Opioid-induced hyperalgesia: a review of epidemiology, mechanisms and management

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ABSTRACT There has been a growing interest in opioid-induced hyperalgesia (OIH), which is an increased sensitivity to pain caused by opioid exposure. Multiple underlying pathways may contribute to the development of OIH, and the mechanism may vary with the duration of opioid exposure, dose, type and route of administration. In addition, the distinction between OIH, tolerance and withdrawal should be made in both the basic and clinical science literature so as to help translate findings to the clinical phenomenon and to help determine the best strategies to prevent or treat OIH.

Keywords: hyperalgesia, opioids, tolerance, withdrawal
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INTRODUCTION

The use of opioids is associated with various adverse effects, including the development of dependence, tolerance, addiction and opioid-induced hyperalgesia (OIH).[1,2] Recently, there has been a marked increase in the number of basic and clinical science literature exploring the mechanisms and clinical significance of OIH. Broadly, OIH refers to an increased sensitivity to pain as a result of opioid exposure. It may manifest as hyperesthesia or allodynia, and may also be accompanied by other signs of opioid toxicity such as myoclonus, delirium and seizures. Furthermore, it may present in the clinical setting as worsening pain despite increasing pain medication doses; worsening pain that cannot be explained by progression of the original condition; diffuse pain or pain at anatomically different sites; or excessive pain from surgical procedures.[1,2]

Recent interest in OIH has grown, and there have been at least four recent reviews[1-4] that discussed various aspects of its biochemical and molecular basis. However, OIH research to date has been complicated by two main factors: (1) OIH may resemble tolerance in that inadequate pain relief leads to increasing opioid doses, and symptoms may also be confused with opioid withdrawal, particularly in the setting of acute opioid use without a taper or maintenance dose; (2) There appears to be plausible development of hyperalgesia in more than one setting of opioid use – OIH has been described with acute and chronic exposure, at high and low doses, and with different types of opioids and routes of administration. Implicit is that different mechanisms might underlie the phenomenon in each specific circumstance. Specific mechanisms should thus be considered when attempting to generalise the conclusions of one study across the entire OIH spectrum.

This concise review aims to discuss the existing literature with respect to these limitations and identify future research directions that would help in the clinical diagnosis and management of OIH.

HISTORICAL EVOLUTION OF UNDERSTANDING

It has been well known within the medical community that patients suffering from opioid addiction seem to express a decreased tolerance to pain stimulus when compared to healthy subjects.[5] Furthermore, formal experiments on opioid addicts have demonstrated their increased pain sensitivity to objective measurements, such as the cold presser test.[6] Evidence now exists that OIH develops not only in addicts, but also in those who are on long-standing opioid maintenance and even those who have received short courses of opioids in the peri-operative period.[7] Recent evidence suggests that contrary to earlier views, OIH is more common than many providers recognise, and is not always limited to high-dose opioid use.[8] The phenomenon of hyperalgesia secondary to opioid administration has been demonstrated under controlled experimental conditions in otherwise healthy adults,[9,10] and is also recognised in patients with a history of narcotic abuse.[11,12]

EPIDEMIOLOGY

The prevalence of OIH has not been reported. Some authors have offered anecdotal observations that it is not a rare complication of chronic opioid use, thus suggesting that it is under-recognised.[8] In a longitudinal study of 197 chronic pain patients on long-term opioids, 27.6% of patients required increasing doses of opioids that could not be attributed to disease progression or increased activity.[13] However, it is difficult to determine whether OIH is responsible for any of these cases.

OIH VS. TOLERANCE VS. WITHDRAWAL

There may be underlying contributory mechanisms that are shared by OIH and tolerance, and possibly withdrawal; however, each is a distinct clinical phenomenon. OIH and tolerance may both present as increasing pain in chronic opioid use, but in theory, OIH is a state where pain sensitivity is changed even at

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baseline,[1,2] and OIH and tolerance would differ in their response to escalating doses of opioid; such a manoeuver should alleviate pain in patients with tolerance but aggravate the pain of OIH.[2] Hyperalgesia and allodynia are classic symptoms of withdrawal,[1] and OIH and withdrawal may both be the consequences of the same underlying nociceptive disequilibrium that opioid exposure precipitates. In the clinical context, however, withdrawal is encountered when there is an abrupt cessation in an opioid-dependent patient, whereas OIH is a consequence even if opioid use is continued or increased.

