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Focused Review

A Comprehensive Review of Opioid-Induced Hyperalgesia

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Opioid-induced hyperalgesia (OIH) is defined as a state of nociceptive sensitization caused by exposure to opioids. The condition is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain could actually become more sensitive to certain painful stimuli. The type of pain experienced might be the same as the underlying pain or might be different from the original underlying pain. OIH appears to be a distinct, definable, and characteristic phenomenon that could explain loss of opioid efficacy in some patients.

Findings of the clinical prevalence of OIH are not available. However, several observational, cross-sectional, and prospective controlled trials have examined the expression and potential clinical significance of OIH in humans. Most studies have been conducted using several distinct cohorts and methodologies utilizing former opioid addicts on methadone maintenance therapy, perioperative exposure to opioids in patients undergoing surgery, and healthy human volunteers after acute opioid exposure using human experimental pain testing.

The precise molecular mechanism of OIH, while not yet understood, varies substantially in the basic science literature, as well as clinical medicine. It is generally thought to result from neuroplastic changes in the peripheral and central nervous system (CNS) that lead to sensitization of pronociceptive pathways. While there are many proposed mechanisms for OIH, 5 mechanisms involving the central glutaminergic system, spinal dynorphins, descending facilitation, genetic mechanisms, and decreased reuptake and enhanced nociceptive response have been described as the important mechanisms. Of these, the central glutaminergic system is considered the most common possibility. Another is the hypothesis that N-methyl-D-aspartate (NMDA) receptors in OIH include activation, inhibition of the glutamate transporter system, facilitation of calcium regulated intracellular protein kinase C, and cross talk of neural mechanisms of pain and tolerance.

Clinicians should suspect OIH when opioid treatment's effect seems to wane in the absence of disease progression, particularly if found in the context of unexplained pain reports or diffuse allodynia unassociated with the original pain, and increased levels of pain with increasing dosages. The treatment involves reducing the opioid dosage, tapering them off, or supplementation with NMDA receptor modulators.

This comprehensive review addresses terminology and definition, prevalence, the evidence for mechanism and physiology with analysis of various factors leading to OIH, and effective strategies for preventing, reversing, or managing OIH.

Key words: Opioid-induced hyperalgesia, opioid tolerance, opioid sensitivity, adverse events, chronic opioid therapy

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The use of opioids for the treatment of chronic non-cancer pain has escalated in recent years, making them one of the most commonly prescribed medications in the United States (1-4). However, this escalation has many problems. Among those problems are a lack of evidence supporting their long-term effectiveness, misuse and abuse of prescription opioids, and multiple adverse events associated with long-term opioid use, including opioid-induced hyperalgesia (OIH) (1-17).

Chronic opioid therapy could paradoxically induce or sensitize patients to acute pain, a condition termed "opioid-induced hyperalgesia" (14,15). Even though direct and indirect experiments from animals and patients shows the evidence for opioid-induced analgesia, the clinical implications of this phenomenon continue to be unclear. However, the implications are that patients on high doses of long-term opioid pharmacotherapy can suffer exquisite acute pain after surgery, but more importantly, escalating doses in chronic opioid therapy might cause OIH by inducing a vicious cycle of increasing dosage and anxiety, both for physician and patient (17). Consequently, as Chapman et al (4) pointed out, the answers to multiple questions are lacking, including the proportion of patients with OIH who receive opioid therapy, the propensities of patients to develop OIH, the preferential effect on certain types of acute or chronic pain, dose relationship and prevalence of OIH, and the duration and prevalence of OIH. Further, there are no well-known strategies which are effective in preventing, reversing, or managing OIH.

Apart from the paucity of literature on OIH and various related factors, systematic reviews are lacking on this subject. Consequently, this comprehensive review is undertaken to evaluate OIH and address the prevalence of OIH; analyze various factors leading to OIH with types of pain, and the relationship between opioid dosage, and identification of acute painful conditions secondary to OIH; and effective strategies for preventing, reversing, or managing OIH.

1.0 Methods

This is a narrative review of the literature from 1966 through November 2010 including reports, systematic reviews, all types of studies, and other literature concerning OIH. The data was collected by doing a search of PubMed, EMBASE, Cochrane Reviews, and a manual search of all pertinent references in the literature. The keywords used were opioid-induced hyperalgesia, allodynia, opioid withdrawal, addiction, opioid or opiate tolerance, neuropathic pain, chemically induced pain, and hyperpathia.

2.0 Historical Considerations

As early as the 19th century, OIH was observed in patients receiving morphine for pain. It was recognized that a potent analgesic such as morphine could actually result in an increase in pain and was observed by Albutt in 1870 (18). Albutt described that, "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." It was questioned that, "Does morphia tend to encourage the very pain it pretends to relieve? In addition, Albutt stated that, "Experience is needed" and, ". . . in the cases in question, I have much reason to suspect that a reliance upon hypodermic morphia only ended in that curious state of perpetuated pain."

