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

Yinghui Low[1], MD, *Collin F Clarke*[2], MD, *Billy K Huh*[1], MD, PhD

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
Singapore Med J 2012; 53(5): 357–360

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

[1]Department of Anesthesiology, Duke University Medical Center, Durham, USA, [2]Department of Anesthesiology, University of Western Ontario, Canada
Correspondence: Dr Collin F Clarke, 932 Morreene Road, Durham, NC 27705, USA. collin.clarke@duke.edu

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.

REFERENCES

1. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006; 104:570-587.
2. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain 2008; 24:479-96.
3. Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. Best Pract Res Clin Anaesthesiol 2007; 21:65-83.
4. Simonnet G, Rivat C. Opioid-induced hyperalgesia: abnormal or normal pain? Neuroreport 2003; 14:1-7.
5. Martin JE, Inglis J. Pain tolerance and narcotic addiction. Br J Soc Clin Psychol 1965; 4:224-9.
6. Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. Drug Alcohol Depend 2001; 63:139-46.
7. Vanderah TW, Ossipov MH, Lai J, et al. Mechanisms of opioid-induced pain and antinociceptive tolerance: descending facilitation and spinal dynorphin. Pain 2001; 92:5-9.
8. Zylicz Z, Twycross R. Opioid-induced hyperalgesia may be more frequent than previously thought. J Clin Oncol 2008; 26:1564; author reply 1565.
9. Compton P, Athanasos P, Elashoff D. Withdrawal hyperalgesia after acute opioid physical dependence in nonaddicted humans: a preliminary study. J Pain 2003; 4:511-9.
10. Compton P, Miotto K, Elashoff D. Precipitated opioid withdrawal across acute physical dependence induction methods. Pharmacol Biochem Behav 2004; 77:263-8.
11. Doverty M, Somogyi AA, White JM, et al. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. Pain 2001; 93:155-63.
12. Schall U, Katta T, Pries E, et al. Pain perception of intravenous heroin users on maintenance therapy with levomethadone. Pharmacopsychiatry 1996; 29:176-9.
13. Ackerman WE, 3rd. Paroxysmal opioid-induced pain and hyperalgesia. J Ky Med Assoc 2006; 104:419-23.

