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A Case Report of Opioid Induced Hyperalgesia: When Pain's Treatment Makes it Worse

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Abstract

Opioid-induced hyperalgesia is a paradoxical state of nociceptive sensitization caused by exposure to opioids. Some patients who were receiving opioids for treating pain become more sensitive to certain painful stimuli.

Its diagnosis may be confounded by a worsening pain pathology, withdrawal, or opioid tolerance.

Several options in treating opioid-induced hyperalgesia include opioid reduction dosage, opioid rotating, or switching to a non-opioid adjuvant, such as ketamine or methadone.

We report a case of oral morphine-induced hyperalgesia in 58-year-old man treated for metastatic lung cancer.

Through this case, we will discuss the mechanisms, the diagnosis, and various modalities of the treatment of opioid-induced hyperalgesia.

Introduction

Opioids are widely used for the management of pain cancer. However, it can paradoxically induce an increased sensitivity to pain. This rare side effect of chronic exposure to opioids has been termed "Opioid-Induced Hyperalgesia" (OIH) [1,2].

Although the exact mechanisms of OIH are still not clear, several lines of studies of evidence strongly support the implication of activation of amino acid receptors such as the N-methyl-D-aspartate receptor (NMDAR) in this phenomenon [3].

OIH is under diagnosis because it is confusing, most time, to tolerance, withdrawal, or disease progression.

Further research is needed to have more knowledge of this topic.

Case Presentation

A 58-year-old man. He had a past medical history of smoking.

He was furthermore known for metastatic non-small cell lung cancer under chemotherapy. The patient suffered from left chest nociceptive pain secondary to an advanced lung tumor. He was treated by: oral sustained-release morphine sulfate 90 mg twice daily and morphine sulfate immediate release 30 mg every 4 hours as needed plus rescue doses (up to hourly) for breakthrough cancer pain and acetaminophen 3 g/day.

The patient developed pain, burning, and tingling sensation in the left arm, shoulder, chest, and back but other areas of his body were intermittently implicated. The pain was neuropathic in nature.

Increasing the dose of morphine does not relieve the pain, but it makes it worse.

We performed a complete history and physical examination, including a neurological examination. Examination revealed allodynia in the left arm, shoulder, chest, and back, and the rest of the neurological examination was normal.

Because of allodynia and increase pain with an increased dose of morphine: diagnosis of morphine-induced hyperalgesia was evoked.

Total daily morphine consumption was 360 mg per day and was decreased by one-fourth every 1 day–2 days as the patient tolerated.

Analgesia was supplemented with Gabapentin 300 mg was started and escalated gradually to BD and then TDS to treat neuropathic pain and Celecoxib 100 mg BD.

The patient has stabilized on oral sustained-release morphine sulfate 30 mg twice daily and morphine sulfate immediate release 10 mg three times a day. Decreasing the dose of morphine induces an obvious reduction of the patient's subjective pain.

The reduction of pain parallel to the decrease of morphine dosage proved that the cause of the pain was opioid-induced hyperalgesia.

Discussion

Opioid analgesics are widely used for the management of moderate to severe cancer-related pain. Besides many known side effects of opioids, OIH is a very rare side effect.

Although much growing body of literature supports that opioids therapy can be associated with the development of OIH in animals, data and evidence in humans are limited. The first studies reporting evidence for the development of OIH in humans were in former opioid addicts maintained on methadone [4,5].

Although OIH is recognized experimentally and clinically [6], the mechanisms underlying this phenomenon remain largely unknown. Based on experimental and clinical studies, high doses or chronic exposure to opioid analgesics can alter the central nervous system's response to nociceptive and may paradoxically increase pain under certain clinical conditions. This process is largely due to the desensitization of opioid receptors and associated intracellular cascades. Animal studies strongly indicate a critical role in activating excitatory amino acid receptors such as the N-nethyl-D-aspartate receptor (NMDAR) in the cellular mechanisms of opioid-induced hyperalgesia. As revealed by Mao and colleagues, the binding of opioids to receptors on spinal neurons such as NMDA receptors increase transmission of nociceptive signals [7,8].

Moreover, others animal studies have demonstrated increased levels of lumbar dynorphin (a κ-opioid agonist with pronociceptive activity) following sustained spinal administration of opioids [9].

Others mechanisms are implicated in OIH. For instance, OIH may result from the activation of supraspinal descending pain facilitation systems arising from μ-opioid receptor activation in the Rostral Ventromedial Medulla (RVM) [10–12]. Specifically the increased levels of the pronociceptive peptide Cholecystokinin (CCK) in the RVM [13,14]. It is suggested that CCK induces activation of descending facilitatory pain pathways from the rostral ventromedial medulla and mediates opioid-induced hyperalgesia [13–15].

OIH is too difficult to recognize, so we need to consider the development of tolerance or the progression of the disease, or the psychiatric comorbidities, when establishing a diagnosis.

Clinicians should suspect OIH in the context of unexplained pain reports or diffuse allodynia unassociated with the site of injury.

Quantitative sensory tests assess and quantify a patient's pain sensitivity before and after initiation of opioid therapy may be the best-suited method to separate OIH from tolerance. However, it is not widely used today [16].

In the absence of quantitative sensory data, the partial or complete resolution of pain after taper provides retrospective evidence for OIH.

Treatment of OIH is based on using opioid rotation to another opioid, for instance, methadone or fentanyl. Because opioids have effects at various receptors (μ, k, δ) and different opioids have different affinities for the subclasses of the same receptor [17], https://clinicaloncologyjournal.com/account/manuscript-sections/1000105 the opioid rotation has been successfully used in OIH. Several reports have shown that opioid rotation to methadone significantly improved or resolved suspected OIH [18].

Another reasonable approach in such situations includes the reduction of opioid doses. Furthermore, based on multiple successful trials and meta-analyses, the use of NMDA-receptor antagonists such as ketamine and dextromethorphan have demonstrated its efficacy in OIH [19,20]. Moreover, adjuvants treatments have been identified as potentially helpful in minimizing OIH, including Gabapentin, CCK antagonists, propofol, and COX-2 inhibitors [21–23].

Further research is needed in this area for choosing optimal OIH treatment options.

Conclusion

Opioids may be a double-edged sword, initially offering pain relief but subsequently evoking hyperalgesia.

The problem of hyperalgesia remains not well understood and is quite challenging to interpret in the clinical setting of cancer patients.

Future investigation in this area is warranted, given the many cancer patients who receive opioids for cancer pain.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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