ALTERNATIVES IN PAIN MANAGEMENT

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Known unknowns: A review of opioid-induced hyperalgesia

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Abstract

Opioid-induced hyperalgesia (OIH) is a relatively new paradigm that has added to the already growing uncertainty surrounding long-term opioid treatment. OIH is the oversensitization to stimuli in the nervous system resulting from opioid exposure and subsequent neuroplastic changes. Because of its novelty and difficulty in identification, the true prevalence of OIH is unknown. Several mechanisms have been proposed for its development. These include changes in the N-methyl-D-aspartate system, descending pathway modulation, dynorphin activity, inflammatory changes mediated by cyclooxygenase, and increased sensitivity to excitatory neurochemicals. The clinical controversy regarding the management of OIH is due largely to the lack of guidance in diagnosis and lack of quality evidence to direct treatment. As a diagnosis of exclusion, several alternative causes of antianalgesia must be ruled out before OIH can be declared. Pharmacodynamic phenomena such as opioid tolerance share overlapping mechanisms with OIH and may present similarly. Pharmacokinetic changes such as drug-induced or disease-induced alterations to the cytochrome P450 or P-glycoprotein systems should also be excluded as causes of increased opioid demand that may be seen as OIH. Certain pharmacologic agents, such as N-methyl-D-aspartate receptor antagonists, alpha$_2$ receptor agonists, and cyclooxygenase inhibitors, have been identified as possible treatments to reverse the effects of OIH. Opioid rotation and dose reductions have also been used with some degree of success. Pharmacist involvement in the identification and management of OIH will be central to success because of the unique expertise they offer. The quality of these studies is limited by study design, small sample sizes, and lack of generalizability to chronic pain patients with long-standing opioid use.

Keywords: opioid-induced hyperalgesia, hyperalgesia, opioids, pain, narcotic, OIH

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Introduction

In recent years, the phenomenon known as opioid-induced hyperalgesia (OIH) has been reported in the literature in growing frequency, and there is a general clinical curiosity surrounding the subject. Volumes of preclinical and clinical studies have made great strides in providing rational pathophysiologic models for how and why OIH may occur. Despite these developments, the prevalence of OIH is unknown, and clinicians are left with very few evidence-based recommendations to guide its management.[1]

At its core, OIH is most simply described as an oversensitization to stimuli in the nervous system as a result of opioid exposure.[2] Several types of OIH exist, and although all have been crucial in leading to the present understanding of the condition, not all are clinically relevant to pain management clinicians. These include OIH in (1) patients on methadone maintenance for management of opioid dependence or addiction, (2) postoperative and perioperative patients, and (3) patients in opioid detoxification or sudden opioid withdrawal.[2,3] Although many of the pathophysiologic explanations regarding OIH have been derived from studies involving these scenarios, the clinical application of this review will be limited to patients with chronic pain who are treated with escalating doses of opioid analgesics. As such, this review will provide pain clinicians with a brief overview of

theorized OIH mechanisms, clinical challenges in identifying a patient with OIH, and strategies that have been shown to manage and prevent cases of OIH.

Mechanisms

A number of complex and overlapping mechanisms are thought to be involved in OIH development. The result of these forces manifests as an imbalance of competing pronociceptive and antinociceptive pathways within the nervous system. Commonly cited mechanisms include (1) spinal descending pathway modulation, (2) increased concentrations of dynorphin-dependent excitatory neurotransmitters, (3) increased sensitivity of dorsal horn neurons to excitatory neurotransmitters, (4) inflammatory processes mediated by cyclooxygenase (COX) pathways, (5) neuronal cell apoptosis, and (6) suppression of endogenous opioid activity.

One mechanism of action that opioids exert involves acting at presynaptic and postsynaptic receptor sites along ascending spinal cord pathways to inhibit signal transduction from afferent neurons to pain centers within the brain. Opioids also influence the descending signal pathways that originate from the midbrain and brain stem and pass through the rostral ventromedial medulla.[4] These descending pathways modulate pain sensitivity in the spinal cord. Under normal circumstances, opioids enhance the inhibitory signals and diminish the facilitating signals in certain sites along these tracts. However, neuroplastic changes that may be precipitated by opioid exposure have been theorized to shift the balance between signal inhibition and facilitation to favor the latter.[2]

Spinal dynorphins are pain transmission chemicals thought to be involved in the pathogenesis of opioid tolerance and OIH. They act primarily at kappa-opioid receptors but also exhibit some affinity for mu- and delta-opioid receptors. Compelling evidence from animal models suggests that elevated dynorphin concentrations have direct and indirect effects on pain sensitization.[5] Opioid exposure can increase spinal concentrations of dynorphins and other pronociceptive neuropeptides, such as calcitonin gene-related peptide.[6,7] The result is that opioid administration, in addition to providing analgesia, is paradoxically implicated in a pronociceptive process.

