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Opioid Induced Hyperalgesia

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Abstract

Objective. To discuss the phenomenon of opioid induced hyperalgesia (OIH) and investigate the data and clinical recommendations available on this topic.

Design. A literature search on the topic of OIH was performed. Relevant studies pertaining to OIH were included in this review.

Results. Existing studies and reviews on the pathophysiology, diagnosis, and clinical management of OIH are discussed with updated data and literature references.

Conclusion. As more opioids are prescribed, especially to treat chronic nonmalignant pain, OIH becomes more of a relevant and significant issue. Although the exact mechanisms of OIH are not clearly understood further research is required to broaden and develop our knowledge of this topic.

Key Words. Opioid; Opioid Induced Hyperalgesia

Introduction

The International Association for the Study of Pain defines hyperalgesia as increased pain from a stimulus that normally provokes pain [1]. Opioid induced hyperalgesia (OIH) is a state of enhanced pain sensitization in patients who are on chronic opioid therapy (COT).

Historically, the phenomenon of OIH has been described as early as the 19th century. In 1870, the physician Albutt described the phenomenon stating, "at such times I have certainly felt it a great responsibility to say that pain, which I know is an evil, is less injurious than morphia, which may be an evil. Does morphia tend to encourage the very pain it pretends to relieve?" [2] In 1880, Dr. Rossbach also drew a similar conclusion to his predecessor saying, "when dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia, and irritability become manifest."[3] Even a hundred years later, the phenomenon of OIH continues to be seen by practitioners treating patients who are on COT.

Although the true incidence of OIH is unknown due to a paucity of literature on the subject and methodological challenges, there are studies in three distinct patient populations that provide some insight into OIH incidence. These populations include: 1) former opioid addicts who are maintained on methadone maintenance therapy, 2) patients who are administered opioids during the perioperative surgical period, and 3) healthy volunteers who are administered opioids acutely and then undergo pain tolerance testing.

In former opioid addicts who are on methadone maintenance therapy, there is some evidence to support that they are at risk for development of OIH. Studies comparing patients who are on methadone maintenance for a history of drug abuse have demonstrated that this patient population has increased pain sensitivity as assessed with a cold pressor test as compared to healthy matched control subjects [4–6]. There are also studies in the same patient population that show when an electrical or mechanical pain stimulus is applied to patients on methadone maintenance therapy there is no difference in pain sensation or incidence of hyperalgesia [5,7,8]. While these studies are cross-sectional in design and do not account for possible differences in preopioid pain processing, there is growing evidence that patients on COT are at risk for OIH. More studies need to be performed to further elucidate how common OIH is in the chronic pain population.

The second patient population that has been studied are patients who were given high doses of opioids during the perioperative period. Two prospective studies showed that patients given high doses of opioids intraoperatively had increased pain scores along with increased postoperative use of opioids [9,10]. One study randomized sixty patients undergoing total abdominal hysterectomy into a low dose (1 $\mu g \cdot kg^{-1}$) and high dose (15 $\mu g \cdot kg^{-1}$) fentanyl bolus at induction of anesthesia. The patients in the high dose group had higher pain intensity scores postoperatively while consuming more opioid as compared to the low dose fentanyl group [10].

The final patient population studied are healthy human volunteers who were studied after short term use of opioids (mostly remifentanil). Using models of secondary hyperalgesia and cold pressor induced pain, these studies have concluded that healthy human volunteers when given opioids, even on a short term basis, may be at risk for development of OIH [11]. One study used a double blind, randomized, crossover and placebo-controlled design in opioid-naive, healthy human volunteers to test whether hyperalgesia would develop within thirty minutes of stopping an infusion with remifentanil. The study reported that in the volunteers, a skin area with pre-existing mechanical hyperalgesia was significantly enlarged after the remifentanil infusion was stopped [12]. In another group of 10 healthy volunteers, who underwent capsaicin induced mechanical hyperalgesia and then received an infusion of remifentanil, all patients experienced enlargement of their hyperalgesic area by up to $180 \pm 47\%$ [13].

Pathophysiology

The mechanisms that are responsible for the development of OIH are complex and still being elucidated. Although there has been debate as to the existence of hyperalgesia from opioids, there is an accumulating body of scientific evidence in both the basic science and clinical literature that supports OIH as a real clinical entity.