In addition, Rossbach (19) in 1880 noted that, "when dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia, and irritability become manifest."

Accumulating evidence suggests that the administration of opioid analgesics leads not only to analgesia, but may also lead to a paradoxical sensitization to noxious stimuli (20). This phenomenon is referred to as OIH. Among the more important human studies documenting this effect are those demonstrating hyperalgesia in former opioid addicts maintained on methadone when compared with matched controls not receiving methadone or other opioids (21-23).

In the early to mid 2000 period, studies had focused toward the toxic effects of opioid metabolites, causative of OIH, such as morphine-3-glucoronide, with central nervous system (CNS) effects of irritability and allodynia (24-26). In addition, hydromorphone 3-glucuronide was also shown to have toxic activity in rats (27). Further, OIH was reported to result only from the phenanthrene class of drugs. However, OIH has been demonstrated with drugs of different classes to include, but not be limited to, methadone and the phenanthrene class, and has been demonstrated in acute opioid administration in the synthetic class to include the piperidines, but not with oxymorphone (24,28-30).

3.0 Terminology

Tolerance and sensitization have been described to have similarities; however, tolerance is a pharmacologic concept which occurs when there is a progressive lack of response to a drug, thus requiring increased dosing, which can occur with a variety of drugs not limited to opioids (15). In addition, tolerance might not only

develop to the analgesia provided by opioids, but also adverse events might develop, which are seen with multiple drugs including opioid administration such as pruritus, nausea, sedation, and respiratory depression.

Other differences between tolerance and sensitization include that tolerance is characterized by decreasing efficacy of the drug, which can be overcome by increasing the dose; whereas OIH cannot be overcome by increasing the dosage since it is a form of pain sensitization induced by the drug which occurs within the CNS. In fact, increasing the dosage would only worsen the pain and conversely, pain is improved by reducing or eliminating the opioid.

OIH is defined as a state of nociceptive sensitization caused by exposure to opioids. The condition is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain might actually become more sensitive to certain painful stimuli. The type of pain experienced might be the same as the underlying pain or might be different from the original underlying pain. OIH appears to be a distinct, definable, and characteristic phenomenon that could explain the loss of opioid efficacy in some cases.

4.0 Mechanism and Pathophysiology

Significant evidence has been accumulating concerning the mechanism and pathophysiology of OIH in the literature.

4.1 Basic Science Evidence

In a systematic review, Angst and Clark (14) reviewed the majority of publications available describing OIH in various animal models. Following this, they described a model for OIH that considers this process to be neurobiologically multifactorial. It seems that, in general, neurobiologic systems that respond to opioids acutely in such a manner as to provide analgesia, might change over time in such a way as to enhance nociception, especially in the setting of declining opioid doses (14,15). The best investigated sites of such plasticity include peripheral effects, spinal effects, and supraspinal effects.

Mao (31) has documented the occurrence of OIH in laboratory animals. He compared dose response effects before and after administration of an opioid. A progressive reduction in baseline nociceptive pain thresholds were illustrated with intrathecal morphine administration (32), with fentanyl boluses (33), and with repeated heroin administration (34). Thus, the concept that desensitization can be present with concurrent or repeat administration of opioids has been demonstrated.

Many laboratories have reported mechanical allodynia and/or thermal hyperalgesia after the acute administration of opioids like heroin and fentanyl (33,35), the chronic administration of intrathecal morphine (36,37), the local peripheral administration of morphine (38), or the chronic administration of systematic opioids of several types (39-41).

Pronociceptive effects of remifentanil in a mouse model of post surgical pain were demonstrated (42). In this model of incisional pain, remifentanil induced pronociceptive effects, which were dose dependent but unaltered by the duration of administration. In addition, a second surgery performed on the same site and experimental conditions induced greater post-operative hyperalgesia that was enhanced when remifentanil was used as an anesthetic.

4.2 Clinical Evidence

Similar to basic science evidence, supporting clinical evidence has also been established (14,21,30,43-55). Clinical OIH has been described after intraoperative remifentanil infusion (30), in patients with detoxification from high dose opioids with improvement in pain (43), and increased pain sensitivity with methadone (21). Further, there have been a host of experimental studies in human volunteers in anecdotal reports of increased pain sensitivity induced or observed with concomitant use of opioids. These studies and the mechanisms of OIH have been extensively reviewed (14).