Researchers have repeatedly observed that N-methyl-D-aspartate (NMDA) receptor blockade can prevent the development of opioid tolerance and OIH. The relationship that the NMDA system has with pain signal transmission is complex, and the effects that opioid exposure may exert on this system are poorly understood. One such unintended consequence of opioid exposure is the upregulation of intracellular protein kinase C within the ascending spinal pathway.[8,9] This protein kinase C overexpression primes NMDA receptors for action and facilitates calcium entry through the receptor channel. Calcium entry subsequently results in the release of excitatory neurotransmitters and pronociceptive neuropeptides, perhaps contributing to the development of hyperalgesia.

Inflammatory processes may also be at play in the development of OIH. Evidence derived from animal models indicates that morphine exposure can increase COX expression and prostaglandin synthesis.[10] Prostaglandins are implicated in spinal nociceptive sensitization as well as glutamate release from dorsal horn cells and astrocytes.[11-13] Elevated cerebrospinal fluid levels of prostaglandin E2 and tumor necrosis factor-alpha have been found in rats with hyperalgesia.[14] These inflammatory mediators, though poorly understood, may be opportune targets for future OIH therapies.

An observed consequence of chronic opioid exposure is neuronal apoptosis mediated through NMDA receptor activity. This process is theorized to contribute to opioid tolerance and may also be involved in the development of OIH. A 2002 study found that prolonged opioid exposure led to excitotoxiciy and cell death in primarily GABAergic (ie, related to gamma-aminobutyric acid) spinal cord dorsal horn cells. The resulting spinal disinhibition was associated with opioid tolerance and pain hypersensitivity in animals subjected to prolonged morphine exposure.[15]

An additional theory of OIH pathophysiology is that exogenous opioid provision suppresses the production of endogenous opioids. These endogenous chemicals may inhibit nociception through mechanisms not exerted by their exogenous counterparts. Although lower concentrations of endogenous opioids have been theorized to be a factor in OIH development, this theory was disputed by Chu et al[16] in a 2011 article.

Clinical Challenges

OIH presents several patient management challenges, the first of which is correctly identifying a patient who has true OIH. Detection of OIH is often a clinical diagnosis of exclusion. As the symptoms of OIH (eg, reduced pain threshold, increasing opiate requirements, and poor functioning) are nonspecific, an important step in the management of OIH is to rule out other pharmacodyamic and pharmacokinetic causes.

Opioid tolerance is a key pharmacodynamic process to rule out. As tolerance and OIH may involve overlapping mechanisms, it should not be surprising that they both

may result in higher opioid doses.[17] In theory, patients who have opioid tolerance and those with OIH should respond differently to opioid dose increases. Dose increases should provide symptom relief to patients exhibiting tolerance but should lead to worsening pain in those with OIH. This concept has been corroborated in the literature; a 2013 open-label study of patients on hydromorphone concluded that OIH incidence was dose-dependent.[18] The study enrolled 30 patients with chronic neuropathic pain who were subjected to escalating doses of hydromorphone over a period of 4 weeks. Hydromorphone was initiated at 4 mg/day and titrated to a maximum of 24 mg/day; the median daily dose at the end of the trial was 12 mg. Though there was significant interpatient variability, the authors found that the change from baseline in experimentally induced pain sensitivity was positively correlated with hydromorphone dose. This finding provides a key insight for clinicians to use when distinguishing between opioid tolerance and OIH.

The primary challenge in distinguishing OIH from opioid tolerance is that there is no widely accepted, clinically suitable instrument or scale to objectify OIH. Practitioners may need to rely on qualitative signs that indicate OIH is present. Pain due to OIH is often of a different quality than that of the original injury or pain site, likely because of the disruption of pain processing that characterizes OIH pathophysiology. This has been reproduced in studies in which patients become hypersensitized to certain painful stimuli (eg, cold press) but not to others (eg, tactile stimuli).[19] Additionally, OIH pain may occur in areas of the body regionally disparate to the original pain site, whereas opioid tolerance typically renders previously effective opioid doses inadequate without new-onset or referred pain.

