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Focused Review

Opioid Induced Hyperalgesia: Clinical Implications for the Pain Practitioner

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Opioids have been and continue to be used for the treatment of chronic pain. Evidence supports the notion that opioids can be safely administered in patients with chronic pain without the development of addiction or chemical dependency. However, over the past several years, concerns have arisen with respect to administration of opioids for the treatment of chronic pain, particularly non-cancer pain. Many of these involve legal issues with respect to diversion and prescription opioid abuse. Amongst these, opioid induced hyperalgesia (OIH) is becoming more prevalent as the population receiving opioids for chronic pain increases.

OIH is a recognized complication of opioid therapy. It is a pro-nocioceptive process which is related to, but different from, tolerance. This focused review will elaborate on the neurobiological mechanisms of OIH as well as summarize the pre-clinical and clinical studies supporting the existence of OIH. In particular, the role of the excitatory neurotransmitter, N-methyl-D-aspartate appears to play a central, but not the only, role in OIH. Other mechanisms of OIH include the role of spinal dynorphins and descending facilitation from the rostral ventromedial medulla. The links between pain, tolerance, and OIH will be discussed with respect to their common neurobiology.

Practical considerations for diagnosis and treatment for OIH will be discussed. It is crucial for the pain specialist to differentiate amongst clinically worsening pain, tolerance, and OIH since the treatment of these conditions differ. Tolerance is a necessary condition for OIH but the converse is not necessarily true.

Office-based detoxification, reduction of opioid dose, opioid rotation, and the use of specific NMDA receptor antagonists are all viable treatment options for OIH. The role of sublingual buprenorphine appears to be an attractive, simple option for the treatment of OIH and is particularly advantageous for a busy interventional pain practice.

Key words: Opioid hyperalgesia, hyperalgesia, tolerance, NMDA receptor antagonists, NMDA receptor induced hyperalgesia, spinal dynorphin induced hyperalgesia, descending facilitation and hyperalgesia, buprenorphine and hyperalgesia, opioid detoxification, office-based detoxification, complications of opioid therapy

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For several decades, opioids have been considered integral components in the treatment of chronic pain. Evidence supports the notion that opioids can be safely administered to patients with chronic pain without the development of addiction or chemical dependency. Major pain and addiction organizations have endorsed this concept (1).

The concept of pain sensitization from the chronic administration of opioids is often referred to as opioid induced hyperalgesia (OIH). There is substantial evidence to support the fact that this does occur with chronic opioid therapy. OIH may complicate the clinical course of pain treatment in a patient receiving opioids. Although the current clinical milieu

emphasizes physician monitoring of addiction, abuse, and diversion, OIH is often overlooked as a potential complication of opioid therapy.

As earlier as the nineteenth 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:

> "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. Here experience is needed. Does morphia tend to encourage the very pain it pretends to relieve?
> "…..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" (2).

This article is a focused review of OIH neurobiology and its clinical implications for the pain practitioner. Practical guidelines are suggested for the clinical management of OIH.

Tolerance Versus Pain Sensitization

Tolerance is a pharmacologic concept. It occurs when there is a progressive lack of response to a drug thus requiring increased dosing. Tolerance can occur with a variety of drugs including opioids (3,4).

Tolerance may not only develop to the analgesia provided by opioids but also develop undesirable side effects which are seen with opioid administration such as pruritis, nausea, sedation, and respiratory depression.

Sensitization to pain occurs in several areas of the nervous system involving the transmission of pain. Peripheral mechanisms have been well documented with respect to neural injury involving mediators of inflammation. This is known as primary hyperalgesia and is seen clinically with peripheral nerve injuries. Secondary hyperalgesia, on the other hand, occurs "downstream" from the initiating nocioceptive stimulus and peripheral injury. In the spinal cord, wide dynamic range neurons become sensitized through a variety of mechanisms which may be mediated by neurotransmitters such as calcitonin gene-related peptide, Vasoactive Intestinal Peptide (VIP), Dynorphin (DYN), Cholcystokinin (CCK), Neuropeptide Y (NPY), and N-methyl-D-aspartate (NMDA) (5).

Since tolerance is characterized by decreasing efficacy of a drug, it can be overcome by increasing the dose. However, unlike tolerance, OIH cannot be overcome by increasing dosage since OIH is a form of pain sensitization induced by the drug which occurs within the central nerve system (CNS) . Pain is worsened with increased opioid dosing and is improved by reducing or eliminating the opioid. Tolerance is a necessary condition for OIH, but the converse is not true. Clinically this is an important distinction that has obvious ramifications with respect to continued use of opioids in a given patient.

