Review Article

Hyperalgesia Induced by Opioid Drugs

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Abstract

Opioid analgesics are very potent and efficacious drugs used both for acute and chronic pain conditions. When used for chronic pain like cancer pain, they have to be given for prolonged time period. Prolonged therapy is associated with many serious problems like drug dependence, addiction and less known hyperalgesia. Opioid induced hyperalgesia (OIH) manifests as increased pain experienced by the patient and is differentiated from development of tolerance by increasing the dose of the opioid drug. Patient with tolerance obtains relief on increasing the dose but not one with hyperalgesia. The concept of OIH has been known since 19th century and scientists focused on finding clinical evidences of OIH as consequence of withdrawal and/ or maintenance therapy. Now-a-days research is ongoing to find molecular basis of OIH and its management. Exact underlying pathophysiology is not known but many hypotheses are there with main focus being on opioid receptors, glutaminergic system, role of CGRP, substance P and dynorphins. Adrenergic system has also been found to be implicated in few studies. Treatment requires great patience on part of both physicians and patients. Treatment strategies include weaning off the patient from opioid and substituting with opioids having unique properties like methadone and buprenorphine. Other drugs which have been found to be effective are NMDA receptor antagonist ketamine, COX-2 inhibitors, and clonidine. Interventional pain management and behavioral therapy also play a role in OIH.

Keywords: Opioids, hyperalgesia, tolerance, NMDA receptor antagonist

INTRODUCTION

Opioid analgesics are the mainstay of pain management in conditions ranging from acute pain to chronic pain, including cancer pain. When used for chronic pain conditions like cancer pain, opioid analgesics have to be given for prolonged period of time. Chronic opioid therapy could paradoxically induce or sensitize patients to acute pain, a condition termed “Opioid-Induced Hyperalgesia” (OIH).[1,2] Data from animal and human studies have shown the evidence for opioid-induced analgesia. The clinical implications are that patients on high doses of long-term opioid pharmacotherapy can suffer exquisite acute pain after surgery

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and escalating the doses in chronic opioid therapy might cause OIH leading to a vicious cycle of increasing dosage and anxiety both for physician and patient.[3] OIH is often overlooked as a potential complication of opioid therapy.

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HISTORICAL CONSIDERATIONS

As early as the 19th century, OIH was observed in patients receiving morphine for pain. It was observed by Albutt in 1870 that a potent analgesic such as morphine could actually result in an increase in pain.[4] For more than a century, hyperesthesia or increased sensitivity to pain has been listed as one of the symptoms of opioid withdrawal. Rossbach[5] in 1880 also noted that, "when dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia, and irritability become manifest."

Six decades later, Himmelsbach gave a comprehensive description of the opioid abstinence syndrome and stated that "aching referred to the bones, joints, and muscles is probably the most common symptom of withdrawal."[6] With time, evidence accumulated showing that the administration of opioid analgesics leads to not only analgesia but to hyperalgesia also.[7]

Human studies demonstrated hyperalgesia in former opioid addicts maintained on methadone but not in controls who did not receive methadone or any other opioid drug.[8] In early to mid-21st century, in studies focused on opioid metabolites like morphine-3-glucoronide as causative factor of OIH, it was found that the metabolite led to CNS irritability and allodynia.[9]

DISTINCTION BETWEEN OPIOID TOLERANCE AND OPIOID INDUCED HYPERALGESIA

It is very important to differentiate between development of tolerance and OIH as clinically both manifest as increased pain experienced by patient.

Tolerance occurs when there is a progressive lack of response to a drug requiring increased dosing. It occurs partly due to enhanced rate of metabolism of opioids (Pharmacokinetic tolerance) but mainly due to cellular adaptation (Pharmacodynamic tolerance). Tolerance is exhibited to most actions including analgesic effect of opioids but not to constipation and miosis. As there is lack of efficacy of the drug, increasing the dose of opioid will overcome this problem i.e. patient will be relieved of his pain.

