Opioid-Induced Hyperalgesia

During opioid treatment of pain, a decline in analgesic efficacy has traditionally been thought to result from the development of pharmacological tolerance (or disease progression), best overcome by dose escalation. More recently, it has been recognized that opioids can also activate a pronociceptive mechanism resulting in heightened pain sensitivity or opioid-induced hyperalgesia (OIH). Although hyperalgesia had previously been observed during opioid withdrawal, new evidence suggests that increased pain sensitivity can also occur during opioid administration, in the absence of an overt, precipitated withdrawal. This paradoxical opioid-induced pain sensitivity may contribute to reduced opioid analgesic efficacy. Therefore, it is possible that a decrease in opioid analgesic efficacy may be a result of OIH (a pronociceptive mechanism), not simply of pharmacological tolerance. Both a sensitization and a desensitization process are taking place.

Although hyperalgesia had previously been observed during opioid withdrawal, new evidence suggests that increased pain sensitivity can also occur during opioid administration.

Opioid-induced hyperalgesia is mediated through distinct cellular mechanisms, including endogenous dynorphin, the glutamatergic system, and descending facilitation.7,8 Interestingly, the cellular mechanisms of OIH have much in common with those of neuropathic pain and opioid tolerance.7,8 For example, both peripheral nerve injury and repeated opioid administration can activate a similar cellular pathway involving activation of the central glutamatergic system.8 NMDA antagonists such as ketamine have been used clinically to reverse the glutamatergic component of pain sensitivity. This issue of Pain: Clinical Updates discusses preclinical and clinical evidence of opioid-induced pain sensitivity and its implications for clinical opioid therapy.

Interestingly, the cellular mechanisms of opioid-induced hyperalgesia have much in common with those of neuropathic pain and opioid tolerance.

Preclinical Evidence of Opioid-Induced Nociceptive Sensitivity

Decreased Nociceptive Threshold Following Opioid Boluses

In rats, repeated administration of intrathecal morphine (10 or 20 μg) over a 7-day period progressively reduced baseline nociceptive thresholds as assessed by the foot-withdrawal test to thermal stimulation.1,3 The decreased nociceptive threshold lasted at least several days after morphine discontinuation.1 In rats receiving subcutaneous fentanyl boluses, baseline nociceptive threshold was
measured using the Randall-Selitto test, in which constantly increasing mechanical pressure is applied to the hindpaw.4,5 A reduction in nociceptive threshold was observed that lasted for 5 days after discontinuation of fentanyl boluses. Likewise, baseline nociceptive threshold was reduced in animals given repeated administration of heroin, a highly potent opioid.6 These findings indicate that repeated opioid administration could lead to a progressive and lasting reduction of baseline nociceptive (thermal and mechanical) threshold, suggesting an increase in nociceptive sensitivity.

Decreased Nociceptive Threshold Following Continuous Opioid Infusion

Hyperalgesia is one of several manifestations of opioid withdrawal. It is possible, then, that the decreased baseline nociceptive threshold observed in animals treated with opioid boluses1-6 may reflect subliminal withdrawal without the more overt withdrawal signs such as diarrhea, wet-dog shake, and jumping. However, a progressive reduction of baseline nociceptive threshold also occurred in animals receiving a course of continuous intrathecal opioid infusion via osmotic mini-pumps.2,3,7 The animals showed opioid-induced thermal hyperalgesia and tactile allodynia during opioid infusion.3,7

Clinical Evidence of Opioid-Induced Hyperalgesia

In animal studies, changes in baseline nociceptive threshold can be assessed by observing changes in reflex responses in a controlled manner. Measuring pain in humans is much more challenging because supratentorial factors obscure reflex responses, and one is left with the more subjective and global self-report of pain scores. It is more difficult, therefore, to distinguish OIH from other causes of pain. Nonetheless, current clinical evidence suggests that a similar phenomenon of opioid-induced hyperalgesia may be found in clinical practice.

Increased Postoperative Pain after Administration of Potent Opioids

Several reports have noted decreased opioid analgesic efficacy as well as increased opioid requirements after administration of potent opioids, such as after intraoperative remifentanil infusion.9-11 One study found no change in opioid analgesic efficacy under similar conditions.15 It is unclear, as yet, whether this acute opioid “tolerance” is a function of acute pharmacological tolerance or acute induced hyperalgesia.

Empirical observation has long suggested that pain sensitivity is increased in individuals with opioid addiction

Increased Pain Sensitivity in Subjects on Methadone

Empirical observation has long suggested that pain sensitivity is increased in individuals with opioid addiction.13-17 A recent study found that sensitivity to experimental pain stimulation such as the cold pressor was significantly greater in opioid addicts.16 In addition, opioid addicts who were on methadone maintenance reported higher pain sensitivity compared to demographically matched opioid addicts who were not taking methadone. Thus, methadone maintenance may further increase abnormal pain sensitivity in opioid addicts.

Chronic Pain Patients on Opioid Therapy

Little is known with respect to opioid-induced changes in pain sensitivity in patients on long-term opioid therapy. Do these patients develop increased pain sensitivity? Clinical observation suggests the presence of OIH in cancer pain patients,18 although one study reported no significant differences in pain sensitivity in a mixed population of cancer and noncancer patients with or without opioid treatment.19 A recent

Fig. 1. Apparent clinical opioid tolerance may result from pharmacological tolerance, a worsening pain state, and/or opioid-induced pain sensitivity. While opioid dose escalation may overcome pharmacological tolerance, it could enhance the pronociceptive process and worsen apparent opioid tolerance and clinical pain if apparent opioid tolerance were a manifestation of opioid-induced pain. OIH = opioid-induced hyperalgesia.
preliminary study has shown that pain sensitivity to cold presor stimulation (but not heat stimulation) increased within 1 month after patients began opioid therapy. More clinical studies are needed to examine the extent of OIH in patients on long-term opioid therapy.

