrome, and gastrointestinal bleeding. These complications can lead to substantial morbidity and death.

In chronic liver disease, there is a significant impact on the pharmacokinetics and pharmacodynamics of drugs. The hepatic dysfunction caused by cirrhosis can affect drug clearance, metabolism, and excretion, leading to altered drug disposition. These changes can result in the accumulation of drugs, increase the risk of adverse effects, and decrease efficacy. For instance, the elimination of drugs is impaired due to decreased hepatic metabolism and biliary excretion, while renal clearance is affected by decreased renal function, including reduced creatinine clearance.

Moreover, there are several theories explaining the mechanisms of these effects. The sick cell theory suggests that the integrity of the hepatocyte is compromised, leading to decreased drug metabolism. The intact hepatocyte theory proposes that the hepatocytes are intact, but the dysfunction is due to the surrounding fibrosis. The impaired drug uptake theory emphasizes the role of increased uptake of drugs by the liver, while the oxygen limitation theory highlights the role of oxygen supply to the liver.

Consequently, the use of analgesics in patients with cirrhosis requires careful consideration. Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used due to their efficacy, but their use may be limited by their renal clearance and potential for acute renal failure. Acetaminophen is another widely used analgesic, but its half-life is doubled in cirrhosis, increasing the risk of hepatotoxicity.

In summary, pain management in patients with cirrhosis is a complex challenge necessitating a careful balance between effective pain control and minimizing the risks associated with drug use. Further research is needed to better understand the pharmacokinetics and pharmacodynamics of drugs in this patient population to optimize pain management strategies.
difficulty during needle placement, column, the presence of an underlying coagulopathy, associated abnormalities of the spinal cord or vertebral.

Clinically significant bleeding increases with age, 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 hemorrhagic complic closure. Epidural analgesia would improve liver blood flow, thus leading to better outcome has been supported by many studies using animal models.

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 heptically 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**

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

**Analgesia**: Absence of pain in response to stimulation which would normally be painful.

**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 response to a stimulus which is normally painful.

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

**Hyperpathia**: A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold (Kanner2003).

**Hypoaesthesia**: Diminished pain in response to a normally painful stimulus.

**Hypoesthesia**: Decreased sensitivity to stimulation, excluding the special senses (Kanner2003).

**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.

**Pain tolerance level:**
The greatest level of pain which a subject is prepared to tolerate.

**Parasthesia:**
An abnormal sensation, whether spontaneous or evoked.

**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:

- **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.
- **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).

**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-PMNs):**
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 (Ay) fibers (Waugh and Grant 2001).

c) **High-Threshold mechanoreceptors:**
These only respond to intensive mechanical stimuli. The afferent stimuli travel in AB 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 propriocepection (Aα). High threshold afferents are thinly myelinated (AY) or unmyelinated (C) fibers located in the dermis and epidermis, which convey pain and temperature (Guyton 2006).
The AY 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 AY 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 AY 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.

The A-fibers, which are the largest and conduct impulses most rapidly, are subdivided into four groups: alpha, beta, gamma and delta, in order of decreasing size. The largest A fibers (alpha) are myelinated fibers with a diameter ranging from 12 to 20 µm. They conduct impulses at a rate of 70 to 120 m/sec. and subserves proprioception and somatic motor function.

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

The Aβ fibers also are myelinated (diameter of 5 to 12 µm) and conduct at a rate of 30 to 70 m/sec. These myelinated fibers which are located in skin, joints, muscles and viscera respond to mechanical stimuli, such as touch, pressure, proprioception and motor function. The Aα fibers are the thinnest myelinated fibers in the A group, about 75% of them respond to mechanical and thermal stimulation and the remaining 25% respond to noxious stimuli (Almeida et al., 2004).

B-fibers are Preganglionic autonomic fibers, which conduct both sympathetic and parasympathetic impulses.

The C fibers are the smallest of the peripheral nervous system, they are unmyelinated, with a diameter ranging from 0.5 to 1 µm, and their conduction rate is from 0.2 to 1.5 m/sec. About 50% of C-fibers respond to pain, whereas the remaining 50% respond to mechanical stimuli (Almeida et al., 2004).

Although both Aα and C fibers transmit nociceptive impulses, the characteristics of the sensations carried are different. Aα fibers carry primarily sharp pain, whereas C fibers carry dull pain. For example, after a pin-prick, an immediate sharp pain is mediated by fast conducting myelinated Aα fibers (called; first pain). This is followed by a dull pain, which is mediated by C fibers (called; second pain) (Almeida et al, 2004).

Although pain result from damage to these free nerve endings, in reality the pain is a result substances released by damaged tissues: prostaglandins, histamine and peptides. These activate receptors located on the nerve endings (Guyton 2006).

II- Central nervous system

1. The spinal cord:

   The spinal cord consists of grey matter and white matter.

   The white matter contains ascending and descending fibers, the grey matter contains cells and central terminals of primary afferents from the periphery.

   The dorsal horn is divided into 6 layers (laminae) and processes sensory information. Lamina (I) is the most dorsal and is a thin layer of large cells, together with small inhibitory interneurons. The axons from the large cells form part of the spinohalamic tract (Waugh and Grant 2001).

   The second layer is lamina (II) or the "substantiagelatinosa". It is where most of the modulation and sensory processing occurs, so, many of the cells are inhibitory but excitatory cells exist as well.

   This region is believed to control the "connectivity" of the other laminae in the dorsal horn. Together, laminae I & II are known as the superficial dorsal horn (lamina terminalis) and receive input from C and Aδ fibers. Functionally, they receive input from nociceptors (high threshold C and Aδ fibers) and contain cell that are nociceptive specific (NS) (respond only to noxious stimuli) or wide dynamic range (WDR) (respond to both innoxious and noxious stimuli) (Haines and Lancon 2003).

   Laminae III & VI receive input from the cutaneous Aβ non-nociceptive afferents and contains cells with low-threshold (LT) receptive fields that respond to innocuous sensations.

   Some lamina V cells are WDRs that receive input from both low-threshold (Aβ) sensory fibers and...
high-threshold (C, Aδ) fibers as their dendrites project dorsally into laminae I & II (Almeida et al., 2004).

The dorsal horn is not just a relay station for the transmission of innoxious and noxious messages. It has an important role in modulating pain transmission through spinal and supraspinal mechanisms. These regulatory circuits involve primary afferents, spinal interneurons and descending fibers. (Almeida et al., 2004).

2. The supraspinal pathways of pain

a) The spinothalamic tract

The major ascending pain pathway is the spinothalamic tract which lies anterolaterally in the white matter of the spinal cord (figure 2). This tract can be divided as lateral (neospinothalamic) tract and medial (paleospinothalamic) tract. (Kandel et al., 2000).

The lateral spinothalamic (neospinothalamic) tract is composed of long, relatively thick fibers (Aβ) that conduct rapidly and projects to the ventral posterolateral nucleus (VPLN) of thalamus. In the VPLN of thalamus, second order neurons synapse with third order neuron that project to the somatosensory cortex (Morgan et al., 2006).

