Opioid-Induced Hyperalgesia

Osmond Morris[1†], Larry Crowley[2]

[1]Anaesthesia Fellow, St James's Hospital, Dublin, Ireland
[2]Consultant Anaesthetist, St Vincent's University Hospital, Dublin, Ireland

Edited by: Dr. Christopher Haley, Anaesthetic Consultant, Kingston Health Sciences, Ontario, Canada

†Corresponding author e-mail: morriso@tcd.ie

Published 3 March 2020

KEY POINTS

- Opioid-induced hyperalgesia (OIH) is a type of secondary hyperalgesia and results in increased sensitivity to painful stimuli in patients who have received opioids.
- There is significant overlap between OIH, acute opioid tolerance, and acute opioid withdrawal. These may occur in response to acute and chronic opioid exposure.
- The mechanism of OIH is not fully understood and is likely multifactorial; however, there is significant evidence that the N-methyl-D-aspartate receptor plays a key role.
- A recent meta-analysis reported OIH following opioid administration, and remifentanil administration had a significant impact on patients' postoperative pain and opioid use.
- Strategies to prevent and manage OIH lack evidence but centre on using a multimodal approach.

INTRODUCTION

Opioids have been administered for analgesic purposes for thousands of years, and as the speciality of anaesthesia has developed over the past 150 years, opioid use has remained a cornerstone of our practice. Since the Sumerians and ancient Egyptians first used opium as a cure for pain, the number of opioids available to us has increased, but so too has an understanding of their side effects. Opioid-induced hyperalgesia (OIH) is one such phenomenon, and there is an increasing appreciation of its prevalence and significance.

In this tutorial, we will discuss OIH, its proposed mechanism, clinical relevance to anaesthetists, and evidence on strategies to prevent and manage it in the perioperative setting.

WHAT IS OIH?

Hyperalgesia is an increased pain response from a stimulus that usually provokes pain. This is different from allodynia (pain from a stimulus that usually does not cause pain). Hyperalgesia may be primary or secondary.

- Primary hyperalgesia occurs in response to a noxious stimulus (eg, a skin incision). It is limited to the area of insult and is due to peripheral nociceptor sensitisation.
- Secondary hyperalgesia is characterised by pain manifesting itself distant to the noxious stimuli. It is thought to be secondary to central sensitisation occurring at the level of the spinal cord.

OIH is a type of secondary hyperalgesia. It is associated with diffuse nociceptive sensitisation due to opioid exposure. It results in a paradoxical hypersensitivity to painful stimuli not necessarily involving the site of insult.

An online test is available for self-directed continuous medical education (CME). It is estimated to take 1 hour to complete. Please record time spent and report this to your accrediting body if you wish to claim CME points. A certificate will be awarded upon passing the test. Please refer to the accreditation policy here.

TAKE ONLINE TEST

OIH may also involve many nonspecific symptoms, such as allodynia (pain from a usually nonpainful stimuli), and as such, there is significant overlap between OIH, acute opioid tolerance, and acute opioid withdrawal. The nonspecific nature of symptoms and the fact that there is no specific diagnostic criteria for OIH can make it challenging to diagnose.

OIH may occur in response to exposure to opioids both in the acute setting (eg, when receiving remifentanil intraoperatively) and in patients receiving opioid therapy long term (eg, for cancer pain or patients receiving methadone for substance dependence).

Opioids act at opioid receptors. There are 3 classical opioid receptors: mu (μ), delta (δ), and kappa (κ), also known as MOP, DOP, and KOP receptors, respectively. A fourth opioid-like receptor was discovered in the 1990s, labelled the *nociceptin*, or NOP, receptor. Opioids bind these G-protein–coupled receptors at locations throughout the body to produce a range of effects.

Mechanism

The exact mechanism of OIH is not fully understood; however, many theories exist, supported by varying degrees of basic scientific and clinical evidence. It is likely due to an imbalance of pro- and antinociceptive pathways, with multiple factors including central and peripheral pathways. Genetics may also play a role. Some of the proposed mechanisms are discussed below.

Central Glutaminergic System

Glutamate, one of the main excretory neurotransmitters, is known to act at the N-methyl-D-aspartate (NMDA) receptor. The NMDA receptor is known to be implicated in the initiation and propagation of the central sensitisation of pain. Both short- and long-term opioid use have been shown to increase NMDA receptor activity at the spinal level.[1] Mao et al[2] demonstrated in animal models that prolonged opioid exposure resulted in a dose-dependent glutamate transporter downregulation in the spinal cord. This resulted in reduced clearance and higher levels of glutamate (an excitatory neurotransmitter) in the dorsal horn of the spinal cord as well as increased NMDA receptor activity. This increased NMDA receptor activity and subsequent downregulation of the reception was associated with an increased level of hyperalgesia.