OIH is a state of nociceptive sensitization caused by prolonged exposure of opioids. The type of pain experienced might be same as underlying pain or might be different from original pain. It cannot be overcome by increasing the dose of the drug, on other hand increasing the dose will aggravate the pain. This pain is relieved only by decreasing the dose of opioid or completely stopping it.

SCIENTIFIC EVIDENCES OF OIH

a) Animal studies

For more than three decades, it has been recognized that systemic administration of

opioids to rodents can lead to a hyperalgesic response during withdrawal.

Early studies documented that such hyperalgesia can be observed after precipitating withdrawal with the injection of an opioid antagonist as well as during spontaneous withdrawal after cessation of opioid administration.[10]

OIH has been tested in rats and mice using different types of nociceptive stimuli like mechanical, thermal, electrical and chemical irritants and variable susceptibility was observed, with greatest seen with mechanical than heat stimuli.

Acute administration of opioids:

Administration of morphine, heroin, fentanyl in high doses within 1 hour in rats and mice evoked a consistent, biphasic and dose-dependent analgesic response. Intense analgesic effect was followed by mechanical hyperalgesia of two-three hours[11] but in one study after administration of high dose of fentanyl, hyperalgesia persisted for five days[12]. Similarly in another experiment administration of high dose of fentanyl after carrageenan induced paw oedema showed hyperalgesia associated with hind paw inflammation lasting for two to ten days.[13]

Chronic administration:

Many studies have also been conducted after chronic i.e. 3-12 days administration of opioids by repeated subcutaneous administration, intermittent or continuous infusion through indwelling intrathecal catheters, or implantation of subcutaneous pellets or pump. When given by continuous infusion, opioid initially produced analgesic effect followed by loss of effect or hyperalgesia during ongoing drug administration.[14] Animals being given repeated systemic or intrathecal opioids developed progressive hyperalgesia to thermal or mechanical stimuli.[15]

Celerier et al noted an interesting finding that animals with normal nociceptive response and after recovering from OIH exhibited recurrent hyperalgesia when given single bolus of opioid agonist or antagonist. This experiment gave an important insight into mechanism of OIH that endogenous opioid peptides oppose hyperalgesia as administration of opioid antagonist unmasked it and also implies that resolution of OIH occurs due to upregulation of descending inhibitory pathways which opposes activity of sensitized excitatory pathways.[14]

b) Clinical evidence

Many studies have been carried out in different clinical scenarios to decipher the clinical significance of opioid induced hyperalgesia.[16]

1. Opioid addicts: Opioid addicts being maintained on methadone have been tested for pain sensitivity to various kinds of pain viz electrical, thermal and mechanical. These individuals showed increased pain sensitivity to thermal stimuli in comparison to mechanical or electrical one. These studies suggest that OIH develops differently for various types of pain.[17]

2. Perioperative exposure to opioids: Two prospective controlled clinical studies have reported increased postoperative pain in patients who were given high doses of opioids during surgery.[18] In contrast other studies have shown no significant difference in postoperative

pain sensitivity because of intra operative opioid use.[19]

3. Healthy volunteers: Several studies have examined the development of OIH in humans after acute short-term exposure to opioids. Multiple investigators, have provided direct evidence for development of OIH in humans using models of secondary hyperalgesia and cold pressor pain.[20]

4. In chronic pain patients:

   Hay et al.[21] in an observational report found that patients with chronic pain management with opioids, and methadone-maintained patients were hyperalgesic when assessed by the cold pressor test. However, there was no allodynia.

   Cohen et al.[22] evaluated 355 patients on a steady regimen of analgesic medications and scheduled for an interventional procedure and who were treated with a standard subcutaneous injection of lidocaine prior to a full dose of local anesthetic. The results showed that both opioid dose and duration of treatment directly correlated with pain intensity and unpleasantness scores compared with patients not receiving opioid treatment. Patients receiving opioid therapy were more likely to rate the standardized pain stimulus as being more unpleasant than painful.