This lateral pathway is concerned with rapid transmission of discriminative aspects of pain, such as location, intensity, and duration (Morgan et al., 2006).

The medial spinothalamic (paleospinothalamic) tract is composed of thin fibers, some long and some short, that project to the reticular formation, periaqueductal gray (PAG), hypothalamus, and medial and intralaminar thalamic nuclei.

The fibers then make contact with neurons that connect with limbic structures and diffuse projections to many other parts of the brain (Raj et al., 1996).

The medial spinothalamic tract is responsible for mediating the autonomic, endocrine and unpleasant emotional aspects of pain that make the organ to take appropriate action when challenged (Morgan et al., 2006).

b) Alternate pain pathway

The spinoreticular tract mediates arousal autonomic responses to pain while the spinomesencephalic tract may be important in activating anti-nociceptive, descending pathways (Kandel et al., 2000).

Thalamo-cortical interactions:

It is well known that each region of the thalamus receiving inputs from pathways of the ventral quadrants of the spinal cord, projects to two regions of the sensory cerebral cortex namely; primary and secondary somatosensory cortices (SI & SII). Also the thalamus receives inputs from several cortical regions, these corticothalamic projections are quite extensive and play a significant role in modifying the behavior of neurons in the various thalamic nuclei (Almeida et al., 2004).

Table (2): Comparison of central pathways for pain transmission, (Kandel et al., 2000)

<table>
<thead>
<tr>
<th>Tract</th>
<th>Direct (fast)</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Lamina I &amp; IV, V</td>
<td>Lamina I, IV, V, (and VII, VIII)</td>
</tr>
<tr>
<td>Body representation</td>
<td>Contralateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Synapse in reticular formation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sub-cortical targets</td>
<td>None</td>
<td>Hypothalamus Limbic system Autonomic centres</td>
</tr>
<tr>
<td>Thalamic nucleus</td>
<td>Ventral posterolateral (VPLN)</td>
<td>Intra-laminar nuclei Other midline nuclei</td>
</tr>
<tr>
<td>Cortical location</td>
<td>Parietal lobe (SI cortex)</td>
<td>Cingulate gyrus</td>
</tr>
<tr>
<td>Role</td>
<td>Discriminative pain (quality intensity, location)</td>
<td>Affective-arousal components of pain</td>
</tr>
<tr>
<td>Other functions</td>
<td>Temperature Simple touch</td>
<td></td>
</tr>
</tbody>
</table>

Role of cerebral cortex in pain:

Little is known concerning the role of the cortex in pain. Although it was believed that the perception of pain took place at the thalamic level; most researchers today believe that pain perception occurs in the cortex. In recent years, a number of studies have described the existence of nociceptive neurons primary sensory cortex (Guyton 2006).

However lesions to primary somatosensory cortex in humans rarely produce a significant or lasting reduction in chronic or evoked pain. It is likely that the cerebral cortex has multiple representations of pain and thus it is difficult to abolish pain perception with a single lesion (Guyton 2006).

Central processing of visceral and deep pain inputs:

Nociceptive inputs from the viscera, muscle and other deep structures converge onto neurons that also receive cutaneous nociceptive inputs (Guyton 2006).

There appear to be no neurons, or very few, that respond exclusively to noxious inputs arising from visceral structures (e.g. uterus & cervix). These findings provide an explanation for the fact that visceral pain is frequently referred to a different site.
The central nervous system has no way of determining the source of noxious inputs if the same neurons receive inputs from multiple sites and therefore the input is referred to the more commonly activated cutaneous site. Pain of cutaneous origin does not usually feel the same as visceral pain; probably due to the fact that it results from activation of a different, although overlapping, group of neurons whose responses are characterized by different firing patterns (Guyton 2006).

Neuromodulators:

A neuromodulator is a substance other than a neurotransmitter, released by a neuron at a synapse and conveying information to a region of neurons, either enhancing or dampening their activities. In contrast, neurotransmitters only convey information between two neurons.

Neuromodulators may alter the output of a physiological system by acting on the associated inputs.

A neuromodulator is a relatively new concept in the field and it can be conceptualized as a neurotransmitter that is not reabsorbed by the presynaptic neuron or broken down into a metabolite. Such neuromodulators end up spending a significant amount of time in the cerebrospinal fluid and influencing (or modulating) the overall activity level of the brain (Kandel et al., 2000).

Neuromodulation also refers to a medical procedure used to alter nervous system function for relief of pain. For this reason, some neurotransmitters are also considered as neuromodulators. Example of Neuromodulators in this category are serotonin and acetylcholine (Stern et al., 2007).

Types of neuromodulators:

- **Opioid peptides**: These substances block nerve impulse generation in the secondary afferent pain neurons. These peptides are called opioid peptides because they have opium-like activity. The types of opioid peptides are:
  - Endorphins
  - Enkephalins
  - Dynorphins

**Substance P**:

It is a short-chain neuro-polypeptide that functions as a neurotransmitter and as a neuromodulator. It belongs to the tachykinin neuropeptide family. The endogenous receptor for Substance P is neurokinin-1 receptor. In the central nervous system, substance P has been associated in the regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, respiratory rhythm, neurotoxicity, nausea/ emesis and pain (Park et al., 2003).

**Octopamine**:

It is a biogenic amine which is closely related to noradrenaline and has a similar action to dopamine. In vertebrates, octopamine also replaces norepinephrine in sympathetic neurons with chronic use of monoamine oxidase inhibitor (Haller et al., 2005).

There are at least two potential types of neuromodulation:

In the first, neuromodulators are released from neurons glia, or true secretory cells to amplify or dampen, that is, set the tone of local synaptic activity by altering the effectiveness of a neurotransmitter.

Unlike neurotransmitter, neuromodulators do not need specific receptors; they might affect neurotransmitter synthesis, release, receptor interactions, reuptake or metabolism (Guyton 2006).

In the second, a neuromodulator is released either within the brain or from other parts of the body to act directly on a large number of neurons at some distances from the release site.

Such effects could be quite-long-lasting, helping to influence either baseline activity or response to other neuronal input (Guyton 2006).

**Pain modulation**

**Gate control theory of pain**:

The transmission of information from primary afferents to secondary neurons in the CNS is subject to "gating" (modulation).

nociceptive sensory information is gated in the substantiagelatinosa of the spinal cord. Gating is of two kinds:

- **Local**: segmental antinociception.
- **Widespread**: supraspinalantinociception which utilizes descending pathways from the brainstem.

The Gate control theory was devised by Patrick Wall and Ronald Meltzack in 1965. This theory states that pain is a function of the balance between the information travelling into the spinal cord through large nerve fibers and information travelling into the spinal cord through small nerve fibers, there should be little or no pain. However, if there is more activity in small nerve fibers, then there will be pain.

So this theory assumes that the various relay stations in the nervous pathway of pain act as gates that can be opened or closed. The most important gates are located at the substantiagelatinosa of Rolandi and at the thalamus (-spinal and thalamic gates respectively). A 3rd gate may also be located in the reticular formation.

