Opioid-induced hyperalgesia

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Key points

Opioid-induced hyperalgesia (OIH) is a phenomenon observed in patients treated with opioids, who paradoxically demonstrate an increased sensitivity to painful stimuli.

Pain is associated with hyperalgesia, allodynia, or both; may be experienced in a different location; and of a different quality than the original pain.

N-methyl-D-aspartate receptor activation may have a central role in the development of OIH.

Quantitative sensory testing for the diagnosis is still limited to research.

Diagnosis and management of OIH is challenging, and requires a skilful multimodal approach.

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Opioids are a widely used pharmacological therapy for moderate-to-severe pain. Their use in the management of chronic non-cancer pain has escalated in recent years, particularly in North America. This escalation has posed many challenges for prescribers such as lack of long-term effectiveness, misuse and abuse, and the occurrence of adverse side-effects. The effectiveness of high-dose opioids can be diminished by two clinical occurrences, which are difficult to distinguish clinically: *opioid tolerance and opioid-induced hyperalgesia (OIH)*.

OIH is a phenomenon observed in patients treated with opioids who paradoxically demonstrate an increased sensitivity to painful stimulus. In contrast, opioid tolerance occurs when prolonged exposure to opioids results in a shift of the dose–response curve to the right; in other words, a larger dose of opioid is needed over time to produce the same level of analgesia.

Chronic opioid exposure may lead to two interrelated outcomes; a desensitization process which leads to reduced clinical efficacy of opioids, and a sensitization process which can facilitate nociception, thereby counteracting the opioid's analgesic effect.[1]

Clinical evidence

Clinical evidence of OIH has primarily come from observational studies of patients exposed to long-term methadone maintenance therapy for the treatment of substance dependence. Patients in this group have shown an increased sensitivity to cold pressor pain when compared with former patients who were no longer using methadone or healthy controls.[2] In a separate prospective preliminary study involving patients with chronic low back pain, researchers have shown significant reduction in pain threshold and pain tolerance after 1 month of initiating oral morphine therapy.[3]

In addition, there have been a significant number of studies that have demonstrated the development of OIH in patients exposed to opioids for short duration. This occurrence has been documented in the perioperative period and also in studies recruiting healthy volunteers who have been acutely exposed to opioids in experimental settings.[4] In one particular study, patients exposed to intraoperative fentanyl and remifentanil reported increased postoperative opioid requirements, suggesting the development of either tolerance or hyperalgesia.[5]

Clinical features

OIH can clinically manifest as hyperalgesia (increased response to painful stimuli), allodynia (painful response to normally innocuous stimulus), or both. Pain is typically described in an anatomically distinct region and is of a different quality than the original pain presentation. The important dilemma facing the clinician in making a diagnosis is to distinguish OIH from other phenomena such as opioid tolerance, disease progression, opioid withdrawal, opioid addiction, or pseudo addiction. Table 1 presents an overview to assist in differentiating these conditions.[6,7]

Opioid receptor physiology

There are four types of opioid receptors recognized by the International Union of Pharmacology: MOP (μ-opioid peptide receptor), DOP (δ-opioid peptide receptor), KOP (κ-opioid peptide receptor), and NOP (nociception/orphanin FQ peptide receptor). These receptors are distributed widely in the brain, spinal cord, peripheral afferent nerve terminals, and other organs. The rostral ventral medulla (RVM) and periaqueductal grey areas of the brainstem also express particularly high levels of opioid receptors.

Opioid receptors are coupled with inhibitory G-proteins and their activation leads to closing of voltage-sensitive calcium channels and stimulation of potassium efflux. These changes lead to hyperpolarization, thereby reducing neuronal excitability and nociceptive afferent transmission.

Investigations have revealed that in addition to these inhibitory effects, opioid receptors can

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Table 1 Differential diagnosis for OIH[6,7]