Clinicians should also be aware of any pharmacokinetic factors that may influence an opioid's analgesic effect. Some of the most commonly prescribed opioids (eg, oxycodone, hydrocodone) are metabolized to their active form through the cytochrome P450 (CYP) system. Hydrocodone and oxycodone require CYP2D6 conversion to hydromorphone and oxymorphone, respectively. Thus, patients who are slow CYP2D6 metabolizers may experience incomplete analgesia, even at adequate doses of these medications. Similar effects may occur with the coadministration of CYP2D6 inhibitors, such as fluoxetine, duloxetine, bupropion, paroxetine, and others. The addition of one of these agents and subsequent CYP2D6 inhibition in a patient on stable opioid doses may lead to a reduction of analgesic effect that can be misconstrued as tolerance or OIH.[20]

An often overlooked source of pharmacokinetic interference on the effects of opioids is P-glycoprotein (PGP) modulation. As PGP presence at the blood-brain barrier regulates opioid entry into the central nervous system, any change in its relative expression may alter analgesic activity. A 2006 study investigating possible genetic links to tolerance and hyperalgesia found that genes coding for PGP expression were strongly associated with OIH in mice.[21] Confirmatory tests revealed that deleting these genes prevented morphine from inducing these changes. As such, coadministration of pharmacologic agents known to induce PGP expression should be screened for and addressed before labeling a patient as opioid nonresponsive or hyperalgesic. Agents that are known to upregulate PGP include rifampin, carbamazepine, St. John's wort, phenytoin, and ritonavir.[22] A recent study also implicates diclofenac as an inducer of PGP expression in the blood-brain barrier.[23]

Management

Once alternative causes are ruled out and a diagnosis of OIH is made, certain strategies have demonstrated benefits. These include opioid dose reduction, rotation to a different opioid, substitution or addition of methadone, and addition of other agents, such as NMDA receptor antagonists, alpha$_2$ receptor agonists, and COX inhibitors. The data supporting each of these is weak; case reports and small, poorly designed studies constitute most of the available evidence. Further, many of the studies enrolled healthy volunteers on short-term opioid regimens rather than patients with chronic pain and long-standing opioid exposure.[24]

One such study, conducted in 2003, investigated the effects of ketamine and clonidine in patients exhibiting opioid-induced hyperalgesia.[24] Thirteen patients were included in this randomized, crossover, placebo-controlled study. Six separate treatments were administered. Four treatments included monotherapy infusions of either the opioid agonist remifentanil, S-ketamine, clonidine, or saline. Two additional treatments administered dual-therapy consisting of remifentanil plus either S-ketamine or clonidine. Each infusion was at least 1 week apart. Electrical impulses were used to induce pain during the infusion and the postinfusion period. Although remifentanil provided an expected degree of analgesia during the infusion, there was evidence of a postinfusion hyperalgesia syndrome. The coinfusion of ketamine or clonidine with remifentanil negated the emergence of postinfusion OIH. Note, however, that these results were seen in the context of short-term opioid administration and not in patients receiving chronic opioid therapy. This limitation is common to many studies investigating treatments of OIH. Nevertheless, the results provide proof for the concept that OIH can be modified by adding NMDA receptor antagonists and alpha$_2$ receptor agonists. These results were corroborated in larger, randomized, placebo-controlled studies by Joly et al[25] ($n = 75$) and Xuerong et

al[26] (n = 90), both of which were conducted in clinical settings rather than experimental settings.

Opioid analgesics with nontraditional mechanisms, such as methadone, have been tapped as possible options to manage OIH. Methadone is a full mu-opioid receptor agonist with weak NMDA antagonist activity. Numerous case reports indicate that methadone has efficacy in reversing the signs of OIH.[27-29] The process of switching from the patient's current opioid to methadone can be complex. Total daily opioid requirements of the patient may be falsely elevated if doses have been increased to manage hyperalgesia rather than the initial source of pain. Thus, when switching to methadone, clinicians should take care to convert based on the dose of opioid that the patient was receiving before the development of OIH. Also, methadone exhibits incomplete cross-tolerance with opioid receptors that have been previously exposed to other opioids. As such, it may be prudent to use a less aggressive conversion ratio. The reduction in opioid activity due to the lower conversion ratio may possibly cause relief of OIH independent of the unique mechanism of methadone. In fact, one case report in which a patient with OIH was converted from fentanyl to methadone indicated that the actual dose of methadone required for relief was 10% of the dose estimated using an institution-specific conversion ratio.[27]