14. Axelrod DJ, Reville B. Using methadone to treat opioid-induced hyperalgesia and refractory pain. J Opioid Manag 2007; 3:113-4.
15. Chung KS, Carson S, Glassman D, et al. Successful treatment of hydromorphone-induced neurotoxicity and hyperalgesia. Conn Med 2004; 68:547-9.
16. De Conno F, Caraceni A, Martini C, et al. Hyperalgesia and myoclonus with intrathecal infusion of high-dose morphine. Pain 1991; 47:337-9.
17. Heger S, Maier C, Otter K, et al. Morphine induced allodynia in a child with brain tumour. BMJ 1999; 319:627-9.
18. Mercadante S, Arcuri E. Hyperalgesia and opioid switching. Am J Hosp Palliat Care 2005; 22:291-4.
19. Sjogren P, Jensen NH, Jensen TS. Disappearance of morphine-induced hyperalgesia after discontinuing or substituting morphine with other opioid agonists. Pain 1994; 59:313-6.
20. Sjogren P, Thunedborg LP, Christrup L, et al. Is development of hyperalgesia, allodynia and myoclonus related to morphine metabolism during long-term administration? Six case histories. Acta Anaesthesiol Scand 1998; 42:1070-5.
21. Lawlor P, Walker P, Bruera E, et al. Severe opioid toxicity and somatization of psychosocial distress in a cancer patient with a background of chemical dependence. J Pain Symptom Manage 1997; 13:356-361.
22. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J Pain 2006; 7:43-8.
23. Cooper DW, Lindsay SL, Ryall DM, et al. Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine? Br J Anaesth 1997; 78:311-3.
24. Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology 2000; 93:409-17.
25. Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005; 103:147-55.
26. Angst MS, Koppert W, Pahl I, et al. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain 2003; 106:49-57.
27. Troster A, Sittl R, Singler B, et al. Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. Anesthesiology 2006; 105:1016-23.
28. Koppert W, Sittl R, Scheuber K, et al. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology 2003; 99:152-9.
29. Luginbuhl M, Gerber A, Schnider TW, et al. Modulation of remifentanil-induced analgesia, hyperalgesia, and tolerance by small-dose ketamine in humans. Anesth Analg 2003; 96:726-32, table of contents.
30. Hood DD, Curry R, Eisenach JC. Intravenous remifentanil produces withdrawal hyperalgesia in volunteers with capsaicin-induced hyperalgesia. Anesth Analg 2003; 97:810-15.
31. Koppert W, Dern SK, Sittl R, et al. A new model of electrically evoked pain and hyperalgesia in human skin: the effects of intravenous alfentanil, S(+)-ketamine, and lidocaine. Anesthesiology 2001; 95:395-402.
32. Cortinez LI, Brandes V, Munoz HR, Guerrero ME, Mur M. No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia. Br J Anaesth 2001; 87:866-9.
33. Hansen EG, Duedahl TH, Romsing J, et al. Intra-operative remifentanil might influence pain levels in the immediate post-operative period after major abdominal surgery. Acta Anaesthesiol Scand 2005; 49:1464-70.
34. Lee LH, Irwin MG, Lui SK. Intraoperative remifentanil infusion does not increase postoperative opioid consumption compared with 70% nitrous oxide. Anesthesiology 2005; 102:398-402.
35. Chu LF, Dairmont J, Zamora AK, et al. The endogenous opioid system is not involved in modulation of opioid-induced hyperalgesia. J Pain 2011; 12:108-15.
36. Andrews HL. The Effect of Opiates on the Pain Threshold in Post-Addicts. J Clin Invest 1943; 22:511-16.
37. Cepeda MS, Alvarez H, Morales O, et al. Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. Pain 2004; 107:41-6.
38. Gan TJ, Ginsberg B, Glass PS, et al. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. Anesthesiology 1997; 87:1075-81.
39. Kayser V, Besson JM, Guilbaud G. Paradoxical hyperalgesic effect of exceedingly low doses of systemic morphine in an animal model of persistent pain (Freund's adjuvant-induced arthritic rats). Brain Res 1987; 414:155-7.
40. Shen KF, Crain SM. Antagonists at excitatory opioid receptors on sensory neurons in culture increase potency and specificity of opiate analgesics and attenuate development of tolerance/dependence. Brain Res 1994; 636:286-97.
41. Woolf CJ. Analgesia and hyperalgesia produced in the rat by intrathecal naloxone. Brain Res 1980; 189:593-7.
42. Woolf CJ. Intrathecal high dose morphine produces hyperalgesia in the rat. Brain Res 1981; 209:491-5.
43. Yaksh TL, Harty GJ. Pharmacology of the allodynia in rats evoked by high dose intrathecal morphine. J Pharmacol Exp Ther 1988; 244:501-7.
44. Yaksh TL, Harty GJ, Onofrio BM. High dose of spinal morphine produce a nonopiate receptor-mediated hyperesthesia: clinical and theoretic implications. Anesthesiology; 64:590-7.
45. Hara N, Minami T, Okuda-Ashitaka E, et al. Characterization of nociceptin hyperalgesia and allodynia in conscious mice. Br J Pharmacol 1997; 121:401-8.
46. Sakurada T, Watanabe C, Okuda K, et al. Intrathecal high-dose morphine induces spinally-mediated behavioral responses through NMDA receptors. Brain Res Mol Brain Res 2002; 98:111-18.
47. Arts KS, Holmes BB, Fujimoto JM. Differential contribution of descending serotonergic and noradrenergic systems to central Tyr-D-Ala2-Gly-NMePhe4-Gly-ol5 (DAMGO) and morphine-induced antinociception in mice. J Pharmacol Exp Ther 1991; 256:890-6.
48. Colvin LA, Fallon MT. Opioid-induced hyperalgesia: a clinical challenge. Br J Anaesth 2010; 104:125-7.
49. Ram KC, Eisenberg E, Haddad M, et al. Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain - new perspective of opioid-induced hyperalgesia. Pain 2008; 139:431-8.
50. Singler B, Troster A, Manering N, et al. Modulation of remifentanil-induced postinfusion hyperalgesia by propofol. Anesth Analg 2007; 104:1397-403, table of contents.
51. Grasshoff C, Gillessen T. Effects of propofol on N-methyl-D-aspartate receptor-mediated calcium increase in cultured rat cerebrocortical neurons. Eur J Anaesthesiol 2005; 22:467-70.
52. Kingston S, Mao L, Yang L, et al. Propofol inhibits phosphorylation of N-methyl-D-aspartate receptor NR1 subunits in neurons. Anesthesiology 2006; 104:763-9.
53. De Kock M, Lavand'homme P, Waterloos H. The short-lasting analgesia and long-term antihyperalgesic effect of intrathecal clonidine in patients undergoing colonic surgery. Anesth Analg 2005; 101:566-72, table of contents.
54. Davies MF, Haimor F, Lighthall G, et al. Dexmedetomidine fails to cause hyperalgesia after cessation of chronic administration. Anesth Analg 2003; 96:195-200, table of contents.