Special Article

Opioid-Induced Hyperalgesia (OIH): A Real Clinical Problem or Just an Experimental Phenomenon?

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Abstract

Although opioid-induced hyperalgesia (OIH) is mentioned as a potential cause of opioid dose escalation without adequate analgesia, true evidence in support of this notion is relatively limited. Most studies conducted in the context of acute and experimental pain, which seemingly demonstrated evidence for OIH, actually might have measured other phenomena such as acute opioid withdrawal or tolerance. OIH studies in patients with chronic pain have used various experimental pain models (such as cold pain tolerance or heat pain intensity). Therefore, the fact that they have yielded inconsistent results is hard to interpret. Thus far, with the exception of a few clinical case reports on OIH in patients with cancer pain and one prospective study in patients with chronic neuropathic pain, evidence for OIH in patients with chronic or cancer-related pain is lacking. Whether experimental pain models are necessary for establishing the clinical diagnosis of OIH, and which specific model is preferred, are yet to be determined.

J Pain Symptom Manage 2015;49:632–636. © 2015 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

Key Words

Experimental pain, analgesia, tolerance, opioid withdrawal, addiction

Introduction

A major increase in the use of opioids for pain control has been reported over the past two decades in many Western countries. For example, according to the International Narcotic Control Board’s most recent report, a nearly sevenfold increase in opioid consumption has been documented in the U.S. over the past 20 years (from 105 mg/capita in 1990 to 693 mg/capita in 2010). This increase likely reflects the broadly accepted definition of chronic pain as a disease in its own right that justifies aggressive use of available means of pain control, including strong opioids. Indeed, the dramatic increase in opioid use is primarily attributed to their prescription for chronic nonmalignant pain, rather than for acute or cancer-related pain.1–3

Intermediate-term randomized controlled trials have demonstrated the efficacy of opioids for various types of chronic pain conditions, clearly indicating that at least some patients benefit from opioid therapy for periods of weeks to months. However, an increasing number of reports show that the risk:beneﬁt ratio with long-term opioid use, especially at high doses, might not be advantageous for many patients.1–3 Significant negative effects of opioids, such as abuse, misuse, addiction, and even death, associated with accidental overdose are now well recognized and raise serious concerns about the appropriateness of long-term opioid administration to patients with chronic nonmalignant pain.3

Although the exact causes for opioid dose escalation in a given patient are not fully understood, several explanations have been proposed, including administration of an opioid for a nonopioid responsive condition, development of opioid tolerance, or even true opioid addiction.

More recently, another possible cause for opioid dose escalation has been suggested. This is the phenomenon termed opioid-induced hyperalgesia (OIH). OIH is defined as a paradoxical condition where the intensity of the perceived pain increases rather than decreases
in response to opioid administration. OIH was long ago described by Albutt, who noted in 1870: “Does morphia tend to encourage the very pain it pretends to relieve?. I have much reason to suspect that a reliance upon hypodermic morphia only ended in that curious state of perpetuated pain.” However, it is only in recent years that OIH has regained interest among both clinicians and researchers, who now suggest it as a potential cause for lack of adequate opioid-induced analgesia.

Several mechanisms for OIH have been proposed. Briefly, they include the following neural changes in response to administration of μ-opioid agonists: 1) sensitization of primary afferent neurons as evidenced by increased levels of the pronociceptive peptides such as calcitonin gene-related peptide and substance P within the dorsal horn of the spinal cord originating at the dorsal root ganglion; 2) plasticity at the spinal level as a result of changes in synaptic efficacy, initiated by N-methyl-D-aspartate excitatory amino acid receptor activation and phosphokinase C translocation; and 3) enhanced descending facilitation to the dorsal horn of the spinal cord originating at the supraspinal level (i.e., the rostral ventromedial medulla), possibly mediated by excitatory peptides such as cholecystokinin and dynorphin.