At the spinal gate, pain transmission can be blocked by:

- a. Collaterals from the thick myelinated fibers in the dorsal column.
- b. Descending fibers from certain higher centers (- corticofugal or centrifugal control). Such block occurs by presynaptic inhibition, and the same mechanism is also believed to occur at the thalamic.
gate and the reticular formation (through the corticofugal control).

The gate theory explains the pain relief achieved by counter-irritants (e.g., liniments and mustard plaster), skin rubbing, and by shaking the painful part (all these methods are supposed to stimulate the mechanoreceptors that activate the neurons in the dorsal column, the collaterals of which relieve pain) (Kandel et al., 2000).

Brain activities subserving attention, emotion and memories of prior experience, exert control over sensory input via descending efferent fibers. This control of spinal cord transmission by the brain is exerted through system:

A. Brainstem projections:

One of the most powerful descending modulating systems, exerting powerful inhibitory control over information projected by spinal transmission, is special neurons in the periaqueductal and periventricular grey matter in the midbrain (Kandel et al., 2000).

These neurons descend in the dorsolateral funiculus to different levels of the spinal cord and make connections with laminae I, II and IV. This descending inhibitory projection is itself controlled by multiple influences, including somatic, visual and auditory projections to the midbrain reticular formation. Higher brainstem areas are involved in descending control (Kandel et al., 2000).

It has been shown convincingly that electrical stimulation of periaqueductal and periventricular grey matter produces profound analgesia without affecting motor function. This is achieved by powerful descending inhibitory action that totally blocks the passage of nociceptive impulses in the dorsal horn. One of the ways of this work is by liberating endogenous opiate peptides: encephalin, endorphins, dynorphins (Dwarakanath 1991).

B. Cortical projections:

The somatosensory cortex is not essential to pain perception, but it is useful in regulating subcortical activity related to pain through complex reflexes and serves as a discriminative function. Impulses from the periphery that reach the cerebral cortex undergo incredible modulation in the process of transmission (Mellzack 1986).

Fibers from the whole cortex, particularly the frontal cortex, project to the reticular formation. Cognitive processes such as past experience and attention which are subserved by cortical neural activity are able to influence spinal activities by way of the reticulospinal projection system (Mellzack 1986).

Cognitive processes can also influence spinal gating mechanisms by means of pyramidal (or corticospinal) fibers. These are large, fast-conducting fibers so that cognitive processes can rapidly and directly modulate neural transmission in the dorsal horn (Barclay L and Hien TN; 2006).

C. Concept of a central control trigger:

It is apparent that the influence of cognitive central control processes on spinal transmission is mediated through the gate control system. Whereas some central activities, such as anxiety or excitement, may open or close the gate for all inputs from any part of the body, others obviously involve selective, localized gate activity.

Mellzack and Wall (1965) have therefore proposed that there is a ventral mechanism which they have called the central control trigger, which activates the particular selective brain processes.

These brain activities do not give rise to sensory experience but instead act by way of central control efferent fibers on gate control system. Part of their function, could be to activate selective brain processes such as memories of prior experience and preset response strategies that influence information which is still arriving over slowly conducting fibers or is being transmitted up more slowly conducting pathways.

Postoperative pain

It is advocated that for success in treatment and clinical diagnosis of pain needs to expand the concept of a pathologic lesion to include psychological; emotional, intellectual, cultural, and societal components and to do so is to acknowledge that even when an anatomic-physiological disorder cannot be cured, and the associated pain remains intractable, that suffering can be lessened or even eliminated, and patients can return to the normal activities of daily living in spite if an otherwise untreatable lesion (Haljamen and Warren 2003).

It is well known that the experience of pain is exceedingly complex. It strikes a patient as the final common pathway that originates in a complexity of anatomical, physiological, psychological, and sociological causes, so that a particular level of suffering often does not correspond in any straightforward way or any specific level of physiologic anatomic pathology as such. It is difficult to quantify the contribution of these elements in the overall experience of acute postoperative pain observed in an individual patient. That is to say there is a great variability in degree of pain perceived in response to tissue damage (Haljamen and Warren 2003).

A revolution in the management of acute postoperative pain has occurred during the past two decades. Widespread recognition of the under treatment of acute pain following surgery by clinicians, economists, and health policy exerts has led
to the development of a national clinical practice guideline for acute pain management by the agency for health care quality and research of the U.S. department of health and human services (Nielsen et al., 2007).

Effective control of postoperative pain remains one of the most important and pressing issues in the field of surgery with significant impact on our health care system, because of the following:

a. Most of the hundreds of millions of people worldwide who undergo surgeries each year experience postoperative pain of variable intensity.

b. In too many patients the pain is treated in inadequately, causing them needlessly suffering and may develop complications as an indirect consequence of the pain.

c. Analgesic modalities, if probably applied, can prevent or at least minimize the needless suffering and complications (Alan et al., 1983).

There are many reasons why postoperative pain should be effectively treated, aside from alleviating a patient's discomfort. Adverse effects of uncontrolled postoperative pain are impairing pulmonary functions, gastrointestinal motility, cardiovascular instability and prolonged decubency with increased risks of deep venous thrombosis.

Yet, it is often inadequately treated for several reasons:

a. Medical personnel often do not completely understand the pharmacodynamics of the analgesics they prescribe.

b. There is exaggerated concern about addictive potential of analgesic medications.

c. Medical personnel are often unaware of many options for treating postoperative pain aside from conventional systemic medication.

Thompson at 1981 has identified four components to this:

1. Behavioral control:
   This describes any maneuver which the patient can use to decrease the perception of pain as; relaxation or breathing exercises or provision of patients controlled analgesia device.

2. Cognitive control:
   This comprises the alteration of pain by thought processes. These can act both to reinforce the pain (e.g. by concentration on or reinterpretation of pain) or decrease the pain (e.g. by denial, dissociation and distraction).

3. Information:
   Provision of adequate information reduces the uncertainty, and therefore the distress of a painful experience. It familiarizes the patient with an unaccustomed experience.

4. Retrospection:
   The re-interpretation of a past painful event may alter the current implications of the event.

Positive and negative feelings:
When the patient anticipates great benefit from the proposed operation, may be more willing to trade short-term discomfort for long-term gain. Whereas the surgery involves mutilation, confirmation of a poor prognosis or no perceived gain in the patient's mind, the additional anxiety may compound the difficulty of providing postoperative analgesia (Mitchell and smith 1989).

Effect of Surgical and Anesthetic Management:
Other factors that influence postoperative pain are the surgical and anesthetic management, including preoperative preparation of the patient, operation and anesthetic technique and postoperative care. The skill of surgeon and extent of the operative procedure help to determine the degree of surgical trauma, which in turn, partly determines the degree of postoperative pain and complications. Similarly, the quality of the pre-anesthetic, intra-anesthetic and post-anesthetic care influences the incidence and intensity of postoperative pain, both directly and indirectly (Macintyre et al., 2007).