A prospective trial in which long-acting morphine was given to participants with chronic low back pain demonstrated measurable hyperalgesia within one month of beginning therapy (44). An observational study in patients with non-cancer chronic pain, taking either methadone or morphine, compared with a control group, indicated that patients with chronic pain managed with opioids and methadone-maintained patients were hyperalgesic when assessed by the cold pressor test, but not by the electrical stimulations test (45). In a review of OIH (46), the findings reinforced the opinion that the development of OIH is based on confounders including the pain modality tested, route of drug administration, and specific opioid in question, specifically in normal human volunteers receiving acute morphine infusions.

In another systematic evidence-based structured review of OIH (47), the strongest evidence came from opioid infusion studies in normal volunteers as measured by secondary hyperalgesia. The authors con-

cluded that there was not sufficient evidence to support or refute the existence of OIH in humans except in the case of normal volunteers receiving opioid infusions (47). They also identified differential effects on pain pathways with respect to hyperalgesia, which was attributed to inherent differences in how opioid exposure modulates different nociceptive systems. Further, they identified the toxic metabolite morphine-3-glucoronide as a possible confounding factor in studies of OIH.

Among other reviews, Mitra (48) found strong association between high-grade tolerance and the development of OIH. Of interest were studies which revealed that morphine administration can cause neuronal cell death, which could be a contributory factor in the development of not only tolerance, but also OIH. They also described that P-glycoprotein inhibition might play a role in the induction, maintenance, and severity of OIH. The P-glycoprotein system is a transport system associated with the system for secreting toxins out of the body, including the removal of morphine and morphine metabolites from the central compartment. Further, inhibition of the P-glycoprotein system can result in rapid escalation and/or higher cerebrospinal fluid (CSF) levels of morphine and morphine metabolites. Current literature suggests that P-glycoprotein inhibitors include verapamil, cyclosporin, quinine, ketoconazole, and reserpine, among others.

4.3 Mechanism

A substantial and growing body of literature supports the conclusion that genetics and other factors influence pain sensitivity and analgesic responses. However, the genetics of OIH are not well explored in part due to the barriers posed by genetic studies. While there are many proposed mechanisms for OIH, 5 mechanisms involving the central glutaminergic system, spinal dynorphins, descending facilitation, genetic mechanisms, and decreased reuptake and enhanced nociceptive response have been described as the important mechanisms.

4.3.1 Central Glutaminergic System

Among the mechanisms proposed to explain OIH or desensitization, the central glutaminergic system is the most common possibility (39). The majority of the studies examining the mechanisms of OIH involve the systemic administration of opioids (31,32). The excitatory neurotransmitter NMDA plays a central role in the development of OIH. The current data suggest that opioid-induced desensitization or pharmacological tolerance, and sensitization or OIH, even though distinct processes, might share common cellular mechanisms in part mediated through activation of the central glutaminergic system (32). Silverman (17) summarized the role of NMDA in OIH as follows:

1. NMDA receptors become activated and when inhibited, prevent the development of tolerance and OIH (37,56,57).
2. The glutamate transporter system is inhibited, therefore increasing the amount of glutamate available to NMDA receptors (58).
3. Calcium regulated intracellular protein kinase C is likely a link between cellular mechanisms of tolerance and OIH (37,59,60).
4. Cross talk of neural mechanisms of pain and tolerance may exist (61,62).
5. Prolonged morphine administration induces neurotoxicity via NMDA receptor mediated apoptotic cell death in the dorsal horn (58,63-66).

Sensitization of spinal neurons accompanies opioid-induced enhanced nociception, the mechanism mediated by the central glutaminergic system via the NMDA and reversed by an NMDA receptor antagonist such as MK801 (64,65). In addition, repeated morphine administration has also been shown to illicit increased levels of the pro-nociceptive peptide calcitonin gene related peptide (CGRP) and substance P within the dorsal root ganglia (64). Another interesting hypothesis is that OIH results from the activation of descending pain facilitation mechanisms that arise from the rostral ventromedial medulla (RVM).

4.3.2 Spinal Dynorphins

Spinal dynorphin plays an important role in OIH in that levels have shown increases with continuous infusions of μ-receptor agonists (67). These increased levels lead to the release of spinal excitatory neuropeptides such as CGRP from primary afferents (68). OIH is therefore a pro-nociceptive process facilitated by increasing the synthesis of excitatory neuropeptides and their release upon peripheral nociceptive stimulation (32).

Increased activity of the excitatory peptide neurotransmitted cholecystokinin (CCK) in the RVM activates spinal pathways that up-regulate spinal dynorphin and consequently enhance nociceptive inputs at the spinal level (41,67-70).

