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Editorial

Opioid-induced Hyperalgesia: Myth or Burgeoning Public Health Crisis?

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There has been considerable discussion recently regarding what, if any, role opioid-induced hyperalgesia (OIH) plays in determining the observed phenomenon occurring in some, but not all patients chronically consuming opioids who seek escalating doses of these potent pain relievers during the course of their disease or condition. In today's climate of drastic and rapid changes in the way interventional pain management physicians view the use of prescription opioids (1-6), the use of the "OIH disclaimer" may become a rallying cry used to try to liberate patients from their beloved narcotics. It has been stated that "clinicians should suspect OIH when opioid treatment's effect seems to wane if the absence of disease progression, particularly if found in the context of unexplained pain reports or diffuse allodynia unassociated with the original pain, and increased levels of pain with increasing dosages" (6). This discussion has led to some insisting to patients that they "must reduce their use of opioid pain medications if they stand a chance of improving their pain, due to opioid-induced hyperalgesia."

Admittedly, despite the identification of 2,359 peer-reviewed articles and letters from a PubMed® engine search conducted on July 01, 2017 utilizing the single key phrase "opioid induced hyperalgesia", the medical community at large continues to be somewhat baffled by agreeing whether or not this is a condition exclusively seen in laboratory animals or whether it may be a phenomenon seen as well in humans. There continues to be debate regarding this somewhat elusive condition and its legitimacy as clinical entity requiring attention and treatment. Most studies conducted in humans revolve around rapid-acting intravenous opioids such as alfentanil (7) and remifentanil (8), in acute hyperalgesic states created experimentally (1), or else in recovering drug addicts, and have not been as precise in defining the role of OIH with chronic oral consumption of opioids. Electrophysiological studies have shown that remifentanil elicits rapid and prolonged upregulation of N-methyl-D-aspartate receptor (NMDAR) currents, which may contribute to the development of OIH. Glia and other toll-like receptors (TLRs)-expressing cells in the neuroimmune interface have been recognized for their role in the development of neuropathic pain, while compromising the analgesic effects of opioids (9). TLR-mediated signaling and an altered opioid-immune system may be mechanisms to explain OIH, if it truly exists in humans (9,10).

OIH is generally considered to be a phenomenon associated with the long-term use of opioids, although the condition has been observed even during short-term administration of these agents under some circumstances in pre-disposed individuals. With chronic use, over time, individuals taking opioids can develop an increasing sensitivity to noxious stimuli, even evolving a painful response to previously non-noxious stimuli. It is differentiated from tolerance, which occurs when a person no longer responds to the drug in the way that person initially responded. Stated another way, with tolerance it takes a higher dose of the drug to achieve the same level of response achieved initially. During chronic opioid treatment, a particular individual's requirement for dose escalation may be due to tolerance (desensitization of antinociceptive mechanisms), opioid-induced hyperalgesia

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(sensitization of pronociceptive mechanisms), or a combination of both.

Research has suggested that several mechanisms might be at play in the development of OIH, including the expression of the transient receptor potential vanilloid type 1 (TRPV1) ion channel and the development of hyperalgesia (11). Recent reports suggest that opioid or TRPV1 receptor agonist exposure has contrasting consequences for anti-nociception, tolerance and dependence. Chronic morphine (and presumably other mu-agonist opioid) exposure modulates TRPV1 activation and induces the anti-nociception effects of morphine. The regulation of many downstream targets of TRPV1 plays a critical role in this process, including calcitonin gene-related peptide (CGRP) and substance P (SP) (11).

Experimental evidence has investigated the effects of remifentanil, along with ketamine (NMDAR antagonist) and naloxone (μ-opioid receptor antagonist), on GluN1 mRNA levels and the amount of phosphorylated GluN1 in primary cultures of embryonic rat dorsal horn neurons (DHNs) (12). DHNs were isolated from 18-19-day rat embryos and treated with remifentanil or vehicle for 1 h. GluN1 mRNA and protein levels, determined by real time reverse transcription polymerase chain reaction (RT-PCR) and Western blot, respectively, were significantly and persistently increased by remifentanil exposure compared with the control group ($P < 0.05$). These results may partially account for the mechanism of remifentanil-induced hyperalgesia. This increase was prevented by ketamine (NMDAR antagonist) and naloxone (μ-opioid receptors antagonist), thus providing a potential therapeutic mechanism for the prevention of opioid-induced hyperalgesia (12).

