Q&A

Demystifying OIH

Q: Some insurance companies have declined to continue paying for medications for patients with chronic pain who are on moderate to high doses of opioids, even if they are functioning well. They often cite opioid-induced hyperalgesia (OIH). What is going on?

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A: In cases like these, many insurance companies state that patients should have their doses tapered in order to decrease their pain. However, clinicians may find that attempts to reduce the opioid dose often result in *increased* pain. *Hyperalgesia* refers to an exaggerated pain response. This is a known feature of some neuropathic pain syndromes. Opioid-induced hyperalgesia (OIH) has been suggested as an explanation for the decreased analgesic efficacy of opioids in some patients treated chronically with high opioid doses.

Studies have shown some evidence of OIH in rats.[1] One study reported a receptor in the genome of rats and mice which may play a role in producing OIH in these animals.[2] Several studies in humans showed that patients who received acute intraoperative intravenous remifentanil, an opioid related to fentanyl, experienced increased postoperative pain in the recovery room, as determined by pain scores, morphine requirement, and/or sensory testing.[3] Such studies have been interpreted to show that acute opioid administration rapidly produces hyperalgesia. This setting is different, however, from those where patients who have chronic pain and are treated with chronic opioids gradually require increasing doses.

Evidence from the Literature

In a study that included 355 patients on chronic opioids for pain and 27 controls without chronic pain, subjects were given a subcutaneous injection of lidocaine and immediately had their resulting pain level measured. Both pain intensity and unpleasantness scores were significantly higher in those subjects on opioid therapy than in the control group.[4] The authors concluded that opioid treatment enhances pain perception and that their study supported the possible presence of OIH in subjects using opioid therapy.

An observational study compared the pain sensitivity in three groups of patients: those with non-cancer chronic pain; patients without chronic pain who were maintained on methadone for addiction therapy; and a control group. The first two groups had increased pain sensitivity to one stimulus (cold pressor test) but not another (electrical stimulation), and none of the groups exhibited allodynia.[5] The results suggested that chronic opioid use may increase sensitivity to specific pain stimuli but not others, and does not produce allodynia.

Despite these experimental studies, no published studies have either specifically evaluated the relevance of OIH to clinical populations of chronic pain patients or provided evidence that OIH actually contributes to increased opioid need in chronic pain patients. One long-term outcome study[6] followed 197 patients who were on chronic opioids for at least 1 year; the mean duration of opioid treatment was 56.5 months and the mean daily dose was 180 mg morphine equivalents. Looking at the pattern of medication usage change over time, 34.5% experienced dose stabilization after the initial titration, another 13.2% had early dose stabilization followed by one dose change and subsequent stabilization, and an additional 14.7% had dose decreases after surgeries or other interventional procedures. Patients who required dose increases with time usually had disease progression. The authors

wrote: "The patients showed no apparent evidence of tolerance or hyperalgesia, despite being on what are considered moderate to high opioid doses…These results demonstrate that a significant proportion of opioid-treated chronic pain patients can remain on the same dose of opioid for years."[6]

Dozens of experimental papers and reviews have been published, some assuming or supporting the existence of OIH and others refuting it. A 2017 study[7] enrolled 20 patients with "suspected OIH" because they had a "more centralized pain state (fibromyalgia-like presentation), which suggests the potential presence of OIH." They were transitioned from full mu agonists to buprenorphine in order to specifically treat suspected OIH. Those on higher opioid doses (≥100 mg morphine equivalents per day) had the most improved pain, pressure sensitivity, and function at 1 week with an eventual return to baseline.

From the Experts

The clinical relevance of opioid-induced hyperalgesia in the setting of opioid therapy for chronic pain has never been shown. Below are the opinions of several pain experts.

- Fishbain, in an evidence-based structured review, concluded: "There is not sufficient evidence to support or refute the existence of OIH in humans except in normal volunteers receiving opioid infusions."[8]
- The conclusion of Reznikov, et al, was: "The clinical relevance of OIH in patients on chronic opioids for pain has never been demonstrated…Administration of commonly used doses of oral opioids does not result in abnormal pain sensitivity beyond that of patients receiving non-opioid analgesia."[9]
- Regarding OIH, Pasternak was quoted as saying: "There is little question that it exists. The animal models can reliably detect it and, if you look closely enough, you might be able to detect it in human subjects. However, in the clinical setting it rarely, if ever, has a sufficiently robust effect to become a significant issue…"[10]
- When asked how one may avoid OIH, Chou responded: "Data to estimate the prevalence and clinical impact of hyperalgesia in humans, or how to avoid it, are quite limited."[11]
- Argoff's answer: "There are truly no good data to support or refute this entity. The quality of currently available studies regarding this matter is generally poor."[11]

What Explains OIH?

How then do we explain the fact that many patients with chronic pain who begin opioid therapy end up requiring increased analgesic doses? Depending on the timing, there are three potential reasons other than OIH:

- When an opioid is initially prescribed, the dose is deliberately low in order to assess side effects and then increased to an effective analgesic dose
- A short time after reaching an initially effective dose, the most common reason for decreased pain relief is increased activity, a desirable outcome often requiring a dose increase
- Decreased efficacy months after a stable effective dose is often due to disease progression.

In other words, there are several well-established reasons other than possible OIH to explain why prescribers often find it necessary to increase the opioid dose in a patient with chronic pain. If a patient is functioning with adequate pain relief on his/her current dose of opioid, decreasing the dose, as the insurance company may suggest, is not in the patient's best interest. The outcome of such a decision is likely to be increased pain and decreased function.

If a patient continues to experience significant pain, the solution is not to simply reduce the opioid dose, but rather to review the entire treatment plan and (if not already a part of the treatment) add other modalities such as behavioral health assessment and treatment, physical therapy and ongoing home exercises, non-opioid medications, complementary medicine, interventional procedures, etc. A reduction in dose may then be possible when the patient is engaged in these modalities. It is also possible that the patient would benefit from an increase in dose, or trial of a different opioid, such as buprenorphine. •

References

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