The NMDA receptor is further implicated; several animal and human studies have demonstrated that NMDA receptor antagonists, such as ketamine, help prevent OIH.[3]

Spinal Dynorphins

Dynorphins are opioid peptides. It has been demonstrated that μ-receptor agonist exposure significantly upregulates spinal dynorphins. This appears to promote increased levels of several excitatory neurotransmitters, which act to increase the nociceptive input at the spinal level.[4]

Descending Facilitation

In the brain, within the floor of the medulla, lies the rostral ventromedial medulla (RVM). The RVM contains both "on-cells" and "off-cell" neurones. These act as descending excitatory and inhibitory neurones, respectively. Subsets of these cells have unique response to opioids. On-cells may be activated by opioids, leading to increased spinal nociceptive processing.[5] Indeed, the interruption of these descending pathways in animal models prevented opioid-induced increases in spinal dynorphins linked to OIH.[5]

Several other mechanisms have been implicated in the origins of OIH, from genetic factors, involvement of neuroimmune cells within the spinal dorsal horn, peripheral sensitisation of primary affect neurones via **μ-**receptors, and enhanced production with reduced reuptake of various excitatory neurotransmitters.[5]

In summary, the development of OIH involves multiple central and peripheral sites, with multiple mechanisms implicated; the exact significance of each currently remains unclear.

EVIDENCE OF CLINCIAL RELEVANCE

Most studies to date attempting to elicit the incidence of OIH have been relatively small and from a single centre. In 2014, the *British Journal of Anaesthesia* published a meta-analysis aiming to determine if OIH had a significant impact on patients' pain postoperatively. Almost 1500 patients were included from 27 randomised controlled trials.[6]

Comparing pain scores over 24 hours postoperatively, the authors found significantly higher pain scores over the first 24 hours in patients receiving intraoperative opioids when compared with the control group. They also found significantly higher morphine usage in those given intraoperative opioid when compared with the control group. This difference between the groups

was driven predominantly by data from trials looking at remifentanil use intraoperatively (not fentanyl or sufentanil).[6] Patients who received remifentanil intraoperatively required an extra 18 mg of morphine on average postoperatively.[6]

Overall, high intraoperative doses of remifentanil lead to postoperative hyperalgesia, and the effects can last for at least 24 hours.[6] The dose at which this occurs is less clear, as trials differed hugely in their administration regimen, with mean cumulative doses ranging from 381 to 5644 μg. Regarding other intraoperative opioids, there were not enough data to draw meaningful conclusions.

PREVENTION AND MANAGEMENT

Pharmacotherapy

Propofol

There is some evidence to support the use of propofol in modulating the effects of OIH, possibly through its effect on gamma-aminobutyric acid receptors. Shin et al[7] found that the high pain scores observed with high-dose remifentanil in a sevoflurane-based anaesthetic were not seen with a propofol-based anaesthetic, and this was supported by subgroup analysis in a subsequent meta-analysis.[6]

Alpha Receptor Agonists

Both clonidine and dexmedetomidine are attractive options for attenuating OIH partly because of their wide availability in operating theatres and anaesthetists' familiarity in using them. However, data supporting their use are limited, and the results of several animal trials are conflicting. There is some evidence in healthy volunteers that a dose of 2 μg/kg intravenously of clonidine abolished the hyperalgesic effect seen after an infusion of remifentanil.[5]

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal agents act via the cyclooxygenase (COX) enzyme to inhibit production of proinflammatory prostaglandins. They have been shown to modulate nociceptive processing and antagonise NMDA receptor function. Indeed, small clinical trials of healthy volunteers have demonstrated that nonsteroidal anti-inflammatory drugs have to potential to attenuate OIH, with selective COX-2 inhibition being more effective.[5]

Ketamine

Ketamine has many binding sites, but its primary effect is mediated by noncompetitive inhibition of the NMDA receptor. It also reduces release of glutamate from the presynaptic junction. Ketamine has shown some efficacy in reducing both postoperative pain and postoperative opioid consumption. Its role in treatment of chronic pain is expanding.

Some studies have shown that S-ketamine, an isomer of ketamine, decreases hyperalgesia induction after remifentanil infusion[8] and that in patients receiving a high versus low dose of remifentanil (0.4 μg/kg/min versus 0.05 μg/kg/min), postoperative opioid requirements were significantly reduced by ketamine (loading 0.5 mg/kg, intravenous infusion of 5 μg/kg/min intraoperatively, and 2 μg/kg/min postoperatively).[9]

Magnesium

Magnesium has multiple known sites of action, including antagonising the NDMA receptor. Its availability and favourable side effect profile make it an attractive option for preventing OIH.