**Clinical Implications**

Diminished opioid analgesic efficacy during the course of opioid therapy has long been considered a sign of pharmacological opioid tolerance or of worsening of an existing pain state. Thus, opioid dose escalation has been a logical approach to restoring effectiveness of opioid analgesics. This practice may be revisited in light of both preclinical and clinical evidence of paradoxical opioid-induced pain sensitivity. As illustrated in Fig. 1, apparent clinical opioid tolerance may result from pharmacological tolerance, a worsening pain state, and/or opioid-induced pain sensitivity. On the one hand, opioid dose escalation may be a reasonable clinical strategy to overcome pharmacological tolerance, assuming there are no contraindications. On the other hand, if apparent opioid tolerance arises from OIH, opioid dose escalation could enhance the nociceptive process and worsen both opioid tolerance and pain. Indeed, clinicians frequently encounter the practical issue of how to distinguish OIH from a worsening pain state and opioid tolerance. Several clinical features of OIH may help clinicians make such distinctions.

**Clinicians frequently encounter the practical issue of how to distinguish opioid-induced hyperalgesia from a worsening pain state and opioid tolerance**

**Opioid-Induced Hyperalgesia Versus Preexisting Pain**

Features of OIH observed in preclinical and clinical studies might be helpful in distinguishing it from the underlying pain condition.

1) Opioid-induced hyperalgesia may differ from preexisting pain in its quality, location, and distribution pattern. The clinical hallmark of pathological pain is hyperalgesia in a dermatomal or generalized distribution. Quantitative sensory testing may reveal abnormalities in the threshold, tolerability, and distribution patterns of pain. A difference between neuropathic pain and OIH might be that for many neuropathic pain conditions, hyperalgesia arises in a distinct anatomical distribution, whereas OIH could be generalized in its distribution. This type of testing is in its infancy, but it may eventually reveal whether OIH is a completely separate phenomenon or can worsen existing neuropathic pain.

2) Opioid-induced hyperalgesia may intensify with opioid dose escalation but improve after supervised opioid tapering. In contrast, undertreatment of preexisting pain and pharmacological opioid tolerance may be overcome by a trial of opioid dose escalation.

**Influence of Opioid Regimens**

Opioid regimens may influence the development of opioid-induced pain.

1) Clinical observation suggests that the degree of OIH may vary with different opioids. For example, morphine is more likely to produce OIH than is methadone.

2) While the exact temporal relationship between the time course of opioid therapy and the development of OIH is unclear, it is conceivable that OIH would be more likely to develop in patients receiving high opioid doses with a prolonged treatment course, although it has also arisen in patients receiving a short course of highly potent opioid analgesics. Patients who are receiving opioid therapy for neuropathic pain may be more susceptible to developing OIH because of the shared cellular mechanisms involved.

3) It may be possible to take advantage of cross-sensitivity to different opioids. That is, if OIH develops after treatment with one opioid, it is possible that switching to a different opioid might reverse it. This issue remains to be investigated.

**Patients who are receiving opioid therapy for neuropathic pain may be more susceptible to developing opioid-induced hyperalgesia because of the shared cellular mechanisms involved**

**Opioid-Induced Hyperalgesia and Preemptive Analgesia**

While the clinical relevance and effectiveness of preemptive analgesia in general remain debatable, one may argue against the use of opioids as the sole agent for preemptive analgesia for several reasons.

1) A large dose of intraoperative opioids could activate a pronociceptive mechanism leading to the development of postoperative pain sensitivity. This effect may confound the assessment of postoperative pain and counteract the opioid analgesic effect.

2) Preemptive analgesia calls for preemptive inhibition of neural plastic changes mediated mainly through the central glutamatergic system. Paradoxically, opioid administration could activate the central glutamatergic system, as discussed above.

3) Neural mechanisms of opioid tolerance and OIH may interact with the mechanisms of pathological pain, such that pathological pain can be exacerbated by opioid administration, at least in animal models.

**Increasing opioid dose may not always be the answer to ineffective opioid therapy, and under certain circumstances a smaller amount of opioid may lead to more effective pain reduction**

**Summary**

Clinicians should consider the possibility of OIH when contemplating an adjustment of opioid dose when (1) previous opioid dose escalation has failed to provide the expected analgesic effect and (2) there is an inexplicable exacerbation of pain after an initial period of effective opioid analgesia. Increasing opioid dose may not always be the answer to ineffective opioid therapy, and under certain circumstances a smaller
amount of opioid may lead to more effective pain reduction. This goal may be accomplished by using opioid rotation, adding adjunctive medications, combining an opioid with a clinically available NDMA-receptor antagonist, or initiating a trial of opioid tapering.\textsuperscript{12-26} Future studies, particularly in patients with chronic pain related to nonterminal diseases, are anticipated to further address this important issue of OIH and its implications for clinical opioid therapy.

Acknowledgment
This work was supported in part by NIH ROI grants DA08835, NS45681, NS42661, and DA22576.

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