DURATION: ACUTE VS. CHRONIC

Chronic exposure

In patients receiving chronic opioids for pain, the development of OIH could complicate the course of therapy. Some of the earliest evidence of OIH comes from a series of case-control studies in former opioid addicts, which showed an increased sensitivity to cold pressor pain in individuals maintained on a stable methadone dose compared to former opioid addicts who were not on methadone or healthy controls.[9-11] However, other studies that used electrically or mechanically evoked pain did not find a difference in pain tolerance or threshold,[11,12] which indicates that OIH may be modality-sensitive. In addition, these observations preclude definite conclusions because an intrinsically increased sensitivity to pain may predispose to both opioid addiction and methadone use to prevent relapse.[1,2] Case reports have also documented the development of hyperalgesia and allodynia following long-term opioid use in chronic pain patients with cancer.[13-21] More recently, a prospective study of six opioid-naïve chronic pain patients who were started on moderate doses of morphine found that hyperalgesia to cold pressor pain develops within four weeks.[22]

Acute exposure

OIH has also been described following acute opioid exposure, in peri-operative opioid use[23-25] and in healthy volunteers under experimental settings.[9,10,26-31] In acute surgical settings, the available evidence is indirect and inconsistent; three studies reported an increased postoperative opioid requirement in patients who received intra-operative fentanyl or remifentanil,[23,24] which may reflect the development of either tolerance or hyperalgesia. However, other authors have found no difference in the postoperative pain or opioid consumption in patients who were exposed to intra-operative remifentanil.[32-34] A more recent study directly demonstrated increased peri-incisional wound allodynia and hyperalgesia with high doses of intra-operative remifentanil during major abdominal surgery.[25]

OIH has also been successfully induced in healthy volunteers under experimental settings. In six studies, remifentanil infusions lasting between 30 and 100 minutes resulted in a significantly enlarged area of secondary hyperalgesia[26-28,31,35] for up to four hours.[30] In two studies cited in a previous review,[2] an increased sensitivity to cold pressor pain was observed during an acutely induced period of opioid withdrawal.[9,10] However, as previously noted, to characterise OIH, one should take into account the distinctions between OIH and withdrawal.

DOSE: HIGH VS. LOW, CONTINUOUS VS. INTERMITTENT BOLUS

High dose

The effect of opioid dose on the development of OIH has not been well studied in humans. Many case reports document hyperalgesia and allodynia with systemic or intrathecal morphine at high doses, and aggravation of pain when the dose is increased.[13-21] This is a concern in patients who may be receiving high doses of opioids and speaks about the importance of a multi-modal approach to therapy in reducing adverse effects, including the development of OIH.

Low dose

There is a dearth of available evidence for low-dose OIH. A case report provided anecdotal evidence that a subset of former opioid addicts experience mild hyperalgesia at low morphine doses but analgesia at higher doses.[36] Studies using simultaneous opioid and very low dose opioid antagonists suggest, albeit inconsistently, that this may reduce postoperative opioid consumption.[37,38] Translated to the clinical setting, hyperalgesia at very low doses may be relevant in patients during the late course of an opioid taper.[2] Unfortunately, prospective observational studies are required in order to better characterise the relationship between OIH and clinical opioid doses.

What is known about the underlying biochemistry behind high- and low-dose opioid use comes mostly from rodent studies, which have revealed that not only does hyperalgesia manifest at both very low[39-41] and high[42-44] doses of opioids, but also that while low-dose OIH is mediated through opioid receptors, high-dose OIH cannot be solely attributed to the opioid receptor system.[2,42-46] This has recently been corroborated in a human study, which found that in healthy volunteers, administering naloxone after a 90-minute induction-dose remifentanil infusion had no significant effect on hyperalgesia.[35] The authors concluded that their findings suggest that OIH is not modulated by the endogenous opioid system, although it is pertinent to note that this conclusion may only be relevant to high-dose, acute opioid exposure. Instead, the spinal N-methyl-D-aspartate (NMDA) receptor system appears to have a significant role in mediating hyperalgesia and allodynia at high doses of morphine,[45,46] an observation that could explain the benefits of NMDA-receptor antagonists in the management of high-dose OIH.