Adding COX inhibitors to the regimen of a patient with chronic pain may be an attractive option. Independent of the analgesic effects these agents may confer there is also limited evidence they may ameliorate the development of OIH. This concept was validated in a 2006 study of 15 healthy volunteers exposed to remifentanil and the COX2 inhibitor parecoxib.[30] Patients received 4 treatments in a randomized order consisting of either placebo, remifentanil alone, remifentanil plus parecoxib pretreatment, or remifentanil plus parecoxib cotreatment. Each session was at least 2 weeks apart. The investigators found that parecoxib may antagonize the pronociceptive properties of the opioid agonist remifentanil. In a similar 2011 trial, 16 healthy subjects were treated with remifentanil and either parecoxib or the nonselective COX inhibitor ketorolac.[31] Both parecoxib and ketorolac reduced the emergence of postremifentanil hyperalgesia, parecoxib to a significantly greater degree than ketorolac. As the subjects for each of these studies were healthy volunteers given a brief exposure to intravenous opioids, the results are not readily generalizable to patients with chronic pain. However, these results provide an interesting hypothesis for future studies to address in clinical settings.

Role of Pharmacists

The expertise of pharmacists can be a valuable asset in the recognition and management of OIH. Outpatient pharmacists practicing in clinic or community settings are uniquely positioned to monitor trends in dosing and efficacy of opioid regimens. With the expanding use of state-specific narcotic monitoring programs, such patterns can be observed even with multiple providers involved in care. Though these systems are primarily designed to detect diversion of controlled substances, they may also be useful clinical tools. As these clinicians see escalating analgesic doses over time, it is recommended that they evaluate patients for their subjective level of efficacy and functioning. A noticeable decrease in these measures in response to increasing opioid doses may warrant communication with the prescriber to express concerns for signs of OIH. Once OIH is suspected, the process of excluding other pharmacodynamic and pharmacokinetic processes is best served by pharmacist involvement. Examples include medication compliance issues, opioid tolerance, and drug interactions mediated by the CYP and PGP systems. In addition to identification of OIH, its management can be guided by pharmacists, as well. As an example, the conversion to methadone as a treatment strategy for OIH can be complex because of the pharmacokinetic nuances of the drug. Pharmacist involvement is crucial in designing a methadone cross-titration that minimizes the risk of toxicity or withdrawal symptoms. Perhaps paramount among pharmacist interventions is appropriate counseling of patients about the challenges related to OIH. The treatment strategy of reducing opioid doses or switching to alternative agents may be met with uncertainty in patients who suffer from chronic pain. The ability to convey information in patient-centered terms is important in overcoming such barriers.

Conclusions

Patients with OIH present many challenges, both conceptually and practically. These challenges extend from the bench sciences to the practitioner to the patient. One clinical challenge that must be addressed involves applying the data garnered from experimental studies that utilize pain stimulation techniques not feasible for use in practice. These techniques, such as cold presses and heat sensory tests, are not practical for routine use and may correlate poorly with clinical OIH. This concern was noted by Suzan et al,[18] who found that experimental OIH is perhaps more apparent than clinical OIH. Practitioners find it difficult to determine if OIH is present as there are no widely accepted diagnostic criteria. Further, such a diagnosis would require a relatively strong and long-standing patient-provider relationship through which time trends in pain control can be assessed. Unfortunately, the current model of pain management provision is often too fractured to ensure that this relationship can be formed. Lastly, the patient faces obvious conceptual barriers

toward understanding how making any medication change other than increasing doses of opioids could be beneficial.

The pool of evidence supporting the currently proposed theories behind the development of OIH is still evolving. In addition, there is a lack of robust clinical data to guide treatment. Many of the studies designed to identify OIH treatments have involved experimentally induced OIH using brief exposures to opioids rather than the long-term opioid exposures that are seen in clinical practice. This collective ambiguity leads to clinical decision-making that varies widely between practices. Though there have been promising results with a select group of agents in managing OIH (eg, methadone, ketamine, COX inhibitors), these have been conducted mainly in experimental situations or in postoperative patients, and their applicability to patients with chronic pain has yet to be proven.

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