Basic Science Evidence of Opioid Induced Hyperalgesia

Mao (6) has documented the occurrence of OIH in laboratory animals. The commonly employed test is to examine the responses of rats, specifically the paw, to withdrawal tests in response to noxious stimuli after receiving multiple boluses or a continuous infusion of opioid. A comparison of dose response effects are measured before and after administration of an opioid. With intrathecal morphine administration there is progressive reduction in baseline nocioceptive pain thresholds (7). Similar findings have been seen in rats receiving fentanyl boluses (8) and in animals receiving repeated heroin administration (9). These preclinical studies support the concept that there can be sensitization to pain with concurrent administration of opioids.

Clinical Evidence of Opioid Induced Hyperalgesia

Supporting evidence has shown that OIH occurs clinically outside the laboratory, and is seen after intraoperative remifentanil infusion, resulting in decreased opioid efficacy (10). Significant pain reduction has been demonstrated in patients who have been detoxified from high dose opioids (11). When challenged with cold pressor tests, opioid addicts maintained on methadone demonstrated increased pain sensitivity (12). There have also been a host of experimental studies in human volunteers and anecdotal reports of increased pain sensitivity induced or observed with the concomitant use of opioids. These studies and the mechanisms of OIH have been extensively reviewed (13).

Neurobiological Mechanisms for Opioid Induced Hyperalgesia

There are many proposed mechanisms for OIH including 3 areas which will be discussed:

- The central glutaminergic system
- Spinal dynorphins
- Descending facilitation

Central Glutaminergic System

The majority of studies examining the mechanisms of OIH involve the systemic administration of opioids (6,7). The excitatory neurotransmitter NMDA plays a central role in the development of OIH. The current data suggest that opioid induced desensitization (pharmacological tolerance) and sensitization (OIH), while distinct processes, may share common cellular mechanisms in part mediated through activation of the central glutamatergic system (7).

The role of NMDA can be summarized as follows:

1. NMDA receptors become activated and when inhibited, prevent the development of tolerance and OIH (14-16).
2. The glutamate transporter system is inhibited, therefore increasing the amount of glutamate available to NMDA receptors (17).
3. Calcium regulated intracellular Protein Kinase C is likely a link between cellular mechanisms of tolerance and OIH (16,18,19).
4. Cross talk of neural mechanisms of pain and tolerance may exist (20,21).
5. Prolonged morphine administration induces neurotoxicity via NMDA receptor mediated apoptotic cell death in the dorsal horn (22).

Role of Spinal Dynorphin

Spinal dynorphin plays an important role in OIH in that levels have shown increases with continuous infusions of mu receptor agonists. These increased levels lead to the release of spinal excitatory neuropeptides such as calcitonin gene-related peptide from primary afferents (23). OIH is therefore a pro-nociceptive process facilitated by increasing the synthesis of excitatory neuropeptides and their release upon peripheral nocioceptive stimulation (7).

Role of Descending Facilitation

Descending facilitation influence on OIH may be seen through several mechanisms. Subsets of neurons (on and off cells) within the rostral ventromedial medulla (RVM) have a unique response to opioids (24,25). Their activities may facilitate spinal nocioceptive processing (26). In addition, lesioning of the descending pathway to the spinal cord (dorsal lateral funiculus) prevents the increase seen in excitatory neuropeptides (23).

Clearly several distinct neurobiological mechanisms may exist for OIH. However, determining which mechanism(s) predominate in any given patient has important implications for the pain practitioner. More studies are needed to examine the interactions between the glutaminergic system, spinal dynorphin, and descending facilitation.

Opioid Induced Hyperalgesia and Clinical Practice

As shown, lack of efficacy may be seen with the administration of opioids for chronic pain. Common solutions to this include opioid rotation, reduction of the administered dose, or detoxification. However, a major dilemma faces the pain practitioner. Is the lack of efficacy seen as a result of tolerance or OIH? The challenge is to distinguish between the 2 since the treatment of each is quite different. In addition, the clinician must be able to distinguish between OIH and clinical exacerbation of preexisting pain.