Traumatic tracheal intubation and generalized muscle pain consequent to succinylcholine-induced muscle spasm contribute directly to postoperative discomfort. Inadequate muscle relaxation and other problems that prolong the operation contribute indirectly by increasing the degree and duration of surgical trauma (Macintyre et al., 2007).

Nature and Pathophysiology of postoperative pain
Surgical trauma produces local tissue damage that evokes nociceptive afferent activity which travel back to the spinal cord. Action potentials also travel antidromically, by axon collaterals into the surrounding vascular bed to release substance P which is proposed to cause vasodilatation and increase vascular permeability that result into local edema and consequent release of algogenic substances and of a barrage of noxious stimuli, which are transduced by nociceptors into impulses that are transmitted to neuraxis by Aβ and C fibers.

Algogenic substances such as potassium and hydrogen ions, lactic acid, serotonin, bradykinin and prostaglandins stimulate and sensitize nociceptors that persist after the operation causing (hyperalgesia).

Note also that nor-adrenaline release may increase the nociceptive sensitivity, further increasing afferent input to the spinal cord and initiating reflex increase in the sympathetic activity that result into vasconstriction, local tissue ischemia, increased hydrogen ion concentration further increase in nociceptor sensitivity. On reaching the dorsal horn, nociceptive impulses are subjected to modulating influences, which, together with other factors
determine their further transmission. Some nociceptive impulses pass to anterior and anterolateral horns of the spinal cord to provoke segmental reflex responses, while others pass to higher parts of neuraxis provoking suprasegmental and cortical responses (Turk and Melzack 2001).

### Segmental reflex response:

Associated with surgery, include a marked increase in skeletal muscle tension, with a concomitant decrease in chest wall compliance. These responses also initiate positive feedback loops that generate nociceptive impulses from the muscles. Stimulation of sympathetic neurons causes increased in heart rate and stroke volume, and thus increase in cardiac work and myocardial oxygen consumption and concomitant decreased tone of gastrointestinal and urinary tracts. The massive nociceptive barrage generated by the operation also sensitizes dorsal horn wide-dynamic-range neurons, interneurons and flexor motor neurons and thus reduces their thresholds and markedly increase their excitability both ipsilateral and contralateral to the site of operation (Bardiau et al., 2003).

This sensitization persists for days after the operation and is in part responsible for the tenderness, hyperalgesia, allodynia and the abnormal reflex responses that cause brief bouts of severe skeletal muscle spasm that in turn produce excruciating pain (Bardiau et al., 2003).

### Supra segmental reflex response:

Nociceptive input to cardiovascular and respiratory control centers in the medulla oblongata that results in marked increase in general neural sympathetic tone with further increase in cardiac output, blood pressure, cardiac workload, metabolism and oxygen consumption. Nociceptive input to hypothalamic centers such as autonomic and neuro-endocrine control centers that result in marked increase in secretion of catabolic hormones as, Catecholamines, Cortisol, ACTH, ADH, Glucagon and Aldosterone and concomitant decrease in secretion of anabolic hormones an insulin and Testosterone.

These endocrine changes produce a number of metabolic effects including increases in blood glucose, plasma cyclic AMP, free fatty acid, ketone bodies and blood lactate levels as well as an increase in general metabolism and oxygen consumption. Such endocrine and metabolic changes result in substrate mobilization from storage sites to central organs and the traumatized tissues and ultimately produce a catabolic state with negative nitrogen balance. The degree and duration of these endocrine and biochemical changes are related to the degree and duration of tissue damage. The trauma of surgery also decreases the patient's immunocompetence including nonspecific immune responses as granulocytosis, reduction in chemotaxis, increases in phagocytic activity and decreases in T & B-lymphocytes and monocytes functions (Bardiau et al, 2003).

### Cortical response:

These occur in awakeuanaesthetized individual. They are provoked by nociceptive impulses that reach highest parts of the brain, in which they activate complex systems concerned with integration and perception or with recognition of the sensation of pain, and also provokes motor responses as well as anxiety and apprehension, which greatly enhances the hypothalamic response. Cortisol and catecholamine secretion in response to anxiety might even exceed the hypothalamic response provoked directly by nociceptive impulses. Moreover, anxiety and emotional stress can cause cortically induced increased blood viscosity and clotting, fibrinolysis and platelet aggregation (Werner et al., 2002).

### Responses during the operation:

Unless excessive concentrations of inhalational agents or anesthetic doses of narcotics are used, the sympathetic, neuroendocrine and biochemical responses provoked by injury-induced nociceptive input are reduced only slightly or not at all. This lack of depression or elimination of reflex responses during general anesthesia is often reflected by increase in cardiac output and blood pressure, even by cardiac arrhythmia provoked by intense noxious stimulation, they are also reflected by all the biochemical changes characteristic of the stress response (Werner et al., 2002).

### Responses in the postoperative period:

Postoperatively, when the effects of surgical anesthesia disappear, the patient's injury persists and algogenic substances continue to be liberated. These substances continue to sensitize nociceptors, so that tenderness ensues and innocuous stimulus such as touch produces pain. Such pathophysiologic changes are greatly enhanced by sympathetic hyperactivity and consequent liberation of norepinephrine, which sensitizes nociceptors and damaged nerve membrane. Moreover, sensitization of dorsal horn neurons, interneurons and flexor motor neurons persists for days after the operation (Werner et al., 2002).

In operations involving abdominal or thoracic viscera, the total pain experience is produced by input from three sites of injury: the skin, the deep somatic structures and the involved visscus or viscera. The cutaneous component, results from liberation of algogenic substances and from damaged cutaneous nerves. Pain is sharp, localized and often accompanied by burning sensation. The deep somatic component, results from liberation of algogenic substances and from consequent lowering of nociceptive threshold, as well as, from damaged nerve axons in the fascia.
Opioids undergo varying degrees of phase 1 and 2 metabolism. Phase 1 metabolism usually precedes phase 2 metabolism, but this is not always the case. Both phase 1 and 2 metabolites can be active or inactive. The process of metabolism ends when the molecules are sufficiently hydrophilic to be excreted from the body. (Totah et al., 2004).

In fact, active metabolites may be more potent than the parent compound. Thus, although metabolism is ultimately a process of detoxifications, it produces intermediate products that may have clinically useful activity, be associated with toxicity, or both. (Mercadante 2000).

**Metabolic pathways:**

Opioids undergoes phase 1 metabolism by the CYP pathway, phase 2 metabolism by conjugation, or both. Phase 1 metabolism of opioids mainly involves CYP3A4 and CYP2D6 enzymes. The CYP3A4 enzyme metabolizes more than 50% of all drugs; consequently, opioids metabolized by this enzyme have a high risk of drug-drug interactions.

The CYP2D6 enzyme metabolizes fewer drugs and therefore is associated with an intermediate risk of drug-drug interactions. Drugs that undergo phase 2 conjugation, and therefore have little or no involvement with the CYP system, have minimal interaction potential. (Quang-Cantagrel et al., 2000).