4.3.3 Descending Facilitation

One of the common mechanisms described in OIH is the activation of facilitative descending pathways from

the RVM (41). The descending facilitation influence on OIH can be seen through several mechanisms. Subsets of neurons (on and off cells within the RVM) have a unique response to opioids (71,72). These activities might facilitate spinal nociceptive processing (73). Further, lesioning of the descending pathway to the spinal cord (dorsolateral funiculus) prevents the increase seen in excitatory neuropeptides (68).

4.3.4 Genetic Influences

While traditional pharmacological, electrophysiological, biochemical and molecular techniques have been useful in the exploration of OIH, now murine genetics are used to identify genomic loci linked to this phenomenon (20). A substantial and growing body of literature supports the conclusion that genetics influence pain sensitivity and analgesic responses and consequently, potentially also OIH (20,65,74-81).

Jensen et al (82) described genetic influence by the activity of the catecholamine breakdown enzyme Catechol-O-methyltransferase (COMT). They described that there are 3 possible genotypes of this polymorphism representing substitution of the amino acid valine for methionine. The breakdown of dopamine and noradrenaline is up to 4 times higher for the valine allele compared to methionine, resulting in different levels of synaptic dopamine/noradrenaline following neurotransmitter release (83). This polymorphism has previously been associated with multiple aspects of memory function, anxiety, and regulation of pain sensitivity (84-87), but not following the single pain stimulus (84,88-91), compared to individuals homozygous for the COMTval158 allele. These mechanisms indicate that COMT influences central pain modulation.

4.3.5 Decreased Reuptake and Enhanced Nociceptive Response

Among the many mechanisms proposed to explain OIH, the decreased reuptake of neurotransmitters from the primary afferent fibers has been considered as the common mechanism (58), along with enhanced responsiveness of spinal neurons to nociceptive neurotransmitters like substance P and glutamate (65,74). Though not previously linked to OIH, the enhanced expression of β2 adrenergic receptors (β2-AR) have been identified as adaptive changes occurring during chronic exposure to opioids (75,76). Likewise, the functional enhancement of β2-AR signaling has been demonstrated after chronic morphine exposure in various nervous system tissues (76,77).

Jensen et al (82) described that sensitivity to pain is a complex interaction of afferent sensory input and cognitive processing of this stimuli. The pain experience is modulated on all levels of the neural axis. Several brain networks act as potent modulators of pain and studies have shown that prefrontal brain regions are involved in the inhibition of nociception (88). A suggested common pathway for these mechanisms is the recruitment of the descending pain defense system, which is partly modulated by the central catecholaminergic system (i.e., noradrenaline and dopamine) (89). The function of these systems is genetically influenced by the activity of the catecholamine breakdown enzyme COMT (83). Further, the reduced capacity to activate the μ-opioid system due to a reduced concentration of endogenous opioids (84) would predict increased pain sensitivity during repeated pain stimulation due to less effective recruitment of endogenous pain inhibition leading to a more pronounced sensitization in some individuals. However, experimental evidence has suggested that the endogenous opioid system did not significantly affect OIH (92). This evaluation also suggested that alternative mechanisms such as pronociceptive stimulation and neuroplastic changes might be responsible for the expression of OIH.

4.3.6 Other Mechanisms

While all the molecular mechanisms are similar, they also have been described based on the site of the plasticity. Some of the mechanism studies based on plasticity include: 1) sensitization of primary afferent neurons; 2) enhanced production and release of excitatory neurotransmitters and diminished reuptake of neurotransmitters; 3) sensitization of second order neurons to excitatory neurotransmitters; and 4) neuroplastic changes in the RVM medulla that may increase descending facilitation via "on-cells" leading to upregulation of spinal dynorphin and enhanced primary afferent neurotransmitter release and pain (15).

4.3.6.1 Peripheral Effect

It has been postulated that it is not required for drugs to reach the CNS in order for some degree of hyperalgesia to emerge from repeated drug administration. Due to the recognition of μ-opioid receptors expressed on both the central and peripheral terminals of primary afferent neurons, it was considered possible that the peripheral injection of selective opioid agonists could cause functional changes in the neurons (15). While these injections were associated

with anti-nociception acutely, repeated injection was associated with tolerance and mechanical hyperalgesia which was interpreted as a sign of "local" physical dependence. This phenomenon was not limited to opioid receptors alone, but also to other receptors.

4.3.6.2 Spinal Effects

Spinal cord plasticity underlying OIH has been demonstrated after both the intraspinal and systemic administration of opioids. One of the first studies in this area involved the daily bolus administration of intrathecal morphine to rats for more than one week (37). The early observations also showed that if intrathecal morphine was infused in a continuous manner, that the degree of OIH which developed was smaller than if bolus administration with intermittent abstinence was employed, which was reduced by spinal blockade of the NMDA receptor (93).

