

The Dilemma of Opioid-Induced Hyperalgesia and Tolerance in Chronic Opioid Therapy

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Sir,

Opioids have been used for decades and continue to be used to treat severe, acute, chronic non-cancer and cancer pain.^{1,2} They work mainly by inhibiting spinal cord neuronal transduction and the ascending pain signals at midbrain nuclei, and through the modulation of limbic system pain perception.³ The main opioids receptors are *mu* and *kappa* receptors.¹⁻³ The use of opioids can be challenging and not without severe or life-threatening side-effects.^{1,2} The World Health Organization (WHO) has recommended the adoption of a three-step analgesic ladder to meet the therapeutic challenges of administering opioids and to reduce the incidence of these side-effects. This can be achieved by starting with non-opioid analgesics followed by weak opioids with adjuvants, reserving strong opioids for cases of severe pain.^{2,3}

When we escalate the opioid dose without getting the expected clinical response, then we may face the dilemma of tolerance, which can be defined as a decrease in pharmacologic response following repeated or prolonged drug administration. In the case of opioids, patients may experience opioid-induced hyperalgesia (OIH), which is a state of nociceptive sensitisation caused by exposure to opioids that leads to an increased response to a stimulus which is normally painful.¹⁻⁴ In our practice, it is not uncommon to face this dilemma, especially during the management of patients who require long-term pain treatment with opioids.^{1,4} Although tolerance is faced frequently, we should not fail to recognise OIH by classifying all cases of poor response to escalating opioids as tolerance. In fact, much of the literature refers to the difficulty in differentiation between these two conditions.^{1,4} All patients with OIH have some sort of tolerance but the reverse is not true.^{1,2} Opioid-induced tolerance is rarely a limiting factor during opioid therapy in clinical practice and should not delay the start of treatment or dose escalation in patients with chronic pain.³ We should not refer to every pain-worsening during the course of therapy, as tolerance unless a detailed clinical evaluation fails to show any clear alternative cause.^{1,4} In OIH, the pain can become more widespread, occur in areas beyond the original pain location, and may be associated with allodynia. It occurs with various routes of administration, happening more frequently in intermittent boluses with cessation in between, than with continuous infusion.^{1,4} OIH is more evident with prolonged use of opioids. However, there is evidence of patients developing hyperalgesia after only short-term intraoperative opioids exposure.^{1,4,6}

The degree or gradation of opioid tolerance is generally related to duration of exposure, daily dose requirement, and receptor association/disassociation kinetics. The mechanism of opioid-induced tolerance may include, among other things, the desensitisation to, or internalisation of opioid receptors. This is marked by a decrease in opioid binding sites that are available to provide pain relief.¹⁻³ Another cause of tolerance is an increase in spinal cord concentrations of dynorphin, which promotes abnormal pain and acts to reduce the antinociceptive efficacy of spinal opioids.^{2,3} The sensitisation of N-methyl-D-aspartate (NMDA)-sensitive glutamate receptors may play a role in opioid-induced tolerance. This is evident as NMDA-antagonists like ketamine can attenuate tolerance development and decreases in dosage, which may delay the onset of tolerance.⁵

The mechanism of OIH is complex and not always clear. Usually more than one mechanism is involved.⁴ In OIH, five possible mechanisms are involved, including activation of the central glutaminergic system;

an increase in spinal dynorphins; activation of descending facilitation due to neuroplastic changes in rostroventral medulla; genetic mechanisms, and decreased reuptake of excitatory neurotransmitters and an enhanced nociceptive response. Among these five mechanisms proposed to explain OIH, the activation of NMDA-sensitive glutamate receptors is the most common possibility.^{1,4} Prostaglandins and cytokines might also be relevant to the development of OIH.²

As a rule, when it comes to tolerance, the increase in pain should be overcome by increasing the dose, thus providing a mode of easy diagnosis.^{2,3} While the diagnosis of OIH might not be straightforward, in general, if the opioids dose-reduction results in an improvement in pain control, OIH is the most likely cause. If the pain worsens, then opioid tolerance is the most likely cause.^{1,3,4} Quantitative sensory testing (QST), which is used to assess neurological function in chronic pain patients, can also be helpful in predicting OIH. It is performed before the initiation of opioid treatment and then repeated at certain intervals. Any changes in pain threshold upon QST can suggest OIH if other causes have been excluded.^{1,4}

Tolerance can be treated by increasing the opioid dose. The addition of adjuvant medications like non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressant (TCA), pregabalin and others may be effective in reduction of the required opioids and delay in occurrence of tolerance.^{2,3} Ketamine has a dual action here as it can be used as an analgesic in low doses in addition to the NMDA antagonist effect, which can attenuate receptor sensitisation and hence, the development of tolerance.^{3,5}

OIH treatment is much more complex and requires a specific strategy which may vary from one patient to another.^{1,4} This can be difficult, time-consuming, and even impractical.¹ Practically speaking, opioid reduction might induce withdrawal symptoms, which can include an increase in pain.^{1,4} That increase in pain will mask the clinical picture and make the differentiation more difficult.^{2,4} The long course of weaning which is required for those patients can cause frustration and they may give up and stop the process. This type of treatment may also require special institutes.¹ Several drugs have been used to reduce the possibility of developing OIH, especially when opioid dose-reduction is not accepted or tolerated by the patient.^{4,6} Evidence showed that low-dose ketamine, an NMDA-receptor blocker, can modulate OIH.^{1,4-6} Methadone, which is a weak NMDA-receptor blocker and buprenorphine, which is a partial opioid *mu* agonist, can play roles in the treatment of chronic pain and OIH.^{1,6} Buprenorphine is an opioid partial agonist with a maximal effect which is less than that of full agonists. Buprenorphine is efficacious for longer-term opioid maintenance with a lower risk of abuse, addiction, and side effects as compared to full opioid agonists. Possible antihyperalgesics mechanisms include kappa-receptor antagonist properties and voltage-gated sodium channels blockade effects. It is an effective opioid detoxification agent with an equivalent or even better effect than methadone. Formulations for opioid detoxification treatment are in the form of sublingual tablets as they have very poor bioavailability. Transdermal patches are also available in Europe and North America for treatment of chronic pain.^{1,6}

Other approaches may include adding NSAIDs (especially COX-2 inhibitors) as an adjuvant which may provide opioid-sparing effects in addition to modulating sensitised receptors by blocking prostaglandins.⁶ Anti-epileptic therapy (gabapentin or pregabalin) and α -2 receptor agonists (clonidine) can also attenuate chronic pain and reduce OIH.^{1,4,6} Opioid rotation is another strategy that can be used to overcome OIH.⁶

Finally, we can conclude that although opioids are widely used in the treatment of pain, especially chronic pain, they cannot be free of side-effects, including serious ones. OIH is one of these side-effects which may contribute to patient discomfort and carry harmful consequences if they are not diagnosed and treated. It is not uncommon to misdiagnose OIH as opioid-induced tolerance, although the treatment modalities may be different. Adding analgesic adjuvants like ketamine, COX-2 inhibitors, or gabapentinoids can reduce the required dose of opioids and attenuate both OIH and tolerance.

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