**PHASE 1 metabolism.**

Phase 1 metabolism typically subjects the drug to oxidation or hydrolysis. It involves the Cytochrome P450 (CYP) enzymes, which facilitate reactions that include N-, O-, and S-dealkylation; aromatic, aliphatic, or N-hydroxylation; Oxidation; sulfoxidation; deamination; and dehalogenation. (Crettol et al., 2006).

The CYP3A4 enzyme is the primary metabolizer of fentanyl and oxycodone, although normally a small proportion of oxycodone undergoes CYP2D6 metabolism to oxymorphine.

Tramadol undergoes both CYP3A4- and CYP2D6-mediated metabolism. Methadone is primarily metabolized by CYP3A4 and CYP2B6, CYP2C8, CYP2D6, CYP2C9 also contributes in varying degree to its metabolism. The complex interplay of methadone with CYP system, involving as many as 6 different enzymes, is accompanied by considerable interaction potential. (Bathun et al., 1999).

The CYP2D6 enzyme is entirely responsible for the metabolism of hydrocodone, codeine, and dihydrocodeine to their active metabolites (hydromorphone, morphine, and dihydromorphine, respectively), which in turn undergo phase 2 glucuronidation. (Mercadante 2000).

**PHASE 2 metabolism**

Opioids primarily in the liver, intended to make a drug hydrophilic to facilitate its lipophilic, which allows them to cross cell membranes.
Phase 2 metabolism conjugates the drug to hydrophilic substances, such as glucuronic acid, sulfate, glycine, or glutathione. The most important phase 2 reaction is glucuronidation, catalyzed by the enzyme uridinediphosphateglucurosyltransferase (UGT).

The most important UGT enzyme involved in the metabolism of opioids that undergo glucuronidation (e.g., morphine, hydromorphone, oxymorphone) is UGT2B7. Research suggests that UGT2B7-mediated opioid metabolism may be altered by interactions with other drugs that are either substrates or inhibitors of this enzyme. Moreover, preliminary data indicate that UGT2B7 metabolism of morphine may be potentiated by CYP3A4, although the clinical relevance of this finding is unknown. (Zhou 2008).

The activity of UGT2B7 shows significant variability between patients, and several authors have identified allelic variants of the gene encoding this enzyme. Although the functional importance of these allelic variants with respect to glucuronidation of opioids is unknown, at least 2 allelic variants (the UGT2B7-840G and -79 alleles) have been linked to substantial reduction of morphine glucuronidation, with resulting accumulation of morphine and reduction in metabolite formation. Moreover, research has shown that variation in the amount of messenger RNA for hepatic nuclear factor 1, a transcription factor responsible for regulating expression of the UGT2B7 gene, is associated with interindividual variation in UGT2B7 enzyme activity. (Zhou 2008).

**Clinical importance of metabolic pathways:**

Most opioids are metabolized via CYP-mediated oxidation and have substantial drug interaction potential. The exceptions are morphine, hydromorphone, oxymorphone, which undergo glucuronidation. In patients prescribed complicated treatment regimens, physicians may consider initiating treatment with an opioid that is not metabolized by the CYP system. However, interactions between opioids that undergo CYP-mediated metabolism and other drugs involved with this pathway often can be addressed by careful dose adjustments, vigilant therapeutic drug monitoring, and prompt medication changes in the event of serious toxicity (Huber et al., 2008).

**PRODUCTION OF ACTIVE METABOLITES**

Some opioids produce multiple active metabolites after administration. Altered metabolism due to medical comorbidities, genetic factors, or drug-drug interactions may disrupt the balance of metabolites, thereby altering the efficacy and/or tolerability of the drug. Moreover, opioids that produce metabolites chemically identical to other opioid medications may complicate the interpretation of urine toxicology screening.

**CODEINE**

Codeine is pro-drug that exerts its analgesic effect after metabolism to morphine. Patients who are CYP2D6 poor (offrapid metabolizers) don’t respond well to codeine. (Codeine Contin 2007).

**MORPHINE**

Morphine is the gold standard for analgesia and remains the most commonly used opioid because of its relatively low cost and the availability of numerous dosage forms. Morphine is metabolized mainly by the liver and its metabolites are excreted via the kidneys. Therefore, it might be excepted that there are alteration in morphine disposition in patients with liver disease. (Kotb et al., 2008).

Morphine is glucuronidated to 2 metabolites with potentially important differences in efficacy, clearance, and toxicity: morphine-6-gluronide (M6G) and morphine-3-glucuronide (M3G). Morphine may also undergo minor routes of metabolism, including N-demethylation to normorphine or normorphine 6-glucuronide, diglucuronidation to morphine-3,6-digluconoride, and formation of morphine ethereal sulfate.

A recent study found that a small proportion of morphine is also metabolized to hydromorphone, although there are no data suggesting a meaningful clinical effect. Like morphine, M6G is a [1-opioid receptor agonist with potent analgesic activity. Although the affinities of morphine and M6G for the [1-opioid receptor are similar, a study of low dose morphine, M6G, and M3G found that morphine had greater analgesic efficacy. The M3G metabolite of morphine lacks analgesic activity, but it exhibits neuroexcitatory effects in animals and has been proposed as a potential cause of such adverse effects as allodynia, myoclonus, and seizures in humans. (Coffman et al., 2003).

There is a need to investigate the disposition of morphine, in patients with cancer pain as a result of primary and secondary liver carcinoma. (Kotb et al., 2008).

Patients with liver cancer showed a 3-4 fold increase in the peak concentration of morphine presumably as a result of the reduction in first pass metabolism secondary to a reduction in liver cell mass; this led to an increase in total systemic bioavailability of morphine. Approximately 70% of the dose entered the systemic circulation in patients with liver cancer compared with 20% in healthy control. This is reflected in an increase in AUC. Systemic clearance was maintained in liver cancer patients with a prolonged elimination half-life in patients with primary liver carcinoma as a result of cirrhosis. (Kotb et al., 2008).

Early studies produced conflicting evidence on the effect of the liver cancer on hepatic drug
metabolism; limited information is available on hepatic drug metabolism in primary and secondary liver cancer. Based on the intact hepatocyte theory Kawasaki and co-workers showed that in a group of six patients with liver cancer (three primary and three metastatic) phenazone clearance was unchanged. (Kotb et al., 2008)

Clearance of antipyrine was also reported to be unchanged by Robertz-Vaupel and colleagues. In cirrhosis, there is usually marked fibrosis and nodular regeneration resulting in circulatory changes of importance expecting a reduced clearance in patients with liver cancer on top of cirrhosis. However, there is evidence of increased hepa-arterial flow that is equal or even above that of normal. Vascular changes as a result of cancer itself may complicate the situation further. These mechanisms can in part explain the maintained clearance of morphine in patients with liver cancer included in this trial. On the other hand, glucuronidation has been shown to be preserved in cirrhosis and even up-regulated. The prolonged half-life in primary liver cancer patients is a result of increased volume of distribution as clearance is maintained in this group of compensated liver patients. Another cause of impaired elimination in patients with liver pathology may be the impaired uptake of the drug across the capillarized endothelium (impaired drug uptake theory). (Kotb et al., 2008).