Since the time of the early observations, more spinal receptor systems have been explored as causative of OIH including spinal dynorphin (67), spinal cyclooxygenase (COX) (94), spinal cytokines like interleukin-1ß (IL-1) and chemokines like fractalkine (95). Thus, biochemical and behavioral observations suggest that the dorsal horn of the spinal cord is central to many of the mechanisms converging to support OIH (15).

4.3.6.3 Supraspinal Effects

There is growing appreciation that higher CNS centers might participate in supporting the hypothesis of supraspinal effects and other forms of abnormal pain sensitivity through enhanced descending facilitation to the spinal cord dorsal horn. The focus of this work has been the RVM. Microinjection of local anesthetic to stop neuronal discharge from this structure or lesioning of the dorsolateral funiculus, which carries descending nerve fibers from the RVM, prevents or reverses not only OIH, but also tolerance to opioids (21,23,41,96,97). Pursuant to these observations, it has been suggested that CCK released in the RVM and acting through CCK-2 receptors might activate the RVM and support the descending influences (98).

5.0 Clinical Prevalence

Over the past decade, several observational, cross-sectional, and prospective controlled trials have examined the expression and potential clinical significance of OIH in humans (15). These studies have been conducted using several distinct cohorts and methodologies: 1) Former opioid addicts on methadone maintenance therapy, 2) perioperative exposure to opioids in patients undergoing surgery, and 3) healthy human volunteers after acute opioid exposure using human experimental pain testing.

5.1 In Former Opioid Addicts

A number of studies have examined pain sensitivity in opioid addicts maintained on methadone using cold pressor, electrical, and pressure pain models (99). These studies show a modality-specific increased sensitivity to cold pressor pain in these patients, compared with matched or healthy controls (21-23,96-98,100). In contrast, hyperalgesia to electrical pain was weak or absent as was hyperalgesia in mechanically evoked pain models (22,96,99). Other investigators studying healthy human volunteers were also unable to show development of OIH in thermal pain models (50,51). Chu et al (44) described that these results suggest that OIH develops differently for various types of pain (15).

Overall, multiple observations provide support for the hypothesis that OIH is caused by chronic opioid exposure, even though there are multiple limitations associated with these studies.

5.2 During Perioperative Exposure to Opioids

A small number of clinical studies have looked at OIH in the setting of acute perioperative period exposure. Two prospective controlled clinical studies have reported increased postoperative pain despite increased postoperative opioid use in patients who received high doses of intraoperative opioids (30,101). However, others have shown no significant difference in postoperative pain sensitivity based on intraoperative opioids (102-104).

Consequently, the observations provide mixed support for the hypothesis of development of OIH after acute perioperative opioid exposure.

5.3 In Healthy Volunteers

Several studies have examined the development of OIH in humans after acute short-term exposure to opioids. Multiple investigators, in combination, have provided direct evidence for development of OIH in humans using models of secondary hyperalgesia and cold pressor pain (51,105-108).

Compton et al (108,109) found increased sensitivity to cold pressor pain in a small cohort of healthy human volunteers following precipitated opioid withdrawal

after injection of acute physical opioid dependence .

It also has been shown that there is a reduction in physical pain sensitivity in response to social exclusion and social encounters (110). Enhanced central thermal nociception has been reported in mildly depressed non-patients and transiently sad healthy individuals.

5.4 In Chronic Pain Patients

OIH is critical in managing chronic opioid therapy (22,40,44,50,54,111,112). Hooten et al (111) evaluated associations between heat pain perception and opioid dose among patients with chronic pain undergoing opioid tapering in a prospective evaluation. Their cohort included 109 patients using opioids who were admitted to an outpatient multidisciplinary rehabilitation program that incorporates opioid tapering. They used a standardized quantitative sensory test (QST) method of levels. Standardized values of heat pain perception were obtained one day following program admission and following completion of the opioid taper at program dismissal. The results showed that a greater baseline morphine equivalent dose was associated with lower or more hyperalgesic values. The dose dependent association retained significance after adjusting for pain severity, pain duration, and pain diagnosis. Tapering of greater morphine equivalent doses was associated with lower values. The association retained significance after adjusting for pain severity, pain duration, pain diagnosis, opioid withdrawal symptoms, and time between completion of the taper and performance of the dismissal QST.

Hay et al (45), in an observational report, indicated that patients with chronic pain management with opioids, and methadone-maintained patients were hyperalgesic when assessed by the cold pressor test. However, there was no allodynia.