Several clinical trials have found that intraoperative magnesium reduces postoperative pain scores,[10] including for thyroidectomy, for which high-dose remifentanil (0.2 μg/kg/min) hyperalgesia was reduced by a bolus followed by infusion of magnesium sulphate (30 mg/kg bolus, infusion at 10 mg/kg/h).[11]

Buprenorphine

Buprenorphine is a potent partial opioid agonist. It is a partial Mu-r agonist, with antagonist activity at Kappa and Delta receptors. Spinal dynorphins are known to have agonist activity at Kappa receptors, and this activity increases during opioid administration. It is hypothesised that buprenorphine may cause a reduction of dynorphin activity via its antagonism of the Kappa receptor.[12]

Low-dose (0.15 mg) buprenorphine has been found to exert a significant lasting antihyperalgesic when given intravenously or sublingually in well volunteers exposed to painful stimuli,[13] while a randomised controlled trial demonstrated that low-dose buprenorphine infusion (25 μg/h for 24 hours) prevented the development of secondary hyperalgesia around the surgical

incision in major lung surgery when compared with morphine in patients reaching a target controlled infusion of remifentanil at 4 ng/mL, although no difference in pain scores at 3 months was noted.[14]

Nonpharmacotherapy

The dose of opioid administered, duration of opioid infusions, and rate of withdrawal of opioid infusion have all been linked to the development of OIH, although a meta-analysis in the *British Journal of Anaesthesia* was unable to determine precise doses and rates at which this effect might occur.[6] In a subgroup analysis, it was observed that between 2 groups receiving remifentanil, postoperative opioid use was significantly increased in the high-dose remifentanil group.

Withdrawal rates after infusion have been examined in several small studies, and results suggest reduced OIH if the infusion rate of remifentanil has been gradually reduced at the end of a procedure (baseline infusion 2.5 ng/mL, reduced by 0.6 ng/mL every 5 minutes).[15]

OIH IN LONG-TERM OPIOID USE

OIH is not seen solely in the perioperative or acute setting. Studies have demonstrated increased sensitivity to pain in several groups receiving long-term opioids, including patients on methadone maintenance therapy and those commenced on a 1-month course of opioids for chronic back pain.[16,17] The dose and duration of opioid therapy required to cause OIH is not clear at this point in time.

The diagnosis of OIH may be particularly challenging in these patients, as the potential differentials include baseline pain progression, increased tolerance, and OIH, all of which may have similar presentations. History and examination are of utmost importance and will typically demonstrate a vaguer, more ill-defined pain and one often involving areas distant from the original site of pain. OIH will also respond differently to an increase in opioid dose, characteristically leading to worsening of symptoms.

CONCLUSION

OIH is a common side effect of opioid administration, occurring in both acute settings and long-term prescriptions. It can be challenging to diagnose, given the similarities to several pain syndromes, and in fact, it may be one of many factors causing pain in a postoperative patient.

Remifentanil has been shown to be a common causative agent of OIH in the perioperative setting, although many opioids can cause OIH in both acute and long-term settings.

More research is needed into specific strategies to prevent OIH. However, using the lowest dose of opioid, for the shortest period of time, in conjunction with a multimodal approach to pain management appears sensible.

REFERENCES

1. Velayudhan A, Bellingham G, Morley-Forster P. Opioid-induced hyperalgesia. *Cont Educ Anaesth Crit Care Pain*. 2014;14:125-129.
2. Mao J, Sung B, Ji RR, Lim G. Chronic morphine induces down regulation of spinal glutamate transporters: implications in morphine tolerance and abnormal pain sensitivity. *J Neurosci*. 2002;22:8312-8323.
3. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. *Pain*. 1995;62:259-274.
4. Gardell LR, Wang R, Burgess SE, et al. Sustained morphine exposure induces a spinal dynorphin-dependent enhancement of excitatory transmitter release from primary afferent fibers. *J Neurosci*. 2002;22:6747-6755.
5. Lee M, Silverman S, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 2011;14:145-161.
6. Fletcherand D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth*. 2014;112(6):991-1004.
7. Shin SW, Cho AR, Lee HJ, et al. Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. *Br J Anaesth*. 2010;105(5):661-667.
8. Koppert W, Sittl R, Scheuber K, et al. Differential modulation of remifentanil induced analgesia and post infusion hyperalgesia by S-ketamine and clonidine in humans. *Anesthesiology*. 2003;99:152-159.
9. Vincent J, Philippe R, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology*. 2005;103(1):147-155.
10. Bujalska-Zadrożny T, Kulik K, et al. Magnesium enhances opioid-induced analgesia—what we have learnt in the past decades? *Eur J Pharm Sci*. 2017;99:113-127.
11. Song J, Lee Y, Yoon K, et al. Magnesium sulfate prevents remifentanil-induced postoperative hyperalgesia in patients undergoing thyroidectomy. *Anesth Analg*. 2011;113:390-397.

12. Velayudhan A, Bellingham G, Morley-Forster P. Opioid-induced hyperalgesia. *Cont Educ Anaesth Crit Care Pain*. 2014;14:125-129.
13. Koppert W, Ihmsen H, Körber N, et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain*. 2005;118:15-22.
14. Marco M, Stefano P, Roberto AI, et al. Low-dose buprenorphine infusion to prevent postoperative hyperalgesia in patients undergoing major lung surgery and remifentanil infusion: a double-blind, randomized, active-controlled trial. *Br J Anaesth*. 2017;119:792-802.
15. Comelon M, Raeder J, Stubhaug A, Nielsen CS, Draegni T, Lenz H. Gradual withdrawal of remifentanil infusion may prevent opioid-induced hyperalgesia. *Br J Anaesth*. 2016;116(4):524-530
16. 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(2):139-146.
17. 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(1):43-48.