Opioid hyperalgesia

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Purpose of review

Opioids are invaluable in the treatment of moderate-to-severe pain. Unfortunately, their prolonged use may be associated with the onset of opioid-induced hyperalgesia (OIH). This review focuses on recent clinical studies that support or refute the existence of OIH in patients.

Recent findings

Whether or not OIH is a clinical reality is an ongoing debate. In recent years, the majority of clinical trials investigating whether chronic-opioid treatment causes paradoxical pain sensations have been conducted in opioid addicts, patients maintained on methadone and human volunteers receiving acute-morphine infusions. That opioid-maintained patients have different nociceptive profiles compared with opioid naïve patients has been both raised and rejected. Independent studies have reinforced the opinion that the development of OIH is based on confounders including pain modality tested, route of drug administration and specific opioid in question.

Summary

Improvements in paradoxical pain intensity upon discontinuation of opioid therapy suggests that a multidisciplinary method of pain relief is favoured for chronic-pain patients. Quantitative-sensory testing of pain is offered as the most appropriate way of diagnosing hyperalgesia. We can, thus far only reliably validate the existence of OIH development in normal human volunteers receiving acute-morphine infusions.

Keywords

clinical data, opioid, opioid-induced hyperalgesia (OIH), paradoxical pain

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Introduction

The worldwide population of patients with terminal cancer and consequently the requirement for palliative and hospice care is ever increasing as the global older population expands. Opioid medications remain the primary source of pain relief for chronic-cancer patients, and so the licit consumption of opioids grows continually. Today, opioids are also prescribed for the successful treatment of acute and chronic noncancer pain. Unfortunately, the unrivalled potency of opioid-induced pain relief may be limited according to the time required for treatment. As early as 1880, Rossbach concluded that 'opioid dependence is an illness itself' citing opposing opioid effects such as 'hyperesthesias and irritability' among the drawbacks of chronic-opioid consumption (translated by Angst and Clark [1]). Since then, laboratory and clinical reports have provided evidence of lowered pain thresholds and heightened atypical-pain sensations unrelated to the original nociceptive stimulus following prolonged opioid use. Increasingly candid reviews have concluded that the administration of opioids does typically result in analgesia [1] (which may be limited by the concurrent occurrence of effects opposing the analgesia). Thus, focus on mechanisms of opioid-induced hyperalgesia (OIH) could further optimize the usefulness of the prescribed opioid.

Changes induced by opioid therapy

The phenomenon of OIH, defined as the need for increasingly high levels of opioids to maintain pain inhibition after repeated drug exposure, is now becoming accepted as a clinical reality, although in many settings, increases in the underlying primary-pain generators could explain this need. However, accumulating evidence indicates that the onset of unexplained paradoxical pain sensitivity in humans receiving opioids, including hyperalgesia, is an unwanted side effect of chronic-opioid consumption alongside-physical dependence, addiction and tolerance. OIH thus proves an unfortunate obstacle in the clinical setting. Simply increasing opioid dose to overcome the complication of tolerance for example could paradoxically aggravate the problem of OIH.

Mechanisms of action of opioids in analgesia

The central nervous system (CNS) acts to maintain a state of homeostasis, in that excitatory events triggered

by activity in pain pathways can be counteracted by opioid inhibitions. In OIH, the opioids inhibition may be offset by compensatory excitations in those neural systems suppressed by opioids. The μ-opioid receptor system is suggested to play a pivotal role in OIH development [2]. Opioid drugs act on a family of receptors that, when activated, produce inhibitory effects on neuronal pathways in the CNS. In terms of clinical practice, the main action of drugs appears to be on the μ-opioid receptor, the receptor for morphine. The roles of the three first established receptors, the μ, δ and κ-opioid receptors, have been well investigated at spinal and supraspinal sites but there are differences in the consequences of receptor activation. For many years, alternatives to drugs that act on the μ receptor have been sought with the idea that agents acting on the δ receptor or the κ receptor may provide analgesia with a different side-effect profile as compared with μ ligands. However, none of these agents has reached the clinic. In more recent times, the opioid-receptor like receptor (ORL-1) has been reported to produce spinal analgesia but can act as an 'antiopioid' at sites in the brain [3].

The endogenous opioid peptides are the natural transmitters for the opioid receptors, with the endomorphins (acting on the μ receptor) and the enkephalins (δ) having clear controlling influences on the spinal transmission of pain, whereas the dynorphins (κ) and nociceptin (ORL1) have complex actions that can include enhancement as well as modulation of pain messages. Inhibitors of the degradation of the enkephalins have been produced in an attempt to enhance endogenous opioid controls, as the opioid peptides have rather transient actions in many cases. Thus, therapy involves exogenous drugs. As morphine acts on the μ receptor, as so do many clinically used opioid drugs, major emphasis is put on this receptor, which seems to be similar in structure and function in all species studied so that preclinical studies should be indicative of clinical practice. The detailed structure of these receptors has been described in full and some polymorphisms, substitutions of one amino acid for another, in the receptor have been reported to impact on opioid effects in clinical practice [4,5•].