   Other studies suggests that the short-term infusion of opioids like the μ-opioid receptor agonist remifentanil, followed by abrupt cessation, exacerbates preexisting hyperalgesia.[23]

5. On administration of very low dose of opioids: Limited data are available, one study demonstrated biphasic effect of morphine in former opioid addicts given morphine.[24]

6. Administration of very high dose of opioids: OIH has been commonly reported in patients receiving high doses of opioids most commonly morphine systemically or intrathecally. Other scientists[25] have reported that OIH caused by high dose of opioids is mediated by non-opioid receptors like NMDA.

MOLECULAR BASIS OF OIH

The precise mechanism underlying OIH is yet not completely understood. It is thought to result from neuroplastic changes in the peripheral and central nervous system that lead to sensitization of pronociceptive pathways.[2] Various proposed mechanisms for OIH are described below:

1. Opioid receptors: Both mu and kappa receptors have been implicated in OIH. Different mu receptor agonists mainly morphine[26] but also fentanyl[27], heroin[28], pentazocine, and nalbuphine elicit OIH. CXBK mice-a strain of mice having mu opioid receptors in very low density, do not develop OIH when compared with wild-type mice.

   Kappa receptor agonists have also been implicated in analgesic as well as hyperalgesic effects.[29] Intrathecal injection of kappa receptor agonists in lumbar region resulted in thermal and mechanical hyperalgesia and aggravated allodynia in dogs, guinea pigs and rats in acute and chronic pain models.[30] Microinjections of kappa agonists in rat brain stem resulted in heat hyperalgesia

at mesencephalictegmentum but analgesic effect at lower medulla.[31] Blocking endogenous kappa agonist dynorphin at the level of mesencephalictegmentum enhanced analgesic effect.[32] Mu agonists produce biphasic response i.e. analgesia followed by hyperalgesia however kappa agonist produce only monophasic response either analgesia or hyperalgesia. Above studies were conducted after intrathecal or spinal administration of opioids, similar results were also seen after systemic administration, the most commonly used route for researches on OIH.

2. Glutaminergic system: Excitatory neurotransmitter NMDA plays central role in OIH as well as tolerance, its inhibition prevent development of both the conditions. Evidences favoring the hypothesis are following:

   - Mao et al in a rat experiment demonstrated that repeated intrathecal administration of morphine for eight days resulted in development of thermal hyperalgesia as well as tolerance and co-administration of MK-801, a NMDA receptor antagonist or antagonist of non-NMDA receptor fully abolished development of OIH and tolerance suggesting role of glutamate in both the phenomena. An important role of protein kinase C (PKC) was also seen as both the phenomena were also prevented by PKC inhibitor-GM1 ganglioside. Administration of opioid evoked OIH in wild type mice but not in mice lacking PKC gene.[33]

   - Dunbar et al demonstrated that NMDA receptor antagonists reduce thermal hyperalgesia caused by administration of morphine intrathecally.[34]

     Chronic intrathecal morphine administration has shown increased levels of glutamate in spinal cord tissue.[35] This increased levels may be due to decrease in activity of glutamate transporter by opioids.[36]

   - Intrathecal administration of glutamate as well as substance P in mice chronically exposed to morphine evoked exaggerated pain response.[37]

     Repeated morphine administration has shown increased expression of CGRP (calcitonin gene related peptide) and substance P in dorsal root ganglia.[38]

3. Involvement of brain stem: experiments conducted by injecting local anesthetics in ventromedial medulla or surgical leisioning of dorsolateral funiculus have demonstrated that descending pain facilitating pathways play a role in OIH.[39]

4. Levels of spinal dynorphins have also been found to increase with continuous infusion of mu receptor agonists which cause further release of CGRP from primary afferents.[40]

5. Chronic exposure to opioids has shown enhanced expression and functioning of beta 2 adrenergic receptors in various nervous tissues.[41] Jensen et al described that functioning of descending pain facilitatory pathway is modulated by COMT enzymes, activity of which is

genetically influenced.[42]

6. Inhibition of P-glycoproteins, an important membrane transporter present in brain which effluxes out drugs including morphine and its metabolites, may also play an important role in induction, maintenance and severity of OIH.[43] This inhibition can result in high CSF levels of morphine and its metabolite.