Cohen et al (49) evaluated 355 patients on a steady regimen of analgesic medications and scheduled for an interventional procedure, and who were treated with a standard subcutaneous injection of lidocaine prior to a full dose of local anesthetic. The results showed that both opioid dose and duration of treatment directly correlated with pain intensity and unpleasantness scores compared with patients not receiving opioid treatment. Patients receiving opioid therapy were more likely to rate the standardized pain stimulus as being more unpleasant than painful. They concluded that the results of this study bolster preclinical and experimental pain models demonstrating enhanced pain perception in patients receiving opioid therapy. In addition, other human data suggests that the short-term infusion of opioids like the μ-opioid receptor agonist remifentanil, followed by abrupt cessation, exacerbates preexisting hyperalgesia (35,51,54).

In contrast to the clinical and experimental evidence, some studies have shown that oral opioid administration of "commonly used" doses of oral opioids does not result in abnormal pain sensitivity beyond that of patients receiving non-opioid analgesia (55). In contrast, another study (7) further illustrated that OIH is present in the opioid addict population. Further, they also concluded that detoxification from opioids does not reset pain perception for at least one month.

5.5 With Administration of Very Low Dose Opioids

A limited amount of direct human data directly supports the notion that low opioid doses cause hyperalgesia (15). In fact, one of the only studies to examine this question demonstrated biphasic effects of morphine in a subset of former opioid addicts given morphine (113). In addition, the question has been approached from another angle and the results have illustrated that the inclusion of very low doses of opioid antagonists might reduce postoperative opioid consumption (114,115). However, the findings have not been reproduced by others (116,117). In contrast, the animal data appear to be more definitive in the heightened nociceptive sensitization (one-thousandth of the systemic analgesic dose) after single dose morphine in arthritic rats (118).

There is no clinical application for extremely low dose opioids.

5.6 In Patients Administered Very High Dose Opioids

OIH more commonly has been seen in patients receiving high opioid doses, rather than low or moderate doses. There are multiple case reports and some studies; however, there has not been any systematic evidence (15). The majority of the reports involve the systemic or intrathecal administration of morphine, raising the possibility that metabolites, such as morphine-3-glucuronide that is known to cause neuroexcitation, could contribute to hyperalgesia (119-121). Chu et al (15) report that contrary to the low dose OIH phenomenon, high dose OIH does not seem to be modified by opioid receptors; rather it is influenced by 2 non-opioid receptor systems: glycine and the spinal cord NMDA receptor system (122-126). This is based on the information that opioid antagonists do not efficiently reduce the OIH of high dose opioids,

and the stereospecificity of high dose OIH does not fit the specificity for binding to opioid receptors (15). One non-opioid receptor system contributing to these effects is glycine. The intrathecal injection of glycine was dose-dependent for reversing allodynia caused by the intrathecal administration of high doses of morphine (126). Further, studies have focused on the spinal cord NMDA receptor system as mediating the hyperalgesia and allodynia effects of large doses of morphine (125).

6.0 Diagnosis And Management

6.1 Diagnosis

Lack of effectiveness might be seen with the administration of opioids for chronic pain more commonly than anticipated and reported. Common traditional solutions to this include opioid rotation, reduction of the administered dose, or detoxification to manage OIH. However, a major dilemma faces the pain practitioner in the diagnosis of OIH and differentiating it from tolerance. Thus, it is a challenge to distinguish between the two since treatment of each is quite different. In addition, the clinician must be able to distinguish among OIH, progression of the disease process, interval injury, and clinical exacerbation of preexisting pain.

There are features that differentiate OIH from increases in preexisting pain, disease progression, increased activity, increased demands, increased stress, and interval injury. In contrast, OIH typically produces diffuse pain, less defined in quality, which extends to other areas of distribution from preexisting pain. Further, OIH mimics opioid withdrawal including pain, since the neurobiology of both is similar (32). Further, OIH has been demonstrated clinically by inducing changes in pain threshold, tolerability, and distribution pattern in opioid-maintained former addicts (21). Finally, if the preexisting pain is undertreated or a pharmacologic tolerance exists, then an increase in opioid dose will result in reduction of pain. Conversely, OIH would be worsened with increasing opioid dosage.

6.2 Modulation of Opioid-Induced Hyperalgesia

Even though precise molecular mechanisms responsible for the development of OIH are just beginning to be understood, preclinical models implicate the glutaminergic system and pathologic activation of NMDA receptors in the development of central sensitization. Consequently, clinical work in attenuating or preventing the expression of OIH has primarily focused on manipulation of the glutaminergic system, either through direct or indirect modulation of the NMDA receptor. However, the clinical efficacy and significance of these approaches has not been evaluated in large prospective clinical trials.

The NMDA receptor is composed of several different subunits (NR1, NR2A-D, and sometimes NR3A/B) that are differentially expressed in various regions of the brain and during development (15,127). Further, the subunit expression of individual NMDA receptors can affect their binding sensitivity to neuromodulators and function (128). However, multiple drugs available have variable and undetermined effectiveness. The first generation NMDARAs, such as ketamine and dextromethorphan, have limited clinical utility in some patients precisely because of these reasons.