Although all the aforementioned possible causes for opioid dose escalation without adequate analgesia are well defined and theoretically distinct from each other, it seems that clinically they all look very much alike and are often not properly diagnosed, especially by untrained physicians. One such example is the difference between opioid tolerance and OIH. In opioid tolerance, the analgesic effect of a repeatedly administered opioid dose declines over time. In that case, pain is usually limited to its original site and improves in response to opioid dose escalation. In contrast, OIH may present as either increased clinical pain, widespread phenomena, or both, which worsen in response to opioid dose increments. Because both phenomena are characterized by pain worsening during opioid administration, the confusion between opioid tolerance and OIH among inexperienced clinicians can easily be understood. Furthermore, in many of the studies on OIH in patients with chronic pain and opioid addicts, OIH has been demonstrated by using experimental pain modalities (i.e., thermal pain thresholds, tolerance to experimental cold pain, etc.) without exploring its clinical relevance.

Although OIH has been widely reviewed in recent years, many of the questions related to OIH remain unresolved. For example, what is the precise definition of OIH? How can OIH be best demonstrated? Is the use of experimental pain modalities necessary for diagnosing OIH?

The present article aims to provide an update on this topic with an attempt to highlight some of the OIH-related controversies. It also suggests a set of clinical criteria for diagnosing OIH. OIH in current or former opioid addicts is beyond the scope of this special article.

Is There Evidence for Postoperative OIH?

Perhaps the most well-studied condition associated with OIH is in the context of postoperative pain. However, close observation of this literature reveals some confusion regarding the definition of OIH. Most of these studies used a similar paradigm in which a short- or an ultra-short-acting opioid was administered during surgery, and OIH was measured postoperatively by collecting data on pain intensity and opioid requirements. In two studies, either intrathecal fentanyl or intravenous remifentanil infusion administered during surgeries led to increased postoperative morphine consumption as compared with placebo administration during surgery. In two additional studies, administration of high compared with low intraoperative opioid (fentanyl or remifentanil) resulted in increased early postoperative pain and opioid consumption. In a third study, using similar methodology, decreased mechanical pain threshold also was found in the high intraoperative remifentanil dose group. Hence, most studies indeed found either increased pain intensity, increased opioid requirements, or both during the early postoperative period and, therefore, concluded that intraoperative administration of short-/ultra-short-acting opioids resulted in OIH.

Is it so? A careful inspection of these findings shows that the time for testing OIH was after the cessation of and not during the administration of the intraoperative opioid infusion. This inspection raises the question of what have these studies actually tested? Was it truly the phenomenon of OIH, acute opioid tolerance, or perhaps opioid withdrawal (abstinence) from the short-acting opioid agonist? The fact that at least in some of these studies an increased postoperative opioid dose was required for adequate pain control points to either opioid withdrawal or tolerance rather than to OIH (where one would expect improved analgesia with a decreased opioid dosage).

Experimental OIH in Healthy Subjects

The phenomenon of OIH also has been studied with the use of experimental pain models in healthy volunteers. The design of these studies consisted of the induction of various types of experimental pain (i.e., area of secondary hyperalgesia or allodynia; electrical pain intensity) before and after termination of administration of the ultra-short-acting opioid remifentanil. Most studies showed evidence for hyperalgesia, whereas at least one study failed to demonstrate...
changes in pain thresholds consistent with hyperalgesia. Although the design of these studies was aimed to test for OIH, it did so only after termination of the opioid infusion. This again raises concerns regarding the nature of the studied phenomenon (Is it OIH, acute opioid tolerance, or opioid withdrawal?).

**Evidence for OIH in Patients With Cancer Pain at the End of Life**

The next question, then, is whether there is clear evidence for the presence of true OIH in patients with prolonged opioid use. Some evidence is derived from patients with cancer pain for whom there is a broad consensus about the use of opioids even at high doses. In a few case reports, patients with terminal cancer reported the exacerbation of existing pain and/or new widespread diffused pain in response to escalating doses of intrathecal opioid administration. A gradual tapering off of the opioids resulted in the resolution of such pain exacerbation. Unfortunately, these reports are sporadic, and clinical trials aimed at studying the extent and characteristics of this phenomenon are still lacking.