Several features of OIH may be helpful in differentiating between it and increases in preexisting pain. OIH will exacerbate a preexisting painful condition and therefore will increase pain intensity above the preexistent pain levels. However, further disease progression needs to be ruled out which would increase pain. The practitioner must also consider additional increased pain resulting from increased activity or demand (often referred to as pseudotolerance). Furthermore, OIH typically produces diffuse pain, less defined in quality, which extends to other areas of distribution from the preexisting pain. OIH is not unlike the pain experienced during opioid withdrawal, since the neurobiology of both is similar (7).

OIH has been demonstrated clinically by inducing changes in pain threshold, tolerability, and distribution pattern in opioid-maintained former addicts (12).

Finally, if the preexisting pain is undertreated or if pharmacologic tolerance exists, then an increase in opioid dose will result in reduction of pain. Conversely, OIH would be worsened with increasing opioid dose.

Opioid Induced Hyperalgesia Treatment Strategies

The pain practitioner has several options when confronted with a demonstrated lack of opioid efficacy. Rational polypharmacy to include non-opioid medication should be utilized when treating any patient with intractable pain. This strategy helps minimize the dose of opioid used, thus reducing the possibility of side

effects and therefore, OIH. Neuropathic pain tends to preferentially respond to non-opioid medications such as antidepressants and anticonvulsants. Rotation to a different class of opioid may yield improvement in analgesia. Interventional pain management can reduce the need for pharmacotherapy altogether. Behavioral management can accomplish similar goals.

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 may mitigate OIH.
4. Utilize specific agents that are NMDA receptor antagonists.

The third option has become particularly attractive with the use of methadone and buprenorphine. Methadone, although a pure mu receptor agonist, has properties that may prevent or reduce OIH (27). 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 mu receptor agonists which may 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 – 50%) and adding "low-dose" methadone (28).

Buprenorphine has been used to treat chronic pain (29). It is a partial opioid agonist with antagonist properties which has been used for decades in anesthesia and for the treatment of pain. The IV/IM formulation (Buprenex) is available in the US 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 (12). Buprenorphine showed an enhanced ability to treat hyperalgesia experimentally induced in volunteers compared to fentanyl (30). 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 may be unique in its ability to treat chronic pain and possibly OIH.

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 may experience transient increases in pain or mild withdrawal which can exacerbate pain. The hyperalgesic effect may 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. In the author's experience, many patients simply give up and seek to resume opioid therapy elsewhere.

Breaking the cycle of pain and hyperalgesia (in some cases opioid dependence and addiction) is an attractive course of action for the interventional pain specialist. Interventional pain management seeks to isolate or block pain input from specific nociceptive points in the nervous system. This usually provides rapid diagnostic information and often results in therapeutic improvement. Medically supervised withdrawal with sublingual buprenorphine also provides a rapid, safe, and effective treatment for opioid dependence, thus breaking the cycle of pain and hyperalgesia.

Sublingual buprenorphine has recently been approved for the treatment of opioid dependence and through its use, a physician can provide rapid and efficient medically supervised withdrawal from opioids in an office setting (31). Office-based detoxification is itself an "interventional medical technique" for the treatment of this complex patient population suffering from pain, chemical dependency, and OIH. Resolution of OIH usually follows quickly during the maintenance phase with buprenorphine. Office-based detoxification provides a means to resolve OIH without the frustrations mentioned earlier.

Methadone can be used to treat OIH. As stated earlier, it may be more effective for treatment of neuropathic pain. Converting a patient to methadone offers a controlled method of weaning from opioids. The pharmacologic rationale for the use of

methadone is its ability to relieve withdrawal. Since methadone has a relatively long half-life (24 to 36 hours), there are fewer variations in plasma levels compared to short acting opioids such as oxycodone and hydrocodone. It is these properties which have made methadone the standard for the treatment of opioid dependence in the U.S. for the past 4 decades (32,33). As long as methadone is not used to treat opioid dependence, any physician can use it for the treatment of pain, and subsequently OIH (34). However, methadone itself can also cause OIH (35), which may also limit its role.

Ketamine has been used to treat OIH and as an adjuvant to opioid therapy for the treatment of chronic pain (33-39). It is an NMDA receptor antagonist and has known intrinsic analgesic properties. Clonidine is an alpha 2 agonist and has been used for the treatment of neuropathic pain, post-operative pain, and severe cancer pain (39-41). It is also widely used to treat the symptoms of opioid withdrawal. Clonidine has also been shown to produce paradoxical pain hypersensitivity in rats (42). Since OIH and the pain from opioid withdrawal share many similarities (both in quality and neurochemistry), it is conceivable that clonidine may be useful in the treatment of OIH.

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 (43). 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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