6.2.1 Ketamine

Even though ketamine binds to many different receptor sites, it is known to be an uncompetitive antagonist of the phencyclidine binding site of NMDA receptor, where its primary anesthetic effects are thought to occur (129). While its role as a clinical anesthetic has been limited (130), its role as NMDA receptor in chronic neuropathic pain has been expanding (131-136).

Meta-analyses of studies examining perioperative low-dose ketamine in conjunction with opioid administration yielded opposing results (49,137-145). Further, a systematic review failed to show any significant evidence that ketamine improves the effectiveness of opioid therapy in cancer pain. However, ketamine has been shown to be significantly beneficial in patients who require large amounts of opioid medications or exhibit some degree of opioid tolerance. Human experimental pain studies have shown that administration of S-ketamine abolishes remifentanil-induced aggravation of hyperalgesia induced by intradermal electrical stimulation (50,51). In addition, the findings were corroborated in the post-surgical patient population.

In summary, there is some evidence to show that perioperative administration of low-dose ketamine might modulate the expression of OIH or analgesic tolerance and that it reduces postoperative wound hyperalgesia after acute intraoperative opioid exposure. However, the clinical significance of these benefits still needs to be demonstrated in larger prospective studies and in chronic pain populations.

6.2.2 Methadone

Methadone has been shown to have weak NMDA

receptor antagonism (146). Thus, it has been shown that methadone is effective in reducing high-dose opioid OIH (147-149). In fact, multiple published reports in the literature have shown that opioid rotation to methadone significantly improved or resolved suspected OIH (147-152).

Methadone offers several advantages for opioid switching or rotation, including incomplete cross-tolerance with opioid receptors and NMDA receptor antagonism (151,153). However, methadone is also associated with multiple disadvantages of complex conversion and toxicity, including Torsades de Points, when high doses are administered. Further, methadone exposure has been linked to increased pain states in studies of former opioid addicts maintained on methadone (22,96-98). Thus, methadone might activate pronociceptive pathways, despite its NMDARA properties. In a case report, OIH was aggravated with methadone rather than reversing it (154).

6.2.3 Dextromethorphan

Dextromethorphan is a non-competitive NMDARA typically used as a cough suppressant. There have been a number of studies indirectly examining the ability of dextromethorphan to attenuate or prevent expression of OIH or analgesic tolerance in patients on opioid therapy. Galer et al (155), in 3 large randomized, double-blinded, placebo-controlled multicenter trials of MorphiDex (morphine and dextromethorphan mixture in a 1:1 ratio) in chronic non-cancer patients, were unable to find any significant difference between MorphiDex and morphine alone in the outcome measures. The study showed analgesic superiority for MorphiDex.

6.2.4 Propofol

Some evidence suggests propofol might have some modulatory effect on OIH, possibly through interactions with γ-aminobutyric acid (GABA) receptors at the supraspinal level (156,157). However, the clinical significance of propofol in chronic pain management is not known.

6.2.5 COX-2 Inhibitors

Because of the sensitization of pronociceptive pathways in the CNS through various mechanisms of which NMDA receptors have been largely implicated and the prostaglandins have also been shown to modulate nociceptive processing (158), and are able to stimulate the release of excitatory amino acid glutamate in spinal cord dorsal horns (159), COX inhibitors have also been shown to antagonize NMDA receptor function in the CNS (160,161). COX inhibitors also have been shown to attenuate development of opioid tolerance in animals (162,163). Thus, it has been hypothesized that inhibition of prostaglandin synthesis in the spinal cord might attenuate or inhibit expression of OIH by modulating NMDA receptor function.

Evidence suggests a role for COX-2 inhibitors in the modulation of OIH in humans (50,51,105). Thus, it is suggested that there is a possible role for prostaglandins in sensitizing the nociceptive system before pathologic activation, and that although OIH is modulated by Cox-2 activity, it probably has a less important role than the NMDA receptor system, at least in human experimental pain models after acute opioid exposure (15).

6.2.6 α2 receptor Agonists

Some studies have examined the role of α2 receptor agonists in modulating OIH. Koppert et al (51) showed that the α2 agonist clonidine attenuated opioid-induced post-infusion antianalgesia and abolished opioid-induced post-infusion secondary hyperalgesia. These data suggest a possible role for α2 agonists in OIH modulation. Further, this effect was seen in patients where coadministration of NMDARA S-ketamine, during acute opioid exposure, abolished opioid-induced post-infusion secondary hyperalgesia, but had no effect on post-infusion antianalgesia (51). However, a study by Quartilho et al (52) found that a single injection of clonidine produced transient antinociception with delayed thermal hypersensitivity after 24 to 30 hours in rats. In addition, these effects were prevented with coadministration of the α2 antagonist idazoxan. In contrast, Davies et al (53) failed to report hyperalgesia after cessation of chronic administration of the α2 agonist dexmedetomidine in mice.

