A case of opioid-induced hyperalgesia

An overview of current evidence and recommendations

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ABSTRACT

This article presents a previously reported case of a 44-year-old woman receiving opioids for malignancy-related pain who presented with increasing pain symptoms. After a detailed examination of the patient's medical history, the pain was determined to be unrelated to her cancer and opioid-induced hyperalgesia (OIH) was diagnosed. The patient was eventually treated through a gradual tapering of opioids, in addition to complementary therapy and counseling. Following the case description, a concise review of the pertinent literature on OIH is conducted, emphasizing distinguishing factors between OIH and other similar syndromes as well as potential molecular targets. Finally, a brief summary of current recommendations is provided, although further research into this area is required to better evaluate the significance and treatment of OIH.

CASE PRESENTATION

A 44-year-old woman diagnosed in 2010 with a temporal glioma - which transformed into a high-grade glioma two years later - was referred to palliative care. She presented to an outpatient appointment at the Day Therapy Unit with sharp pain in the left arm, shoulder, and back that had developed over the past 5 weeks, alongside background dull pain 'all over' her body. The pain was noted by her husband to be worse following each rise in oxycodone dosage. She was subsequently admitted to the hospice for more effective pain management.¹

The patient had allodynia - central pain sensitization following normal, non-painful stimulation - whereby even light touch and contact produced burning pain. The constant pain in the patient's left arm, shoulder, and back was found to be exacerbated by movement. Furthermore, she had been experiencing auditory and visual hallucinations, and had fallen recently, prompting concern over potential memory and central nervous system effects. Her other medical history was significant for headaches, seizures, and hypothyroidism.¹

For pain in the outpatient setting, the patient received long-acting oxycodone (55 mg twice daily), short-acting oxycodone (20 mg four times daily), codeine phosphate (60 mg three times daily), and paracetamol (1 g four times daily). Her other medications included: levothyroxine (25 µg), carbamazepine (600 mg twice daily) and levetiracetam (1.5 mg twice daily), movicol (1 sachet three times daily), lansoprazole (15 mg twice daily), and metoclopramide (10 mg three times daily). These medications had not changed for the past three months.¹

In terms of social history, the patient lived downstairs in

her family living room, and had become housebound due to her symptoms. Her relationship with her teenage children was fraught, and her husband was struggling with her increased care requirements. The resulting stress was reported to be affecting her mood.¹

Her physical examination was complicated by the presence of allodynia, but notable findings included bilateral tense masseter and temporalis muscles. Additionally, she was determined to have upper limb weakness (with a noted deficiency on the left side). Complete blood count, urea and electrolytes, calcium, and liver function tests were all normal, and a magnetic resonance imaging (MRI) scan of the brain showed that the glioma was static.¹

Differential diagnosis

While a wide array of potential diagnoses exist for increasing pain in patients with chronic diseases on strong opioids, a worsening in the primary condition must be carefully assessed. However, often pain caused by deterioration in the patient's primary condition will typically respond to increasing pain relief.¹ Conversely, a patient with opioid-induced hyperalgesia (OIH) will generally not have their pain ameliorated by increases in opioid dosages, making the medical history - especially timing of increased pain and relation to opioid dosages - key to its diagnosis. Medical history factors that may confound diagnoses and must be further investigated include: low mood and anxiety influencing potential somatization of pain, drug interactions and metabolism, and pain of different aetiology (i.e. headaches, muscle pain).¹

CASE OUTCOME AND RESOLUTION

In this case, the patient's oxycodone intake was decreased from 200 mg to 130 mg daily, distributed in regular doses every four hours. This was then further reduced by 5 mg per dose every 1-2 days. Complementary therapy and counselling were also employed to improve the patient's mood and distract her from the pain. Lorazepam was prescribed to address the patient's anxiety and muscle tension in the jaw. Eventually, the patient was stabilized on oxycodone (5 mg every 4 hours), with a dramatic decrease in her subjective pain description, thus supporting the diagnosis of OIH. The patient was followed up weekly, and remained on her new opioid dosage until four months later when an MRI indicated increased tumor size.¹

BRIEF REVIEW OF OPIOID INDUCED HYPERALGESIA

The use of opioids for chronic non-cancer pain has significantly increased in Canada, and it has precipitated a host of novel clinical considerations.^{2,3} Although first described in 1943, OIH has recently

been garnering attention.³ Though there is currently a lack of consensus on the definition of OIH, a recent review of the subject put forward the following operational definition: “worsening pain sensitivity without a new injury or exacerbation of an old injury, in a person chronically exposed to opioids”.³

Often compounding the difficulty of diagnosing and treating OIH are its similar symptom profile with opioid tolerance, allodynia, and withdrawal-associated hyperalgesia (WAH).³ Opioid tolerance occurs when increasing opioid dosages are required to produce the same effect; increasing dose would in this case improve pain relief.³ Allodynia is a phenomenon involving increased pain sensitization to a benign stimulus.³ It can often be treated effectively with opioids, non-opioid analgesics, and surgical interventions.³ Finally, WAH often involves a diffuse polyarthralgic pain occurring when detoxifying from opioid use; treatment often involves NSAIDs or monitored opioid dosing.³ Distinction between these syndromes involves a detailed and comprehensive review of medications and pain history.