**Opioid Treatment for Chronic Nonmalignant Pain and OIH**

Interestingly, although considerable numbers of patients with chronic nonmalignant pain receive high doses of opioids nowadays, the reports on OIH in this population are rather scarce. Two snapshot studies deserve attention in this regard. In one study from Australia, a significantly shortened time for hand withdrawal from an ice-cold water tank (i.e., cold pain tolerance) was demonstrated in a small group of patients with chronic pain who received morphine or methadone, as compared with nonopioid-treated controls \((n = 10\) for each group). In contrast, in a second study, Ram et al. were not able to demonstrate similar differences in tolerability to cold pain between opioid-treated and nonopioid-treated patients with chronic pain, although larger groups of patients were studied. Notably, the two studies have not assessed or discussed the clinical aspects of these experimental findings.

OIH in patients with chronic pain has been investigated in three prospective studies. The first trial was conducted in patients with chronic nonmalignant back pain, who were randomly assigned to receive either morphine or placebo for a period of one month. No evidence for OIH was demonstrated by means of cold pain tolerance and heat pain thresholds. Furthermore, morphine treatment, but not the placebo, resulted in a significant decrease in the intensity of clinical back pain. In contrast, Hooten et al. studied heat pain thresholds in patients on admittance to and at the end of a pain rehabilitation program, which included a graduated cessation of opioid use. They found elevated heat pain thresholds and slightly reduced clinical pain intensity at the end of the program as compared with baseline. The observations by Hooten et al. provide indirect evidence for OIH in patients with chronic pain, suggesting two types of relationships: first, between opioid dose reduction and reduction in clinical pain (similar to what has been seen in the case reports of patients with cancer pain); second, between experimental pain and clinical pain. However, two points should be taken into consideration. First, no correlations between experimental pain, clinical pain, and opioid dosage were measured, meaning that the true nature of these potential relationships has not been explored. Second, the program encompassed additional components of rehabilitation that were not controlled but might have contributed to the changes in both clinical and experimental pain. Suzan et al. demonstrated evidence for OIH, assessed by heat pain intensity in a pain-free area, in 55% of the patients with chronic neuropathic (radicular) pain. Clinical analgesia was also found in response to four weeks of individual titration of oral hydromorphone treatment. Interestingly, OIH was negatively correlated with the clinical analgesic effect of hydromorphone, such that patients with a larger increase in heat pain intensity exhibited a smaller decrease in their clinical pain. In addition, opioid dose was directly correlated with the extent of OIH and reversely correlated with the magnitude of clinical analgesia. Taken together, these results suggest for the first time significant relationships between opioid dosage, analgesia, and hyperalgesia in patients with chronic pain. By looking at individual patients rather than at

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<th>Table 1</th>
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<td><strong>Suggested Clinical Criteria for Diagnosing OIH</strong></td>
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<td>• Increased pain intensity during ongoing opioid treatment.</td>
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<td>• No evidence for underlying disease progression.</td>
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<td>• No evidence for either clinical or pharmacological opioid withdrawal (i.e., symptoms and signs of opioid withdrawal; increased pain as a result of end of previous opioid dose effect).</td>
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<td>• No evidence for opioid tolerance: to be tested clinically by decreased pain in response to an adequate opioid rescue dose.</td>
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<td>• Decrease in pain intensity in response to a reduction in opioid dose (gradual dose reduction might be required to avoid abstinence syndrome).</td>
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<td>• No evidence for addictive behavior.</td>
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OIH = opioid-induced hyperalgesia.
the entire group, this study highlights the fact that future studies related to OIH should include within-group analyses in addition to between-group analyses.

Conclusions

Although OIH is mentioned as a potential cause of opioid dose escalation without adequate analgesia, true evidence in support of this notion is relatively limited. Most studies conducted in the context of acute and experimental pain, which seemingly demonstrated evidence for OIH, actually might have measured other phenomena such as acute opioid withdrawal or tolerance. OIH studies in patients with chronic pain have used various experimental pain models (such as cold pain tolerance or heat pain intensity). Therefore, the fact that they have yielded inconsistent results is hard to interpret. Thus far, with the exception of a few clinical case reports on OIH in patients with cancer pain and the study by Suzan et al., evidence for OIH in patients with chronic or cancer-related pain is lacking. To improve the understanding of this complex phenomenon, we suggest using a set of clinical criteria for diagnosing OIH in future trials (Table 1). Whether experimental pain models are necessary for establishing the clinical diagnosis of OIH, and which specific model is preferred, are yet to be determined.

References