In the basic science literature, a systematic review performed by Angst and Clark led them to develop a model of OIH that is neurobiologically multifactorial, meaning the mechanisms that may be causing OIH are diverse and take place at multiple locations along the peripheral and central nervous system [14]. Over time it seems that neurobiological systems that at first responded to opioids and provided analgesia, changed over time in a way that actually enhanced nociception [15]. A multitude of laboratory studies have shown that mechanical allodynia and/or thermal hyperalgesia occurs after the administration of heroin [16], fentanyl [17], and intrathecal morphine [18].

Clinical studies have also shown OIH occurring in patients after intraoperative use of remifentanyl, [9] along with decreased hyperalgesia after subsequent opioid dose taper [19]. A prospective study in which patients with chronic back pain were administered morphine also demonstrated the development of hyperalgesia within a month of commencing the morphine [20]. The mechanisms that are involved in the creation of OIH are still being studied but there are currently several theories in the evolution of this disease state.

A common mechanism proposed for the development of OIH involves the central glutaminergic system. In this system the excitatory NMDA neurotransmitter may play a role in the development of OIH. In a 2009 review article, Silverman outlined the role that NMDA plays in the development of OIH [21]. Highlighted facts from the review include: 1) NMDA receptors become activated and when inhibited, prevent the development of tolerance and OIH, 2) when the glutamate transporter system is inhibited, there are increases in the amount of glutamate available to NMDA receptors, 3) cross talk of neural mechanisms of pain and tolerance may exist, and 4) prolonged morphine administration induces neurotoxicity via NMDA receptor mediated apoptotic cell death in the dorsal horn. These four findings taken together propose a mechanism where the NMDA receptor if inhibited can lead to the prevention of OIH. This NMDA mediated mechanism via the central glutaminergic system sensitizes the neurons and may partially explain the development of OIH. Spinal dynorphins also may play a role in OIH by increasing the presence of excitatory neuropeptides which can enhance nociceptive input.

Another proposed mechanism for OIH is the activation of descending pain pathways from the rostral ventromedial medulla which causes certain neurons to respond uniquely to opioids. One set of studies suggests involvement of descending pain pathways in the development of OIH. Experiments using injections of local anesthetics into the rostral ventromedial medulla or surgical lesioning of the dorsolateral funiculus demonstrate that descending pain pathways play a role in the genesis of OIH [22,23]. Finally, decreased reuptake of neurotransmitters enhancing certain aspects of the pain pathway, as well as individual genetic factors, may play a factor in the pathophysiology of OIH. It is evident from these proposed mechanisms that the underlying pathophysiology of OIH is complex and interconnected. Although advances have been made to untangle this web, much more work and discovery lay ahead.

Diagnosing Hyperalgesia

OIH has been demonstrated in multiple animal models [24] and in humans volunteers [14,25]. The majority of experiments in humans test for thermal or mechanical alterations in pain and it is unclear how this may apply clinically. The exact mechanisms for the development of OIH are still not clearly understood; thus formulating a set of criteria for diagnosing OIH is not a standardized process. Broadly speaking, there is a general imbalance

between pronociceptive and antinociceptive pathways. It is postulated that due to sensitization in the nociceptive pathways, higher doses of opioids ironically causes more pain [26]. There are no official criteria or guidelines for diagnosing OIH. Recently however, Eisenberg [23] published suggested clinical criteria for diagnosing OIH, some of which are discussed in the following section.

Pain from OIH is not necessarily located at the source of injury or disease. Instead, pain manifests as generalized, diffuse, and ill defined; all despite increasing opioid doses. It is important to note however that increasing pain is not explained by a progression or worsening of the underlying condition and should always be ruled out [27]. OIH can often be confused with tolerance or even withdrawal at times, which can both exhibit similar symptoms to OIH. Symptoms of allodynia and hyperalgesia can manifest in tolerance, withdrawal and OIH and can be difficult to differentiate. However OIH is considered a separate and distinct condition.

Typically, OIH is suspected when there is an increase in perceived pain with an increase in opioid use. Opioid use does not necessarily need to be chronic as this condition can arise in patients receiving a short course of opioids, and as mentioned previously, even in the peri-operative setting [28]. However, there may be some debate as to whether postoperative OIH may be confused with acute opioid withdrawal or with acute development of tolerance especially with the use of remifentanyl [7]. Tolerance is defined as decreasing efficacy of a drug over time. There is a desensitization of the antinociceptive opioid pathways [2]. When the opioid dose is increased, pain from tolerance improves. The pain from OIH differs from tolerance in that it does not improve when higher doses of opioids are given [23,28]. There is often a paradoxical increase in pain with OIH seen longitudinally over time. Withdrawal from opioids also can sometimes mimic symptoms of OIH. Myalgesia, cramping, abdominal pain, and hyperalgesia associated with withdrawal can be confused with OIH. Even pain that returns after opioid doses have been missed or not taken, can lead to confusion between opioid withdrawal and OIH. The clinical picture of abrupt cessation of opioids however, would suggest withdrawal rather than OIH. Finally, in addition to distinguishing OIH from tolerance or withdrawal, behaviors stemming from opioid abuse or addiction could also confuse the diagnosis of OIH [29].

