Opioid induced hyperalgesia: A focus on opioid use in chronic pain

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ABSTRACT

Opioids are a well-established treatment option for chronic pain. However, opioid therapy is associated with many side effects, including opioid induced hyperalgesia (OIH). This article reviews studies which have evaluated OIH in chronic pain patients on opioids.

KEYWORDS

opioid, hyperalgesia, pain, allodynia

The use of opioids has become a well-established treatment option for the management of chronic nonmalignant pain (CNMP).[1] However, chronic opioid treatment in chronic pain is a controversial issue and careful patient selection and ongoing monitoring is recommended. Along with the commonly recognized side effects from opioids such as constipation, dizziness, memory issues and dry mouth, as well as concerns of dependence and addiction, there are also less understood and appreciated endocrine effects in addition to the risk of opioid induced hyperalgesia (OIH).[2,3,4]

The concept of OIH is not new to practitioners. This was first documented in the late 1880's by Rossbach, stating that "opioid dependence is an illness itself" citing opposing opioid effects such as "hyperesthesias and restlessness" as translated by Angst and Clark.[4] Common definitions for OIH include the need for increasingly high levels of opioids to maintain pain inhibition after repeated drug exposure,[3] and a state of nociceptive sensitization caused by exposure to opioids.[5] This sensitization is thought to result in hyperalgesia and allodynia.

Hyperalgesia is an increased response to a painful stimulus. Allodynia is a painful response to a normally innocuous stimulus. An example of hyperalgesia in an experimental model would be if a patient were pricked with a pin and experienced a painful response. Later, when administered the same painful stimulus of the pin prick, a greater painful response was evoked. Conversely, allodynia would be a painful response from a normally non-painful stimulus such as a light breeze on your skin.

PATHOGENESIS FOR OIH

Opioids are often classified based on their interactions with opioid receptors, as agonists, partial agonists, agonist/antagonist or antagonists.[6] Opioid agonists bind to the opioid receptors and exert an action through the stimulation of endogenous opioids (endorphins, enkephalins, and dynorphins) which prevent the spread of nociceptive information between neurons, resulting in the inhibition of ascending pain pathways.

The mechanism for the development of paradoxical hyperalgesia with the administration of opioids remains unclear. During the 1970's there was increased interest in describing the phenomenon which resulted in multiple animal studies being performed.[4] The majority of these studies involved rodent models which demonstrated an opioid-induced hyperalgesic response during maintenance or withdrawal from opioids, primarily morphine. Celerier and colleagues also demonstrated a sustained hyperalgesic effect following opioid discontinuation.[7] These animal studies have been very useful in the development of the proposed mechanism of action for OIH.

Opioid medications have activity at the mu, delta and kappa receptors. The mu receptor is thought to have a significant role in the development of OIH. This was demonstrated in a rodent model when the mu-opioid receptor agonist, fentanyl, induced both thermal and mechanical hyperalgesia and a complimentary experiment in mice with reduced mu-opioid receptor binding had no significant hyperalgesia.[8] This study utilized a thermal (heat) stimulus and a mechanical (punctuated pressure) stimulus to measure pain responses. This type of pain stimulus along with cold stimulus, are commonly used to assess hyperalgesia in a simulation setting for both animal and human subjects.

In addition to opioid receptors, multiple sites of action have been proposed including the afferent neurons, spinal-cord tissue and supraspinal centers in the CNS. N-methyl-D-aspartate (NMDA) receptor activation may cause an increase in excitatory neurotransmitter activity, causing pain signals similar to neuropathic pain. This was demonstrated in a rodent model where the administration of an NMDA receptor antagonist prevented hyperalgesic responses.[9]

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Data in human subjects have varied in results. Fishbain and colleagues completed an evidence-based structured review concluding there is not sufficient evidence either to support or refute OIH in humans with the exception of normal, volunteer subjects.[10] The studies with the greatest strength to support the OIH hypothesis involved the administration of high dose mu opioids perioperatively and subjects postoperatively developed increased pain and opioid requirements compared to patients administered lower doses of opioids perioperatively.[11,12] Case reports provide anecdotal evidence of hyperalgesia and allodynia with higher doses of opioids used in patients with chronic pain.[4,5] These case reports have concluded that the reduction of the opioid or substitution with a different opioid has either improved or completely resolved symptoms of allodynia. Opioid rotation to methadone, in particular, has been associated with improvement in OIH, potentially due to NMDA antagonist activity.[13,14] However, contrary case reports have shown lack of improvement with methadone substitution.[15]

Indirect evidence from a retrospective review of a population of patients who voluntarily sought detoxification from prescription opioids documented significantly improved self-reported pain.[16] The majority of the patients in this study had back pain as the primary pain complaint. Self-reported pain scores improved from an average of 5.5 on admission to 3.4 on discharge (pain scale of 0-10, with 10 being the most pain).