There was complete pain control and good patient satisfaction in all liver cancer patients while side effects were more frequent in the primary liver cancer group, especially respiratory depression. In two cases in the study, a high serum morphine concentration was noticed in patient above 65 yr of age with normal renal function. Altered blood-brain transport in patients with cirrhotic liver may partly be responsible for this. (Kotb et al., 2008).

HYDROMORPHONE

The primary metabolite of hydromorphone, hydromorphone-3-glucuronide, has neuro-excitatory potential similar to or greater than the M3G metabolite of morphine. Hydromorphone is available only in short acting formulations and extended-release formulations are recommended in patients with chronic pain requiring long-term therapy. (Wright et al., 2001).

TRAMADOL

Like codeine, tramadol requires metabolism to an active metabolite, O-desmethyltramadol (M1), to be fully effective. Both tramadol and its M1 metabolite exert analgesic effects through opioidergic mechanisms (μ-opioid receptor) and through 2 non-opioidergic mechanisms, serotonin reuptake inhibition and norepinephrine reuptake inhibition. Although M1 has more potent activity at μ-opioid receptor, tramadol is the more potent inhibitor of serotonin and norepinephrine reuptake and the more potent promoter of serotonin and norepinephrine efflux. (Raritan & Ortho-McNeil 2000).

Tramadol is centrally acting synthetic opioid analgesic commonly prescribed for moderately to severe pain. Its increasing use may relate to the fact that it has less side effects than other opiates, in particular, less addictive potential less respiratory depression. (Loughreya et al., 2003).

Tramadol has a dual mode of action; weak binding to μ-opiate receptors and reuptake inhibition of serotonin and noradrenalin neurotransmitters. It is extensively metabolized by the liver and primarily excreted in urine. Dose reduction is recommended in severe renal impairment and liver cirrhosis. The most common side effects are dizziness, nausea, constipation and headache. We report the first case of accidental overdose of tramadol leading to fatal acute hepatic failure. (Loughreya et al., 2003).

Tramadol in hepatic patients

Tramadol is used in low doses in patients with cirrhosis who are experiencing intractable pain because of its impact on peripheral pain pathways, partial inhibition of serotonin reuptake, and low affinity for opioid receptors, thought to result in less sedation, respiratory depression, and potential for tolerance; however, constipation can still be problematic because of anticholinergic adverse effects. Caution should be exercised in administering tramadol to epileptic patients this drug is known to lower the seizures threshold. (Kotb et al., 2008).

Morphine, selective serotonin reuptake inhibitors, tricyclic antidepressants (TCAs), or anticonvulsants because it can precipitates serotonin syndrome. Doses may need to be reduced in patients with renal failure. (Viczaychipi et al., 2007).

Hepatitis and liver failure are listed as possible adverse effects in some US (Ultram®, Ortho-McNeil) but no UK datasheets for tramadol products. Sixteen individual nonfatal cases of hepatobiliary dysfunction associated with tramadol ingestion have been reported to the Medicines Control Agency. Deaths related to tramadol have been reported, both when ingested alone in overdose and when taken in combination with potentially interacting drugs. However, in these previous reports, death usually followed the ingestion of large doses and occurred within 24 h of ingestion. Blood tramadol concentrations were extremely high (up to 38 mg/L). In none of the cases were biochemical liver dysfunction or post-mortem hepatic necrosis noted. (Loughreya et al., 2003)

Patients who are apparently ingested more than the recommended daily dose of tramadol, although a deliberate overdose was not suspected. Death followed the onset of fulminant liver failure, without seizure activity. The autopsy blood tramadol concentration...
(3.7 mg/L), although well above the therapeutic range, was much lower than previously reported with fatal ingestion. It is possible that in these previous cases, death occurred at an early stage due to central nervous system or respiratory depression before liver injury became apparent. We have found no previous cases of fatal hepatic failure following tramadol ingestion, nor induced any cases of fatal tramadol ingestion in a therapeutic setting. This case emphasizes the need for careful explanation to patients of the maximum daily dose and the necessity of monitoring liver function when prescribing tramadol in a primary care environment. (Loughreya et al., 2003).

**OXYCODONE**

Oxycodone is metabolized by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone. Noroxycodone is a weaker opioid agonist than the parent compound; but the presence of this active metabolite increases the potential for interactions with other drugs metabolized by the CYP3A4 pathway. (Stamford & BurduePharma 2007).

**PETHIDINE**

Pethidine is metabolized in the liver via 2 separate pathways, hydrolysis to pethidinic acid (inactive metabolite) or demethylation by cytochrome P450 to norpethidine, a non opioid active metabolite. After 3.6 hours however the elimination half-life of norpethidine is around 14-21 hours with normal renal function and 35 hours in renal failure. Norpethidine has half the analgesic potency of pethidine but two to three times the potency as a central nervous system (CNS) excitatory agent and may cause anxiety, hyperreflexia, myoclonus, seizures and mood changes. There is not a clear relationship between neurotoxicity, cumulative dose and serum norpethidine. 6 several cases of seizures have been reported, including when pethidine was used for patient controlled analgesia (PCA). (Mather & Meffin 2000).

In Australia alone, between 1975 to 1997, ADRAC (Adverse Drug Reactions Advisory Committee) received 35 reports describing convulsions in association with pethidine, in 17 of which pethidine was the only suspected drug. Risk factors include repeated dosing of pethidine, with associated renal insufficiency, Sickle-cell anemia, high doses of pethidine, and the concurrent administration of phenothiazines or drugs that induce hepatic enzymes. (Jiraki 2001).

**FENTANYL**

Fentanyl is a strong opioid agonist, a Schedule II substance.

Fentanyl is the oldest synthetic piperidine opioid agonist, interacting primarily with mu receptors. It is approximately 80 times more potent than morphine and is highly lipophilic and binds strongly to plasma proteins. (Pratt & Kaplan 2000).

Fentanyl undergoes extensive metabolism in the liver. When administered as lozenger for oral transmucosal absorption, a portion is swallowed and is subject to first-pass metabolism in the liver and possibly small intestine. It is metabolized to hydroxyfentanyl and norfentanyl. (Botta et al., 2003).

Fentanyl is metabolized by CYP3A4, but to inactive and nontoxic metabolites. However, CYP3A4 inhibitors may lead to increased fentanyl blood levels. The transdermal formulation has a lag time of 6-12 hours to onset of action after application, and typically reaches steady state in 3-6 days. When a patch is removed, a subcutaneous reservoir remains, and drug clearance may take up to 24 hours. (Ferraris et al., 2002).