Management of OIH

Treating OIH is often very challenging and time consuming. One option available to manage OIH includes weaning off opioids completely. When ceasing opioids, patients often do not understand the paradoxical nature of OIH and decreasing doses of opioids, the very medicine prescribed to attenuate the pain, does not make sense. The reasoning behind weaning should be thoroughly explained. Fostering a collaborative patient–physician relationship is of utmost importance in order for this type of management to succeed. A strong support system, including psychological therapy, helps when weaning down or off opioids. It should be emphasized to the patient that opioid weaning can be a prolonged process and can even at times cause an exacerbation of pain or mild withdrawal symptoms. Tolerance, progression of disease or new pathology should be ruled out before embarking on opioid cessation. Surprisingly, there are no studies looking at opioid weaning for OIH and there is limited data to support tapering opioids. Recent recommendations were published by Berna et al. outlining current guidelines for weaning opioid therapy [30].

Another option to manage OIH is to rotate to a different class of opioids. An alternate opioid is started at a reduced amount due to incomplete cross-tolerance which can allow for an overall reduction in opioid dose. Multiple case studies have been reported with improved analgesia with opioid rotation [31]. Rotation to methadone in particular, can improve OIH and is discussed in more detail below. Also adding opioid sparing adjuvant medications such as a NSAID, acetaminophen, an anticonvulsant or an antidepressant can help reduce the need for opioids.

Other medical options for managing OIH primarily focus on the class of NMDA antagonists. NMDA antagonists have shown to prevent tolerance to opioids but data and evidence are not robust. Ketamine is a NMDA antagonist that is showing promise in neuropathic pain states and is also being used for patients who are on large doses of opioids. There is some evidence that ketamine might modulate OIH when given in the perioperative period [32]. However there are no large randomized controlled trials proving this in a substantial cohort of patients.

Methadone, although primarily an opioid agonist, does show some weak NMDA antagonism. Chu et al. in multiple studies demonstrated significant improvement of OIH with methadone [33]. However, studies of opioid addicts on methadone maintenance have also shown that methadone can worsen OIH. Again, this may be in part due to the complex imbalance of pronociceptor and antinociceptor pathways that occurs in OIH especially in the context of methadone which works both as an opioid and NMDA antagonist.

Dextromethorphan, more commonly used as a cough suppressant, is also a NMDA antagonist. Dextromethorphan when previously combined with morphine showed superior pain relief compared to morphine alone. However, a follow up study showed the same combination (Morphidex®) failed to prove any clinical efficacy with pain or OIH [34].

Buprenorphine, a partial opioid agonist and kappa antagonist, has been used as an analgesic and more recently, in combination with nalaxone (Suboxone®), for the treatment of opioid dependence. A study by

Koppert et al. [35] examined the effects of both sublingual and intravenous buprenorphine in hyperalgesia in a randomized controlled trial. Results showed positive antihyperalgesic properties of buprenorphine. The long term effects of buprenorphine in OIH are still questionable. Finally, pure opioid antagonists, such as naloxone, might intuitively make sense to use for OIH and has been shown in animal studies to help the antinociceptive effects of opioids [36] but do not seem to modulate or reverse the effects of OIH. Ultra-low doses of naloxone used intraoperatively with remifentanyl can reduce opioid tolerance but does not seem to alter hyperalgesia [37].

Other agents such as pregablin, propofol, and Cox-2 inhibitors can play a role in modulating OIH. Each medication interacts at different aspects of the pain pathway; pregablin at neuronal tissues, propofol at the GABA receptors, and COX-2 inhibitors through inhibition of prostaglandin synthesis [38]. Clinical data for all of these drug classes however, is limited. α-2 agonists may show some promise for modulation of OIH as well, but evidence is mixed as animal and human studies did not always produce similar outcomes.

Conclusion

As more opioids are prescribed, especially to treat chronic non-malignant pain, OIH becomes more of a relevant and significant issue. Although the exact mechanisms of OIH are not clearly understood and it is questionable as to how animal models of OIH translate into human models and clinical application, further research is required to broaden and develop our knowledge of this topic. As patients experience the paradox of OIH, physicians need to be equipped with options for dealing with this complex phenomenon.

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