Overall, animal studies provide contradictory evidence for the ability of α2 agonists. α2 agonist might or might not directly cause hyperalgesia. However, human studies provide direct evidence in support of the ability for these drugs to attenuate expression of OIH in human experimental pain models after acute opioid exposure.

6.3 Treatment Strategies

While the pain practitioner has several options when confronted with a demonstrated lack of opioid efficacy and the diagnosis of OIH is established, the treatment can be time-consuming and, at times, impractical. In managing these patients, weaning from high doses of

opioids usually requires time and patience, along with understanding on the part of the patient and the family. While reducing the opioid dose, patients might experience transient increases in pain or mild withdrawal which can exacerbate the already exacerbated pain. Further, the hyperalgesic effect might not be mitigated until a certain critical dose of opioid is reached. During this process, patients and physicians become frustrated and develop differences in philosophy, which could require multiple office visits or could even sever the relationship between the patient and physician. These patients often seek opioid treatment elsewhere.

The treatment includes rational polypharmacy with non-opioid medications, minimizing opioid usage and reducing the adverse events of withdrawal and OIH. However, certain pain conditions, including neuropathic pain, tend to preferentially respond to non-opioid medications such as antidepressants and anticonvulsants. Rotation to a different class of opioid might yield improvement in analgesia. Interventional pain management can reduce the need for pharmacotherapy or eliminate it altogether (3,164-205). Further, behavioral management can accomplish some or all of the goals (206-208).

However, if these options are not feasible, then the practitioner is faced with several choices to diagnose and treat OIH:

1. Increase the dose of opioid and evaluate for increased efficacy (tolerance)
2. Reduce or eliminate the opioid and evaluate OIH.
3. Utilize opioids with unique properties that might mitigate OIH
4. Utilize specific agents that are NMDA receptor antagonists
5. Provide combination therapy with COX-2 inhibitors

The third option has become particularly attractive with the use of methadone and buprenorphine. Methadone, although a pure μ-receptor agonist, has properties that might prevent or reduce OIH (209). It is a racemic mixture in which the d-isomer is an NMDA receptor antagonist. Methadone also displays incomplete cross-tolerance properties unique from other μ-receptor agonists which might create a niche role for it in the treatment of OIH and other forms of intractable pain, especially neuropathic pain. Anecdotal reports exist of patients who have been thought to have OIH and been treated with combinations of option 2 and option 3, i.e., reducing the dose of opioid (by 40% to 50%) and adding "low-dose" methadone (210).

Buprenorphine has been used to treat chronic pain (211). It is a partial opioid agonist with antagonist properties which has been used for decades in anesthesia and for the treatment of pain. The intravenous/intramuscular (IV/IM) formulation (Buprenex) is available in the United States for the treatment of pain and in Europe is available as a transdermal preparation. Most recently, it has been used for the treatment of opioid dependence in its sublingual form (Suboxone, Subutex).

Buprenorphine has been shown to be intermediate in its ability to induce pain sensitivity in patients maintained on methadone and control patients not taking opioids (21). Buprenorphine showed an enhanced ability to treat hyperalgesia experimentally induced in volunteers compared to fentanyl (212). In addition, spinal dynorphin, a known kappa receptor agonist, increases during opioid administration, thus contributing to OIH. Buprenorphine is a kappa receptor antagonist. For these reasons, buprenorphine might be unique in its ability to treat chronic pain and possibly OIH.

6.4 Practical Considerations

The treatment of OIH can be time-consuming and at times, impractical. Weaning patients from high dose opioids usually requires time and patience (for both the physician and patient). While reducing the opioid dose, patients might experience transient increases in pain or mild withdrawal which can exacerbate pain. The hyperalgesic effect might not be mitigated until a certain critical dose of opioid is reached. Patients often become frustrated and managing the appropriate dose reductions often requires multiple office visits. This can be extremely impractical in a managed care environment. Consequently, many patients simply give up and seek to resume opioid therapy elsewhere (17).

7.0 Conclusion

As with any therapy, side effects and complications can occur. An exit strategy should exist when utilizing opioids to treat chronic pain because of the potential complications in managing these patients such as opioid dependence, addiction, and abuse. OIH is a less recognized side effect of chronic opioid therapy. However, it is becoming more prevalent as the number of patients receiving opioids for chronic pain increases (1-5). OIH should be considered in the differential when opioid therapy fails. Prior to instituting treatment with opioids, OIH should be addressed with patients as part of a comprehensive informed consent/agreement.

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