μ Opioids act at a number of sites in the CNS and, in terms of analgesia, key sites of action of morphine are at spinal and brain stem/midbrain loci. Opioid receptors are also found at the highest centres of the brain but their contribution to analgesia is not well understood and may relate to cognitive and sedative effects of the drugs [3].

Opioid receptors are made in the dorsal-root ganglion of the C and A-δ fibres as well as by spinal neurones and are located presynaptically on the terminals of incoming pain fibres as well as on the spinal neurones that convey the pain messages onto the brain. As spinal neurones need to be activated by afferent-sensory fibres when the origin of the pain is peripheral, and then project to both cortical (sensory-discriminative aspects of pain) and limbic areas (affective components of pain), the ability of opioids to both block spinal inputs and outputs has a powerful effect on the pain experienced by a patient. Spinal actions of opioids are evidenced by the therapeutic effects of epidural or intrathecal opioids in the clinic [3].

Opioids also have actions on some of the descending pathways that run from the midbrain and brainstem and modulate spinal nociceptive function. Main transmitters in these pathways include noradrenaline, 5-hydroxytryptamine and endogenous opioids. Within the rostral-ventromedial medulla there are descending inhibitory and facilitatory pathways subserved by off-cells and on-cells respectively. Opioids switch off-cells on and on-cells off and so push the descending modulations towards inhibition. The spinal and supraspinal actions will both be brought into play when opioids are given systemically and likely synergize, as both anatomical actions lead to inhibitory function being enhanced at spinal levels [3].

Opioidergic-induced mechanisms, which could counteract analgesia and enhance pain sensitivity leading to OIH, have been shown to be located in afferent neurons, spinal-cord tissue and supraspinal centres of the CNS, the same areas where opioids reduce pain. This common location supports the idea of opposing compensatory changes behind OIH. Understanding the molecular mechanisms involved in the genesis of OIH will be paramount to devising ways of tackling the issue in the clinic. The neuronal mechanisms underlying OIH include NMDA receptor activation, increased spinal dynorphin content and evoked release of excitatory neuropeptides at spinal levels [6–9], and so, interestingly, appear to be similar to some of the mechanisms seen during the development of neuropathic pain at this level. Furthermore, neuroplastic changes resulting, in part, from activation and enhancement of descending facilitatory pathways from higher CNS centres to the dorsal horn of the spinal cord, may also support the manifestation of OIH [10,11]. Studies investigating the effects of sustained morphine exposure on animal behaviour have demonstrated the development of tactile allodynia and thermal hyperalgesia following intrathecal administration of an opioid μ agonist [12]. These data are in agreement with electrophysiological recordings showing signs of neuronal hypersensitivity following chronic-morphine exposure in rats [11]. Contrastingly, in an animal model of bone cancer, bi-daily systemic morphine infusions attenuated-pain behaviour [13], suggesting that the presence of a pain state to begin with may dampen down the otherwise ensuing paradoxical hyperexcitability caused by prolonged opioid exposure. The balance between facilitation and opioid inhibition within active-pain circuits may, in the presence

of hyperinhibition as might occur with chronic-morphine dosing in the absence of pain, be tipped in favour of facilitation causing OIH. Unfortunately, there is a dearth of data regarding the presence or lack of OIH in animal models of chronic pain.

Opioid-induced hyperalgesia

As well as elucidating the factors that underlie the pathology of OIH, collecting clinical evidence for, and defining, OIH in the human patient is crucial. The clinical characteristics of OIH are yet to be assigned and the context in which OIH is relevant is uncertain. Existing data so far suggest that former opioid addicts on methadone maintenance therapy, postsurgical-pain cohorts and human volunteers given acute-opioid infusions are settings that coincide with the development of OIH. Detecting OIH in chronic-pain patients is difficult and confounders are sure to include the opioid type prescribed, dose, and route of administration and whether or not the patient is hyperalgesic before opioid therapy. Other factors may include concurrent changes in the pain state, other therapies and possibly genetic polymorphisms in opioid-receptor function as well as other related neuropharmacological events.