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### Table (3): Metabolic Pathway/Enzyme Involvement

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Phase 1 metabolism</th>
<th>Phase 2 metabolism</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>None</td>
<td>Glucuronidation via UGT2B7</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>CYP2D6</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2CYP3D4</td>
<td>CYP2D6</td>
<td>None</td>
</tr>
<tr>
<td>Methadone</td>
<td>CYP3A4, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2D9</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>CYP3A4, CYP2D6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>None</td>
<td>Glucuronidation via UGT2B7</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>None</td>
<td>Glucuronidation via UGT2B7</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>None</td>
<td>Glucuronidation via UGT2B7</td>
<td></td>
</tr>
</tbody>
</table>

One of the metabolites of hydrocodone is hydromorphone, which undergoes phase 2 glucuronidation. Oxycodone produces a small amount of oxymorphone, which must undergo subsequent metabolism via glucuronidation.

CYP3A4 and CYP2B6 are the primary enzymes involved in methadone metabolism. Other enzymes play a relatively minor role.
Opioids Without Clinically Relevant Active Metabolites

Fentanyl, oxymorphone, and methadone do not produce metabolites that are likely to complicate treatment. Fentanyl is predominantly converted by CYP3A4-mediated N-dealkylation to norfentanyl, a non-toxic and inactive metabolite; less than 1% is metabolized to despropiofentanyl, hydroxyfentanyl, and hydroxynorfentanyl, which also lack clinically relevant activity. An active metabolite of oxymorphone, 6-hydroxy-oxymorphone, makes up less than 1% of the administered dose excreted in urine and is metabolized via the same pathway as the parent compound, making an imbalance among metabolites unlikely.

Methadone does not produce active metabolites, exerting its activity both analgesic and toxic through the parent compound. However, methadone has affinity for N-methyl-D-aspartate receptors; this affinity is thought to account not only for a portion of its analgesic efficacy but also for neurotoxic effects that have been observed with this opioid. (Kreek et al., 2003).

HEPATIC IMPAIRMENT

The liver is the major site of biotransformation for most opioids. It is therefore not surprising that the prescribing information for most frequently prescribed opioids recommends caution in patients with hepatic impairment.

For example, in patients with moderate to severe liver disease, peak plasma levels of oxycodone and its chief metabolite noroxycodone were increased 50% and 20%, respectively, whereas the area under the plasma concentration-time curve for these molecules increased 95% and 65%. Peak plasma concentrations of another active metabolites, oxymorphone, were decreased by 30% and 40% respectively. Although oxymorphone itself does not undergo CYP-mediated metabolism, a portion of the oxycodone dose is metabolized to oxymorphone by CYP2D6. Failure to biotransform oxycodone to oxymorphone may result in accumulation of oxycodone and noroxycodone, with an associated increase in adverse events. (Foster 2008).

The differential effect of hepatic impairment on the metabolism of oxycodone relative to its active metabolite illustrates the complexities associated with opioids that have multiple active metabolites. Hepatic impairment may also affect metabolism of opioids that undergo glucuronidation rather than CYP-mediated metabolism, such as morphine and oxymorphone. In a 1990 study, the elimination half-life and peak plasma concentrations of morphine were significantly increased in 7 patients with severe cirrhosis. The bioavailability of morphine in these patients was 101% compared with approximately 47% observed in healthy participants. The ratio of morphine to its inactive metabolite M3G was significantly higher in cirrhotic patients than in controls. In another study, morphine hepatic extraction was compared in 8 healthy participants and 8 patients with cirrhosis. (Levine 2003).

The pharmacokinetics of fentanyl and methadone, of the frequently used opioids, are not significantly affected by hepatic impairment. Although dose adjustments for these opioids may not be required in certain patients with hepatic impairment, clinicians should nonetheless be extremely cautious when prescribing any opioid for a patient with severe hepatic dysfunction. (Murtagh et al., 2008).

Pain management in hepatic patient using non-opioid analgesics:

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. In general, acetaminophen at reduced dosing is a safe option.

In patients with cirrhosis, non-steroidal anti-inflammatory drugs should be avoided to avert failure, and opiates should be avoided or used sparingly, with low and infrequent dosing, to prevent encephalopathy. (Lin & Kim 2008).

OTCA Medications:

Over-the-counter analgesics, principally acetaminophen and NSAIDs, are commonly used medications worldwide. Guidelines for the use of OTCAs in patients with chronic liver disease are not readily available despite the possibility that such patients may be more susceptible to adverse reactions. Patients are often counseled to modify use of these drugs. Health care professionals frequently recommend avoidance of use of acetaminophen in patients with liver disease or cirrhosis, whereas NSAIDs are more commonly endorsed. Variability and misconception regarding the safety of OTCAs for patients with hepatic dysfunction are widespread among health care professionals. (Rossi et al., 2008).

Nonsteroidal Anti-inflammatory Drugs:

NSAIDs as a class are largely metabolized by CYPs, and most are heavily protein bound. As such, altered metabolism and bioavailability that result in increased serum levels can be anticipated in cirrhotic patient. NSAID induced (and idiosyncratic)
hepatotoxicity has also been well described. (Rossi et al., 2008).

However, in cirrhotic patients with portal hypertension, the greater concern with NSAID use is the associated renal impairment, in particular hepatorenalsyndrome. This is thought to be due to the inhibition of prostaglandins, which leads to a profound decrease in renal perfusion, reduction in GFR, and marked sodium retention. (Lee 2008).

Cirrhotic patients require prostaglandins to counteract the renin-angiotensin-aldosterone and sympathetic systems that reduce perfusion to the kidneys. Hepatorenal syndrome is a dreaded and frequently fatal complication of advanced liver disease. (Laffi et al., 1997).

NSAIDs can cause mucosal bleeding in patients at increased risk of bleeding as a result of thrombocytopenia and coagulopathy associated with advanced liver disease. (Castro-Fernandez et al., 2006).

This risk is even greater in patients with portal hypertension-related complications, such as esophageal/gastric varices and portal hypertensive gastropathy or gastric antral vascular ectasias. (Castro-Fernandez et al., 2006).

NSAIDs may be tolerated in patients with mild chronic liver disease, but they should be avoided in all patients with cirrhosis because of the increased risk of hepatorenal syndrome and the dire consequences relating to this complication. Preventive medicine, including avoidance of NSAIDs, is exceedingly important in maintaining the clinical stability of patients with well-compensated cirrhosis. (Castro-Fernandez et al., 2006).

No prospective studies have assessed the safety and efficacy of COX-2 inhibitors in the management of chronic pain in patients with cirrhosis. Studies comparing NSAIDs with COX-2 inhibitors in patients without underlying liver disease have demonstrated similar effectiveness in the treatment of musculoskeletal pain. (Hur et al., 2006).

Although some COX-2 inhibitors may protect against gastrointestinal bleeding compared with NSAIDs, an increased risk of cardiovascular adverse events has been observed. Cyclooxygenases are highly regulated in response to changes in intravascular volume, and COX-2 is implicated in the mediation of rennin release, sodium regulation, and the maintenance of renal blood flow. COX-2 inhibitors may reduce portal pressure in cirrhotic patients, but pilot data suggest a decreased GFR in patients with cirrhosis and ascites treated with celecoxib. The safety of COX-2 inhibitors needs further study in patients with cirrhosis. (Guevara et al., 2002).