OPIOID TYPE

A summary of both long- and short-acting opioids that have been investigated for their role in OIH can be found in a previous review.[3] This paper additionally explores mechanisms that might be specific to a particular type of drug. For instance, a dose-dependent accumulation of morphine metabolite morphine-

3-glucuronide (M-3-G) may lead to OIH due to M-3-G's anti-glycinergic action on NMDA receptors.[4] On the other hand, methadone has some antagonist properties at the NMDA receptor, and it is suggested that the hyperalgesia observed with methadone therapy may be a result of transient withdrawal that results from a dosing schedule that outlasts its short analgesic half-life,[3] as opposed to OIH. As the use of synthetic opioids increases, one would hope to see papers speculating the mechanisms of OIH for this particular class.

ADMINISTRATION ROUTE

As described above, many studies and case reports have described OIH with oral, intravenous or intrathecal opioid administration. OIH has also been documented with epidural use, and in rats, local subcutaneous injections of opioids have been shown to produce hyperalgesia.[47] Taken together, these demonstrate that OIH can be mediated both centrally and peripherally.

MECHANISMS

It has been postulated that opioid use leads to an imbalance of pronociceptive and antinociceptive pathways, and there are numerous contributory molecular and cellular mechanisms, various aspects of which have been discussed in previous reviews.[1-3,48] In the periphery, TRP-V1 and cytokines appear to be involved in OIH. Central OIH pathways may be mediated by opioid receptors, NMDA receptors, substance-P via the NK1-R receptor, 5HT3 receptors in descending pathways, and cholesystokinin in the rostral ventral medulla (RVM).[3,48] Opioid receptors may be involved in multiple ways; for instance, an increased release of spinal dynorphin or the increased expression of opioid receptors in the excitatory Gs-coupled state, as opposed to the Gi/Go-coupled state.[1,2] In addition, descending spinal facilitation mediated by opioid-sensitive "on"-cells in the RVM may contribute to OIH.[3] Another theory is that exogenous opioids suppress the endogenous opioid system and lead to an increased sensitivity to pain. This suppression of antinociceptive pathways has been demonstrated in studies measuring diffuse noxious inhibitory control (DNIC),[49] which is used as a measurement of antinociceptive processes. DNIC is blocked by morphine but is reversible by naloxone, and chronic pain patients treated with oral opioids appear to have significantly lower magnitude measurements of DNIC.[2] While a recent study has concluded that OIH may not be mediated by the endogenous opioid system,[35] it is pertinent to note that these results may be specific to acute, high-dose exposure to the pure μ-agonist remifentanil and attempts to block its effects with naloxone, and it remains to be seen whether the results are consistent in different opioid exposure profiles.

PREVENTION/MANAGEMENT

Case reports and animal studies have successfully employed various methods to modulate OIH. The two primary aims are an opioid taper or switch and the addition of adjuvant therapy, in particular, one that has NMDA-receptor antagonist activity, such as methadone or ketamine. Rotating to a different opioid has been reported to improve OIH,[1,2,16,17,20,21] and in particular, switching to methadone has been shown in six case reports to significantly reduce or resolve OIH,[14,15,18-21] which could be the result of methadone's aforementioned weak antagonist activity at the NMDA receptor.[2] Adjuvant therapies could be beneficial in OIH in two ways: by tempering nociceptive sensitisation and by reducing the required dose of opioid. NMDA-receptor antagonists like dextromethorphan[31] and ketamine[3,25,26,28,29] have been most well-studied and most promising, while inconsistent evidence is emerging for the $GABA_A$ receptor antagonist propofol,[50-52] the α_2-agonists clonidine[53] and dexmedetomidine,[54] and COX-2 inhibitors.[27]

FUTURE DIRECTIONS

To better appreciate the significance of OIH as a clinical problem and make better guidelines for opioid administration, answers are needed regarding its prevalence, in both acute peri-operative exposure and long-term opioid therapy and with different types of opioids. It would also be useful to know which methods of adjuvant therapy are effective in reducing or treating OIH in either the acute or chronic setting. Ketamine, for instance, appears to be an excellent tool for decreasing OIH risk in acute opioid exposure, but may not be an ideal candidate for chronic opioid users.

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