CHRONIC PAIN PATIENTS AND OIH

As research in this area continues, emphasis should be placed on high quality studies in the chronic pain population to further substantiate the existence of OIH with the use of chronic opioids and determine risk factors for development of OIH. The following review will focus on the limited number of studies that have been completed in patients with chronic pain, without a significant opioid addiction history and the resulting evidence for OIH.

An open label, prospective study in patients with moderate to severe nonradicular low back pain, assessed OIH with cold pressor and heat pain testing.[17] This study was a small sample of six patients. Patients were assessed prior to and one month following the initiation of sustained release morphine with a median dose of 75 mg/day. At each testing of pain sensitivity, patients also received a remifentanil infusion to achieve and maintain three different levels of concentration to determine opioid tolerance. Results showed patients developed significant hyperalgesia to cold pressor pain after completing one month of oral morphine therapy. Heat pain tolerance did not show significant changes after one month as most patients tolerated the maximum allowed temperature at both time points. Secondary outcome measures for this study included a visual pain analog score, Beck depression score, Roland-Morris disability index, and objective opiate withdrawal scale. None of the secondary outcomes showed significant changes at the conclusion of the study.

The same authors subsequently completed a similarly designed double-blinded, randomized, placebo controlled trial.[18] Eligible study participants were either not on an opioid medication or on a low dose (less than 30 mg oral morphine equivalents daily). Subjects with a substance abuse history, severe psychiatric disease or taking medications for neuropathic pain were excluded. Forty-eight patients in the morphine treatment group (average dose 78.3 ±37.5 mg) and 55 patients in the placebo group completed the study. Placebo patients had a decrease in cold pressor pain threshold of 8% compared to 13% for the morphine group. Although the change in the opioid group between tests was significant, the differences were not statistically significant when compared to the placebo control group. Similar to the initial observational study, no changes were seen in the heat pain tolerance or with secondary outcomes. Limitations to these two studies include small sample sizes, low to moderate doses of opioids and a relatively short opioid exposure period of 30 days.

A prospective, open label study, in a multidisciplinary pain rehabilitation program consisting of patients with a variety of chronic pain diagnoses, evaluated the presence of hyperalgesia following opioid tapering using heat pain perception.[19] Patients were eligible for the study if they were on opioids for 6 months or longer and had been receiving daily doses of ≥30 mg of morphine equivalents. Patients taking low potency opioids (codeine, propoxyphene, or tramadol) were excluded. The pain rehabilitation setting was a 3 week program with a focus on functional and emotional gains. Opioids are tapered off and discontinued as an additional program goal. This study enrolled 109 patients with a mean morphine equivalent dose of 192 mg/day on admission. Pain diagnoses in this study included low back, abdominal, generalized, pelvic, fibromyalgia, facial, lower and upper extremity, neck, chest wall, and chronic headache pain. Analysis using univariate linear regression found an association between higher doses on admission and an increased hyperalgesic response to heat pain.

This supports a dose-dependent relationship with OIH. Patients on higher opioid doses also continued to exhibit significantly greater hyperalgesic responses after tapering and discontinuation of opioids, as measured at a mean (SD) of 5.2 (4.3) days following the last opioid dose. This

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supports the theory of persistent molecular changes following opioid use even after the discontinuation of the opioid. A dose relationship was also found in a different analysis of chronic pain patients, with a lower heat pain threshold in patients receiving morphine equivalent doses ≥ 75mg/day.[20]

The most recently published report is a prospective, open-label evaluation of 30 patients with chronic neuropathic, radicular pain evaluating experimental heat and cold pain with a comparator control group.[21] Patients were required to discontinue all previous analgesic medication, with the exception of acetaminophen, and undergo a 7-day washout period prior to study initiation. Study subjects were then administered controlled-release hydromorphone which was titrated to a maximum dose of 24mg/day, with a mean dose of 11.6 mg ± 4.8 mg/day. The authors report this mean dose is equivalent to an oral morphine dose of ~80 mg/day although references vary in the reported equivalent dose of hydromorphone to morphine.[22] This study found a significant increase in pain from the heat pain stimulus as measured with a visual analog scale (VAS) but no difference with cold pain intensity before opioid treatment and after 4 weeks of treatment. Higher doses of hydromorphone also correlated with increased hyperalgesia. However, patient rated daily VAS pain scores during the course of the study significantly improved with opioid treatment.

CONCLUSIONS

At this time medical research has been limited with few well-designed studies evaluating OIH in the chronic pain patient on opioids. Future research is needed in several areas to help identify risk factors and develop clear consensus on the diagnostic tools and criteria needed in a clinic setting. Additionally, studies that are molecular in nature are needed to help to understand why some individuals develop OIH while others do not. Finally, studies are needed to define the expected resolution of OIH symptoms with opioid discontinuation.

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