Acetaminophen is the most common cause of fulminant hepatic failure in United States, creating the perception that it may be dangerous in patients with chronic liver disease. (Larson et al., 2005).

Moreover, concern is increasing regarding the safety of acetaminophen at a maximal dosage of 4 g/d in the general population. (US Department of Health and Human Services; US Food and Drug Administration 2010).

Surveillance data from the United States from 1990 to 1998 estimated 56,000 emergency department visits, 26,000 hospitalizations, and 458 deaths per annum because of acetaminophen overdose. (Benson et al., 2005).

When one considers that 28 billion doses of products containing acetaminophen were consumed in 2005 alone, the probability of an individual patient without preexisting liver disease or concomitant alcohol consumption developing clinically important hepatotoxicity or nephrotoxicity when acetaminophen dosing is limited to less than 4 g/d is exceedingly rare. However, liver failure can occur with a 1-time ingestion of high doses of acetaminophen (>12 g in adults or 250 mg/kg in a child). (Temple et al., 2007).

Case reports have demonstrated that long-term ingestion (often accidental) of supra-therapeutic doses (> 4 g/d) of acetaminophen in patients without known liver disease, and therapeutic doses in alcoholic patients without cirrhosis, resulted in acute liver failure. (Mofredj et al., 1999).

To address the fact that approximately half of all cases of acetaminophen-induced acute liver failure are due to unintentional overdosing, advisory committees to the Food and Drug Administration (FDA) endorse relabeling of acetaminophen-containing products to better inform the consumer of the potential for liver injury with supra-therapeutic doses, and while concurrently consuming 3 or more alcoholic drinks per day. In addition, the advisory committees support lowering the maximal dosage of acetaminophen to 2600 mg/day and eliminating or reducing the availability of combination analgesics, most commonly combinations of opioid with acetaminophen. Opiates can be addictive, and patients may develop tolerance to these agents, necessitating dose escalation and thereby increasing the risk of acetaminophen toxicity. (US Department of Health and Food Administration 2010).

These recommendations have not been instituted. Unfortunately, no prospective, long-term studies have assessed the safety of long-term use of acetaminophen in patients with cirrhosis. In such patients, the half-life of oral acetaminophen is double that in healthy controls, but hepatic injury and renal injury are rare when the dosage is limited to less than 4 g/d. This assumption is supported by a double-blind, 2-period
crossover study of 20 patients with chronic stable liver disease (8 with cirrhosis), who tolerated acetaminophen at a dosage of 4 g/d for 13 days without adverse effects. (Mofredj et al., 1999).

The prevailing mechanism of acetaminophen-induced hepatotoxicity includes altered metabolism via CYP activity in combination with depleted glutathione stores that cause accumulation of a hepatotoxic intermediate, N-acetyl-pbenzoquinone imine (NAPQI). (Bolesta & Haber 2003).

Studies in patients with cirrhosis have shown that CYP activity is not increased and glutathione stores are not depleted to critical levels in those taking recommended dose of acetaminophen. Glutathione stores are variable in patients with and without underlying liver disease but generally have not been found to be depleted in cirrhotic patients. On the basis of these data, the longer half-life, and very limited clinical studies, our recommendation (expert opinion) for long-term acetaminophen use (>14 days) in cirrhotic patients (not actively drinking alcohol) is for reducing dosing at 2 to 3 g/d. For short-term use or 1-time dosing, 3 to 4 g/d appears safe; however, with the new FDA guidelines in mind, a maximum dosage of 2 to 3 g/d is recommended. (Benson et al., 2005).

Other Analgesics:

Not infrequently, patient with cirrhosis experience neuropathic pain due to neuropathies from a variety of causes, including diabetes, alcoholisms, nutrient deficiencies, and cryoglobulinemia. Tricyclic antidepressant such as amitriptyline and imipramine have been the mainstay treatment of neuropathic pain for decades, although their use in this capacity is off-label. The exact mechanism of antineuralgic action of these agents is unknown, but they may diminish chronic pain by blocking presynaptic serotonin and/or noradrenaline reuptake in neurons involved in pain transmission or dampened endogenous opioid systems. Tricyclic antidepressants rely on hepatic biotransformation with first-pass effects (via CYP2D6 largely) and renal elimination. (Harvey 2008).

Health care professionals should start a TCA at a low dose because these agents are sedating, and patients may be more susceptible to the anticholinergic adverse effects, including dry mouth, blurry vision, drowsiness, tachycardia, and orthostatic hypotension due to altered metabolism in the setting of liver dysfunction. The clinician and patient must be particularly watchful for intestinal stasis as an adverse effect of a TCA because this can precipitates hepatic encephalopathy. if TCAs are deemed necessary, nortriptyline and desipramine are less potent and appear to be less sedating than other TCAs. Additionally, nortriptyline and desipramine may have less tachycardia and hypotension associated with their use than older and more potent TCAs, particularly amitriptyline and doxepin. (Einarsdottir & Bjornsson 2008).

Anticonvulsants such as carbamazepine or gabapentin also have an established role in neuropathic pain management. The rationale for their use is that neuropathic pain presumably involves an imbalance of excitatory and inhibitory neurotransmitters, and anticonvulsants may modulate peripheral and central components of neurotransmission to correct this imbalance and thus diminish pain. Most anticonvulsants are metabolized by the liver (via CYPs) and excreted by the renal system, once again necessitating lower and less frequent dosing in cirrhotic patients. (Einarsdottir & Bjornsson 2008).

Carbamazepine has been reported to cause hepatotoxicity in the general population; it may precipitates a rapid deterioration in cirrhotic patients and thus should be avoided. (Harvey 2008).

Gabapentin is unique among anticonvulsants because it is not metabolized by the liver or bound to plasma proteins, making it a preferred anticonvulsant in patients with cirrhosis. However, the general use of gabapentin in patients with cirrhosis may be limited by other potential adverse effects, including sedation, nausea, and dizziness. (Sylvestre 2002).

Doses should be adjusted for renal failure because gabapentin is renally excreted. Pregabalin is another anticonvulsant shown to be effective for neuropathic pain; its mechanism of action is as a potent ligand for the <-2™ subunit of voltage-gated calcium channels in the central nervous system. (Harvey 2008).

Like gabapentin, it is not subject to hepatic metabolism and hence may be an appealing agent of choice in cirrhotic patients with neuropathic pain. A recent case report from Sweden determined that pregabalin was a probable cause of acute liver failure in a 61-year-old healthy man with no previous liver disease. (DiMartini et al., 2006).

Although this may have been an idiosyncratic event because no further case reports have been published in literature, clinicians must be mindful of increased risk of drug-induced liver injury in patients with underlying liver disease. (Vizcaychipi et al., 2007).

References