Condition	Clinical features	Onset	Response to opioid treatment
Opioid-induced hyperalgesia (OIH)	Characterized by a paradoxical increase in pain associated with allodynia and hyperalgesia. Pain may occur at a different location and can be widespread. It is usually poorly defined in terms of region and quality	Abrupt or gradual	Pain worsens
Opioid tolerance	Characterized by persistent pain and is localized. Tolerance may occur to therapeutic or side-effects	Gradual	Pain improves
Disease progression	Pain gradually worsening despite being on opioids. Pain may be present in other than original site	Gradual	Pain improves
Opioid addiction	It is characterized by behaviour that includes impaired control and compulsive use of the drug, continued use despite harm, and craving. Pain may or may not be present	Gradual	Pain may improve, but aberrant behaviour may worsen
Pseudo-addiction	Characteristically occurs when pain is under-treated, resulting in patients seeking opioids for pain relief. It is usually mistaken for addiction. Pain presents at the original site	Variable	Pain improves
Opioid withdrawal	Characterized in the acute phase by adrenergic symptoms such as tachycardia, hypertension, and sweating. Flu like symptoms associated with abdominal pain and diarrhoea can also be observed. Pain sensitivity increases and distribution of pain may extend beyond that of the pre-existing pain	Abrupt	Pain improves
Physical dependence	Characterized by a state of adaptation with chronic opioid use, which results in tolerance and even physical withdrawal symptoms when the drug is abruptly stopped or dosage reduced Pain presents at the original site	Gradual	Pain improves

also have excitatory effects on cells. *In vitro* studies have shown that excitatory actions of morphine can be observed at doses 1000-fold smaller than clinical doses. This has supported a theory of bi-modally acting opioids. In clinical settings, this excitatory function is masked as the high doses in clinical use activate inhibitory functions. This mechanism of stimulation has been postulated to involve G-protein-linked secondary messenger signalling pathways, which are excitatory in function.[8]

A number of different opioid molecules exist (morphine, fentanyl, buprenorphine, etc.), which have different selectivities for opioid receptor subtypes. This explains the phenomenon of incomplete cross-tolerance, which may be used to overcome opioid tolerance by using opioid rotation strategies.

Mechanism and pathophysiology

The exact mechanism of OIH is not clearly understood. However, several theories exist which are briefly summarized below.

Central mechanisms

Central glutaminergic system

Glutamate is thought to play a central role in the development of OIH. Acute and chronic opioid use increases *N*-methyl-D-aspartate (NMDA) receptor activity, which can be prevented through NMDA receptor antagonism. Mao and colleagues[9] have shown that prolonged morphine administration induces down-regulation of spinal glutamate transporters in the spinal cord, leading to increased glutamate levels available for NMDA receptors. Glutamate-associated activation of NMDA receptors can cause spinal neurone sensitization, possibly contributing to the development of OIH. This phenomenon has been prevented by NMDA receptor inhibition.

Spinal dynorphins

Dynorphins are opioid peptides, which have been shown to increase with continuous infusions of μ-receptor agonists. These increased levels of dynorphins lead to the release of excitatory neuropeptides such as calcitonin gene-related peptide (CGRP) from primary afferent neurones and cholecystokinin (CCK) from neurones. These excitatory neuropeptides act as pronociceptive agents that enhance nociceptive inputs at the spinal level.[10]

Descending facilitation

Subsets of neurones within the RVM can mediate nociceptive transmission. These cells are identified as *on cells* (ON), which facilitate incoming pain signals and *off cells* (OFF) which inhibit pain signals. Descending facilitation mediated by opioid-sensitive ON cells in the RVM may promote spinal nociceptive processing and thus contribute to OIH.[4]

Change in opioid receptor responsiveness

Chronic exposure to opioids may alter G-protein activity, such that the G-protein second messenger systems are converted from an inhibitory to an excitatory-coupled mode via alteration in a specific glycolipid complex on the neuronal cell membrane. This increase in excitatory activity has emerged to be a possible contributor to analgesic tolerance and OIH. *In vitro* studies have demonstrated that when opioids are combined with ultra low doses of an opioid antagonist, excitatory effects can be blocked.[11]

Peripheral mechanisms

Activation of serotonergic ($5HT_3$ and $5HT_2$) receptors in certain chronic pain states may be involved in the development of OIH by shifting the balance from descending inhibitory control towards

pro-nociception. In animal models, ondansetron, a $5HT_3$ antagonist, can block the signs of OIH.

Activation of Substance P, alteration of cytokine production, and changes in calcium channels and nitric oxide synthetase have all been implicated in the development of OIH in various studies.[11]

Investigations

Quantitative sensory testing

Quantitative sensory testing (QST) is a pain assessment tool that is being investigated as a modality to diagnose OIH. QST involves application of different mechanical and thermal stimuli of controlled intensity to measure an individual's pain threshold. Testing assesses the function of Aβ, Aδ, and C nerve fibres and also central pain processing pathways. It has been utilized in the diagnosis of painful conditions such as peripheral neuropathies and radiculopathies.