7. Monoxide signaling pathway—in few studies it has been observed that blocking of monoxide signaling pathway like hemeoxygenase and nitric oxide synthase (NOS) reverses OIH in mice which had been chronically treated with morphine. Both these pathways have also been implicated in development of opioid tolerance and link has been found between NMDA receptor activation and enhanced NOS signaling underlying this phenomenon.[44]

DIAGNOSIS OF OIH

A major dilemma is faced by the pain practitioner in the diagnosis of OIH and differentiating it from tolerance. Thus, it is a challenge to distinguish between the two, since treatment of each is different. In addition, the clinician must be able to distinguish among OIH, progression of the disease process, interval injury, and clinical exacerbation of preexisting pain.

OIH typically produces diffuse pain, less defined in quality, which extends to other areas of distribution from preexisting pain. OIH will exacerbate a preexisting painful condition and therefore will increase pain intensity above the preexistent pain levels. If the preexisting pain is undertreated or if pharmacologic tolerance exists, then an increase in opioid dose will result in reduction of pain. Conversely, OIH would be worsened with increasing opioid dose.

TREATMENT

Once diagnosis of OIH has been made, treatment requires time, patience and complete faith of patient on his physician. Firstly patient has to be weaned off from high dose of opioids and while reducing the dose patient may experience transient increase in pain or mild withdrawal symptoms. Hyperalgesia is abolished only when critical level of opioid is reached.

Treatment includes:

- Reduction in opioid dose
- Switching to opioid with unique properties like methadone, buprenorphine
- Use of drugs with NMDA receptor antagonistic properties
- COX-2 inhibitors,
- □2 receptor agonists
- Interventional pain management strategies
- Behavioral therapy

1. Reduction in opioid dose and switching to opioid drugs with unique properties:

   The dose of opioid being administered to the patient is reduced by 40 to 50% and methadone is added in low dose.[45] Methadone, although a pure μ-receptor agonist, has some unique properties that prevents and reduces OIH. It is a racemic mixture in which the d-isomer is an NMDA receptor antagonist.[46] However, methadone itself can also cause OIH47, which may also limit its role.

   Buprenorphine has also shown an enhanced ability to treat hyperalgesia experimentally induced in volunteers compared to fentanyl.[47] It is a partial

opioid agonist with antagonist properties which has been used for decades in anesthesia and for the treatment of pain.48 In addition, spinal dynorphin, a known kappa receptor agonist, increases during opioid administration and contributes to OIH. Buprenorphine is a kappa receptor antagonist hence may be effective in OIH.

2. **NMDA receptor antagonists:** Ketamine has been used to treat OIH and as an adjuvant to opioid therapy for the treatment of chronic pain. It is an NMDA receptor antagonist and has known intrinsic analgesic properties.[49]
3. **COX-2 inhibitors:** Prostaglandins have known to stimulate release of excitatory amino acid glutamate in spinal dorsal horns.[50] COX inhibitors have been shown to antagonize NMDA receptors in CNS.[51] Thus it has been hypothesized that COX inhibitors by inhibiting prostaglandin synthesis in the spinal cord might inhibit OIH by modulating NMDA receptor functions.
4. **α2 receptor agonists (clonidine):** Though animal studies provide contradictory evidence for the ability of □2 receptor agonists to attenuate OIH, human studies have shown that clonidine does prevent expression of OIH in human experimental pain models after acute opioid exposure.
5. **Interventional pain management:** These include epidural steroid injection, intradiscal steroid injection, chemonucleolysis, radiofrequency denervation, spinal cord stimulation, percutaneous adhesiolysis and many more reduce or completely abolish the need for drugs.[52]
6. **Behavioral therapy:** Cognitive behavioral therapy has been found to be effective chronic pain conditions like low back ache.[53]

CONCLUSION

Chronic opioid therapy is associated with many problems like drug dependence, addiction and abuse. OIH is less recognized consequence of chronic opioid therapy. The disappearance of opioid treatment effects coupled with unexplained increase in pain complaints should raise suspicion of OIH. In this setting, slowly weaning off from opioid used and careful administration of non-opioid drugs can provide relief.

Before initiating opioid therapy, OIH should be addressed with the patient as part of comprehensive informed consent.

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