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BRIEF COMMUNICATION

Opioid-induced Hyperalgesia: An Entity not so Common, but exists

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ABSTRACT

Reported are cases of opioid-induced hyperalgesia (OIH) which is a rare entity to be seen by pain physicians. It occurs in patients treated with long term opioids which is perceived in the form of hyperalgesia or allodynia. It is a clinical challenge to treat such cancer patients and opioid addict individuals. The understanding of OIH mechanism, manifestations as well as treatment is important for any pain physician.

Keywords: Allodynia, Hyperalgesia, Opioid.

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INTRODUCTION

It is a universal notion by pain physicians to prescribe opioids for chronic pain management. Morphine is one of the cheapest and commonly used opioids for chronic cancer as well as noncancer pain. Apart from the more common side effects of morphine, such as sedation, respiratory depression, hypotension, pruritus, etc., opioid-induced hyperalgesia (OIH) does exist. In very simple words, OIH is a paradoxical response of opioid medication due to pain sensitization.

Tolerance to opioids can also develop on long-term use. It is to be differentiated from OIH by simple dose escalation. If increasing the opioid dose results in aggravation of pain, it is termed OIH, whereas if the pain intensity reduces, it is opioid tolerance. The primary mechanism of tolerance is desensitization of antinociceptive pathways. It is in contrast to OIH, where pain sensitization is the main culprit.

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The OIH was first described by Albutt[1] in patients receiving chronic morphine therapy. It has also been observed with long-term use of hydrocodone, oxycodone as well as methadone.[2-4] We diagnosed OIH in our patient, who was implanted a morphine intrathecal pump to control her pain due to adenocarcinoma rectum, chemotherapy, and radiotherapy. She developed hyperalgesia after a span of 1 year as seen on dose escalation on refilling the pump during regular follow-ups. Another was a postthoracotomy patient with intercostal tube drainage *in situ*. He was an opioid addict as found on past medical history. Due to his severe pain intensity, he was given morphine intravenously. As the dose requirements were too high, escalation of the dose was done. It was found that the pain severity got increased on visual analog scale (VAS) score. Both the patients were diagnosed as OIH due to chronic opioid administration.

Various mechanisms have been postulated in the past for OIH. These patients have increased sensitivity to painful stimuli (hyperalgesia) as well as to nonpainful stimuli (allodynia). They have reduced threshold to pain and in an effort to relieve their pain, the dose of the opioid was augmented that consequently led to enhanced pain intensity on VAS score. Pain map and area rose linearly with escalation of the dose of opioid and the patient landed up with generalized and widespread pain that usually now extends beyond the site of injury or painful stimuli.

Out of the multiple mechanisms responsible for OIH, *N*-methyl-D-aspartate (NMDA) receptors have been found noteworthy as the main culprit. Glutamate-mediated NMDA receptor activation results in spinal neuron sensitization. Apart from this, there is cross-talk of pain neurons. Prolonged morphine administration induces neurotoxicity via NMDA receptor-mediated apoptotic cell death in the dorsal horn.[5-7] Inhibition of glutamate transporter system and facilitation of calcium regulated intracellular protein Kinase C have also been observed.[7] Spinal dynorphins also plays some role. There is an enhanced synthesis of spinal excitatory neuropeptides, such as calcitonin gene related peptide. Subsequently, their release also stimulates peripheral nociception.[8,9] Cholecystokinin levels also rise in the rostral ventromedial medulla (RVM) activating the spinal pathways and spinal dynorphins. A role of descending

facilitation through on and off cells within the RVM is also identified and proved.[10,11]

Treatment always starts with the confirmation of the diagnosis. The OIH is to be differentiated with tolerance by assessing the patient's response on enhancing the opioid dose. The mainstay of treatment is NMDA antagonist. Meanwhile, one can shift to another opioid, taper off the opioid to a minimum, or start nonopioid medications. In our first case, OIH was diagnosed as escalation of the intrathecal morphine dose initially resulted in better VAS scores, but later caused paradoxical increase in pain. After giving a test dose of intrathecal ketamine, patient was shifted to ketamine infusion through intrathecal pump. In the second case, patient was given fentanyl infusion at a low dose of 20 µg/hour along with dexmedetomidine infusion of 0.2 to 0.7 µg/kg per hour after loading the patient with 1 µg/kg over 10 minutes. Both the cases achieved satisfactory pain relief as observed on VAS score.

Methadone has also shown weak NMDA receptor antagonism and can be helpful to treat OIH.[7] It has a role in opioid rotation too. The results with methadone are, however, conflicting, as there have been cases where methadone treatment resulted in undesirable pain states and toxicity causing torsades de pointes, while treating opioid addicts. Other treatment strategies include dextromethorphan (cough suppressant with noncompetitive NMDA receptor antagonism), propofol (through interactions with gamma-aminobutyric acid receptor at supraspinal level), cyclooxygenase 2 inhibitors (inhibition of prostaglandin synthesis), and alpha-2 agonists.[7]

The OIH is not so frequently encountered in everyday medical practice. But, with the growing demand for the use of opioids in treatment of chronic pain, the number of patients diagnosed as OIH is on an increase.[12] Although it is a standard practice to think about more common opioid tolerance, dependence, abuse, or withdrawal in patients on chronic opioid medication, the possibility of OIH should always be ruled out.

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