Although the exact mechanism of OIH has yet to be elucidated, many theories have been proposed; these include sensitization of primary afferent neurons leading to enhanced release of glutamate, hyperexcitability of second order neurons to excitatory neurotransmitters, and up-regulation of nociceptive neuromodulators.^{4,5} In addition, several potential molecular targets have been found to be associated with the development of OIH including: the NMDA-glutamatergic system, K/Cl co-transporter and Cl homeostasis, transient receptor vanilloid 1, transient receptor potential member 8, 5HT-3 receptor, and the mammalian target of rapamycin.⁶

Due to the lack of clarity and consistency in the literature surrounding OIH, many recent reviews have been undertaken to better consolidate individual study results. In a review conducted by Fishbain *et al* (2009) on the subject, literature on OIH was examined in the context of better understanding the etiology of OIH in humans.⁷ The authors discovered that although there was a paucity of literature on the subject, there was sufficient evidence to support the presence of OIH in normal volunteers receiving opioid infusions.⁷ Furthermore, a recent systematic review examined OIH in post-operative patients, specifically looking at acute pain intensity at rest 24 hours after surgery.⁸ It was discovered that the group that had received high-dose intraoperative opioids had significantly increased pain scores at rest compared to the control group.⁸ This suggests that OIH can occur in otherwise healthy individuals, and thus re-emphasizes the need for further understanding in terms of clinical manifestations.

CURRENT RECOMMENDATIONS

Despite the insufficient amount of clear literature on the subject, certain treatments have been found to be effective in tackling OIH. Often, opioid tapering can be used to help alleviate symptoms and provide effective control.¹ In order to successfully reduce dosages, clinicians can utilize and adjust existing frameworks, including the Canadian Guideline for Safe and Effective Use of Opioids for

Chronic Non-Cancer Pain, Appendix B12: Opioid Tapering.⁹ Created by a group from McMaster University, these guidelines provide important precautions to consider when tapering, in addition to suggested dose reductions and time intervals for monitoring.⁹

In cases where reduction in opioid dosages are unacceptable to the patient, ketamine has been found to be successful in the treatment of OIH in outpatient case reports and clinical trials.³ However, there are limitations to the usage of ketamine, as currently it is only available in the US though injections.³ Trials are ongoing to further assess its use as well as other delivery models. In addition, gabapentin has also been shown to have a limited impact on reducing OIH in methadone-maintained individuals.³

Methadone has also been shown to be effective in reducing high-dose OIH, in part due to its incomplete cross-tolerance with opioid receptors and its NMDA receptor antagonism.^{4,10} However, methadone, at high doses, is also associated with disadvantages including toxicity and Torsades de Pointes.⁴ Other therapeutic agents that may prove efficacious include: dextromethorphan (a non-competitive NMDA-receptor antagonist), propofol, and COX-2 inhibitors.⁴ Other treatment strategies that may be effective include rational polypharmacy with non-opioid medications, minimizing opioid usage, and careful monitoring of withdrawal and OIH-associated adverse events.⁴

Furthermore, while there is limited supporting evidence, a recent review identified several strategies that should be considered to prevent OIH.¹¹ These include: utilizing opioid combinations, limiting opioid dosage, administering co-analgesics and non-opioid analgesics, gradual withdrawal, utilizing regional/local anesthetics, and formal and documented dose equivalence calculations for chronic pain patients.¹¹ While intuitive, these strategies may be effective in preventing the development of OIH, especially in chronic pain patients.

CONCLUSION

In this report, we examined a case of OIH in a patient receiving high-dose opioids for malignancy-related pain. The case highlights the importance of including OIH on the differential diagnosis for patients with escalating pain requirements. In addition, a brief review of the literature on the subject is conducted, specifically looking at syndromes with similar symptom profiles and potential etiology for OIH. Finally, a summary of current treatment recommendations is provided. Overall, there is a need for further study in this area, especially considering the current trends with regards to opioid usage and prescription in Canada.

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