In patients managed with long-term opioid therapy, QST has demonstrated changes in their perception of pain. For example, individuals with histories of opioid abuse being treated with methadone have shown reduced pain tolerance and enhanced sensitivity to cold pressor stimuli when compared with QST responses in control subjects.[2]

In the laboratory setting, QST has been used to assist in the identification of remifentanil-induced hyperalgesia. For example, Compton and Athanasos[12] could document changes in QST scores between an individual's baseline pain sensitivity and the pain sensitivity at repeated intervals after a dose of remifentanil.

There is accumulating evidence that the use of QST may help to identify development of OIH. However, the nature of test results can vary depending on the modality of testing used (e.g. electrical stimulation or cold pressor test) and other factors such as opioid serum concentrations. Further work will be needed to refine these tools before they can be used for widespread clinical use.

Management options

Strategies to minimize the development of OIH

Reducing the total dose of opioid being consumed can mitigate OIH. This can be accomplished by improving analgesia through the use of co-analgesics and interventional strategies as discussed below.

Pharmacotherapy

This can include the combination of anticonvulsants, antidepressants, and non-steroidal anti-inflammatory drugs (NSAIDs), as appropriate, for treating patients with neuropathic pain or nociceptive pain. These opioid-sparing therapies form the basis for the prevention of opioid-related adverse effects.

Interventional therapy

Interventional therapies can block nociceptive input and often serve a dual function of assisting in diagnosing pain generators and providing therapeutic benefit. Regional blocks, peripheral nerve blocks, and spinal cord stimulation can be considered as alternative management strategies for chronic painful conditions in lieu of or in conjunction with oral analgesics.

Psychological therapy

Studies have shown that cognitive behavioural therapy can be an effective treatment strategy in patients with chronic pain conditions. With psychological interventions, pain and disability may improve, leading to opportunities to reduce opioid dosages.[13]

Strategies to manage symptoms once OIH occurs

An important aspect in the management of OIH is to establish the diagnosis. An initial step to consider is to increase the dose of opioids and evaluate for increased efficacy. If pain is reduced with the increased dose, this suggests the presence of opioid tolerance rather than OIH. Alternatively, if the pain worsens, this may suggest that the patient is experiencing OIH. The following pharmacological strategies can help to manage OIH. Table 2 also gives a brief summary of treatment options available.

Opioid dose reduction

A reduction in the dose of opioid may lessen hyperalgesia and improve pain scores. Although it may seem a counterintuitive course of action, various case studies in the literature have successfully used this strategy. One strategy reported uses an opioid dose reduction of 40–50% and substitution with low-dose opioid agonist such as methadone.[14]

Opioid rotation/switching

Exposure to a new opioid may recapture the efficacy of opioid analgesia in a patient who has developed tolerance to one particular opioid.

Equi-analgesic opioid dosing charts can be used to assist in calculating doses that will provide approximately the same analgesic response based on potency and bioavailability. When converting patients from one opioid to another, a suggested protocol is to decrease the dose of the new opioid by 25–50% to account for incomplete cross-tolerance. The dose of the new opioid can be titrated upwards if the pain is worsened or inadequately controlled.

Table 2 Summary of treatment options for OIH

Increase the opioid dose and evaluate for tolerance
Reduce or discontinue the opioid and evaluate for OIH
Consider opioid rotation, by using opioids with unique properties that might mitigate OIH, for example, fentanyl, buprenorphine, methadone
Consider adding medication with NMDA receptor antagonist, for example, ketamine
Consider other opioid-sparing medications such as antidepressants, anticonvulsants, and NSAIDs
Consider non-pharmacological interventions, for example, physical therapies, psychological therapies, or interventional therapies including spinal cord stimulators

Commonly used drugs in opioid switching are fentanyl, methadone, and buprenorphine. There are no well-designed studies that have evaluated the benefits and harms of opioid rotation.

Fentanyl

An opioid rotation from a phenantherine derivative such as morphine to a piperidine derivative, fentanyl may be helpful for some patients exhibiting tolerance. The physicochemical properties of fentanyl make it an ideal drug to be delivered via transdermal route. It has a low molecular weight, high lipophilicity, high potency, and optimal skin flux.