While Remifentanil and Alfentanil use in experimental circumstances has been associated with likely development of OIH, does this translate in human models of patients exposed to these ultra-rapid opioids in a clinical, surgical setting? The answer remains murky, as noted in one of the largest reviews on the topic conducted to date (13). In a review of twenty-seven studies involving 1,494 patients, patients treated with high intra-operative doses of opioid reported higher postoperative pain intensity than the reference groups at 4 hrs, and at 24 hrs on a 100 cm visual analogue scale. They also showed higher postoperative morphine use after 24 hrs. There was no difference in the incidences of nausea, vomiting, and drowsiness. These results were mainly associated with the use of remifentanil. The impact of other opioids is less clear because of limited data (13).

It appears that the intraoperative use of ketamine (NMDAR antagonist) may be useful if administered acutely and concurrently to minimize the development of OIH in patients undergoing surgery who receive Remifentanil. Seventy-five patients undergoing gynecologic surgery under remifentanil-based anesthesia were assigned to one of the following groups: (1) group RL (remifentanil 0.05 μg/kg/min), (2) group RH (remifentanil 0.3 μg/kg/min), or (3) group KRH (remifentanil 0.3 μg/kg/min + ketamine 0.5 mg/kg bolus with 5 μg/kg/min infusion intraoperatively). Desflurane was administered for maintenance of anesthesia. All parameters related to OIH and its attenuation induced by ketamine were investigated. Additional analgesic consumption, numerical rating scale scores at 6 and 24 hrs, and cumulative fentanyl dose were significantly higher in group RH than in the other two groups. The value difference of the Touch-Test sensory evaluation was significantly higher negative in group RH than in the other two groups. Remifentanil-induced hyperalgesia was significantly attenuated by intraoperative bolus and infusion of ketamine. Ketamine also decreased tactile sensitization, as measured by Touch-Test sensory evaluation (14). In chronic pain patients chronically consuming opioids, intraoperative ketamine infusion was noted to reduce morphine PCA consumption and sedation in a group of 147 patients undergoing lumbar spinal fusion surgery (15). Studies such as these demonstrate the ability of ketamine administered contemporaneously to ultra-short opioid use to prevent OIH development, but until now nobody has demonstrated, in a clinical setting, the ability of ketamine to treat OIH once it has developed.

In this edition of Case Reports in Interventional Pain Management, Liang et al describe, for the first time, the use of ketamine infusion used to treat a rapidly evolving condition of probable OIH not during surgery with opioids, but rather in a post-surgical patient requiring escalating and prohibitive doses of opioids to manage postoperative amputation pain (16). The authors detail the story of a 56 year-old man with

multiple medical co-morbidities who was chronically opioid dependent following multiple spine related surgical interventions who presented for an above-the-knee amputation related to a diabetic peripheral neuropathy. On the first post-operative day, some 24 hours after undergoing the amputation, his opioid requirements became exponentially higher each hour, with each escalation being associated with escalating pain levels, until a decision was made to eliminate opioids and substitute a ketamine infusion to manage his symptoms. This proved to be successful over several days, illustrating for the first time the use of a "ketamine-rescue" protocol to arrest an evolving OIH condition in the postoperative period.

While we still have a great deal to learn about OIH, and its clinical presentation in the chronic pain sufferer, as well as what opioids trigger it and in what doses, and who is most likely to be predisposed, this case is an example of using available scientific information conducted on human (17-19) and in laboratory animals to present a possible strategy, yet unproven, to combat an evolving critical situation in a post-operative patient treated with opioids who actually worsened with each successive opioid dose escalation. While ketamine has not been deemed the most appropriate pharmacological agent for all patients suspected of having OIH, and while the feasibility of using similar NMDAR drugs like Memantine orally in these patients remains to be proven, this case study does demonstrate that OIH should be suspected when paradoxically pain increases concomitant to increasing opioid administration. While reducing or eliminating opioids would seem to be intuitive, having agents available that can reverse the hyperalgesia while simultaneously treating the painful condition remains a challenge, and doing so after the OIH has already occurred is a greater challenge still.

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