Buprenorphine

Buprenorphine is considered another possible option, because of its highly lipophilic and unique properties such as partial agonism at μ-receptor and antagonism at κ-receptor. Buprenorphine may be effective in managing symptoms of OIH, as it counteracts the effects of spinal dynorphins (known κ-receptor agonists), which increase during opioid administration. It is available as transdermal patch or in sublingual form and has also been used, as 'Office based detoxification' for supervised withdrawal from opioid and breaking the cycle of pain and hyperalgesia.[13]

Methadone

An opioid rotation to methadone may help to improve OIH through its ability to act as an NMDA receptor antagonist in addition to its opioid receptor agonism and norepinephrine and serotonin reuptake inhibition. The other advantages of this drug include its incomplete cross-tolerance with opioid receptors, relatively long half-life (24–36 h), fewer variations in plasma concentrations compared with short-acting opioids. The main disadvantages of this drug are that drug interactions are more frequent than with other long-acting opioids, and the conversions from one opioid to methadone are complex and require experience.

NMDA receptor antagonists

Ketamine

Ketamine exerts its analgesic effect primarily by non-competitive antagonism at the NMDA receptor. It has shown some beneficial effects in patients requiring large doses of opioids for analgesia or for those exhibiting opioid tolerance in the perioperative setting.

Its use in a chronic pain setting has been explored particularly for neuropathic pain and it has been administered through various routes, doses, and regimes.

Ketamine is available as a racemic mixture or as the *S*-ketamine isomer. In an evidence-based review of ketamine for chronic pain management, Hocking and Michael[15] have suggested that an i.v. or subcutaneous administration, in the range of 0.125–0.3 mg kg h^{-1}, is considered to be optimal. There are various other studies, which had used either much higher doses or lower doses than this. As it provides short-term analgesia and requires intensive monitoring for infusions, there is an option to consider oral dosing for patients who respond to this intervention. This must be produced by a compounding pharmacist as there is no commercial producer.

For patients naive to ketamine, the recommended oral administration is to start with a single dose of 0.5 mg kg^{-1} of racemic mixture or 0.25 mg kg^{-1} *S*-ketamine and evaluate the analgesic response and duration. The dosage can be further increased in steps of 0.5–0.25 mg kg^{-1} according to the response including any adverse effects. The mean effective dose available from the literature is 200 mg day^{-1}.[15] It has a poor bioavailability of only 16% and it is metabolized to nor-ketamine, a pharmacologically active metabolite. The doses are frequently adjusted to 3–4 times per day in clinical studies to correlate with the half-life of ketamine of 2–3 h and nor-ketamine of 4 h. Overall, orally administered ketamine is a pharmacotherapeutic option, but is not comprehensively studied and its use is limited because of undesirable psychotropic side-effects, lack of available commercial oral preparations, and its potential for abuse. Its routine use is not promoted, but it may have a role in managing cases that are particularly difficult to treat.

Dextromethorphan

This drug is a non-competitive NMDA antagonist. It can influence peripheral pain transmission at the spinal NMDA receptors. There have been a number of studies looking at the ability of dextromethorphan to suppress OIH, but none has demonstrated any clinically significant effects.

Practical considerations

There are some important practical considerations to be acknowledged while evaluating and treating patients for suspected OIH with chronic pain. The process can be time-consuming and challenging. Titration of existing opioid doses may reveal patterns of improving or worsening hyperalgesia if opioid doses are changed. Patients may also experience withdrawal if opioid doses are reduced, which can exacerbate pain. Careful documentation of dose alterations and patient responses with such a strategy is required to distinguish between various conditions.

In addition, weaning patients from high-dose opioids requires time and patience for all involved. The patient's quality of life can transiently worsen leading to distress and frustration with the process. Furthermore, titrating doses requires multiple visits, which can become impractical for patients. If such circumstances arise, discontented patients may elect to seek treatment elsewhere if they are struggling with changing opioid doses.

Conclusion

OIH is a recognized clinical entity, which challenges our long-held assumptions about the usefulness of opioids for pain. To differentiate whether worsening pain is due to disease progression or OIH

requires skilful application of a multimodal, patient-centred approach. At the moment, the best way to prevent OIH is judicious use of opioids in non-cancer pain-related conditions.

Declaration of interest

None declared.

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Please see multiple choice questions 21–24.