The data available from human studies investigating dosing schedules in terms of OIH development are limited and conflicting. Prospective controlled clinical studies have reported increased postoperative pain despite increased postoperative-opioid use. A study investigating the effects of cumulative-morphine consumption in patients undergoing surgery found that a large dose of intraoperative remifantanil increased postoperative pain and morphine consumption [7]. In contrast, no increased pain or postoperative-opioid consumption in patients receiving intraoperative remifantanil during elective gyneacological surgery has also been reported [14], offering mixed support for the evidence of OIH development after acute-perioperative opioid exposure. The contradictory reports could have arisen due to differences in opioid dosing. Comparatively, the patients in the Cortinez study had lower total intraoperative-opioid exposure, suggesting that the development of OIH could be opioid-dose dependent.

Whether or not responses to noxious stimulation are different in chronic-pain patients who have been treated with or without chronic-opioid therapy is an important question. Opioid addicts are proposed to have an altered sensitivity to pain that is modality dependent but not associated with allodynia, rendering OIH in this population difficult to recognize and measure. A very recent study investigated whether pain sensitivity in noncancer chronic-pain patients taking methadone or morphine was similar to patients maintained on methadone for dependence therapy compared with opioid naïve individuals. Here, the nociceptive profile of the methadone or morphine-maintained patients was not significantly different to that of opioid-naïve individuals with regards to mechanical allodynia or electrical pain. However, a significant difference was apparent in opioid-treated patients compared with opioid-naïve individuals with the cold-pressor test [15••]. The modality specificity of increased sensitivity to pain, in particular the cold-pressor test, was in agreement with earlier studies where hyperalgesia to mechanically evoked pain was absent [16–18]. A study of three separate groups of patients, one with neither pain nor opioid therapy, one with chronic pain plus opioid therapy and one with chronic pain but minus opioid therapy, found that the group of patients with chronic pain plus opioid therapy had decreased heat-pain thresholds and increased temporal summation of secondary pain to thermal stimulation, with no differences in cold or warm sensation [19••].

Pain sensitivity to cold-pressor testing was previously measured in opioid addicts on day of admission, day 7 and day 28 subsequent to cessation of opioid consumption. A decrease in cold-pressor tolerance was observed consistent with the observations outlined earlier [20]. However, this 2006 study found no change in pain sensitivity after the 4 week period of opioid abstinence in the opioid addicts, contrasting with prior reports documenting increased pain tolerance and decreased pain sensitivity in opioid addicts abstinent for periods greater than 6 months [16]. The data suggest that OIH may be reversible but possibly requires a long period before the system is able to reset.

In contrast, a separate study in 2005 found no difference between opioid and nonopioid-treated patients in terms of thresholds for mechanical-punctate pressure pain or thermal pain, and provided no evidence for the development of OIH [21]. Whether or not the pain thresholds of chronic-pain patients treated with opioids are different to those who are not is inconclusive from the studies outlined and suggests that the development of OIH could be the result of other confounders in a population including genetics and expected or experienced pain. As the pain indices and modalities investigated were not the same [20,21], and since the oral route of administration could have influenced the lack of OIH development in the case of the Reznikov investigation, the studies are not directly comparable. This study aside, changes in pain threshold and tolerance are more likely observed than not alongside opioid therapy.

Prospective, randomized control studies allowing validation of clinical findings are likely to provide the most reliable source of information regarding the aetiology of

OIH. A preliminary prospective study performed in 2006 investigated a small number of patients with chronic lower back pain and used qualitative-sensory testing (QST) to document the possible development of OIH. One month of oral-morphine therapy for this patient cohort was associated with reduced tolerance to the cold-pressor test compared with results prior to the onset of opioid treatment [22]. Despite a sample size of only six and the lack of a placebo group, this prospective study documented the development of OIH in previously opioid-naïve chronic-pain patients, and suggested that this could occur within just 4 weeks of morphine exposure.

Studies in animals have shown delayed, long-lasting enhancement of pain sensitivity after opioid treatment. Does apparent OIH render the suffering patient susceptible to enhanced pain sensitivity even after opioid withdrawal and supposed recovery from OIH? An earlier study showed that animals apparently recovered from OIH remained sensitized to the hyperalgesic effects of opioids. As injection of an opioid antagonist in these animals 'unmasked' hyperalgesia, it was suggested that sensitization is likely opposed by an endogenous-opioidergic system [23]. The knowledge that OIH may be resolved because of upregulated inhibitory pathways opposing activity of sensitized excitatory pathways rather than desensitization of excitatory pathways could provide a tangible angle at which to treat the underlying neuronal mechanisms responsible in part for the development of OIH.

A retrospective study in 2008 analysed lower back chronic-pain patients who had undergone different types of lumbar-spine surgery. Improvements in paradoxical pain intensity upon discontinuation of opioid therapy in these patients led to the suggestion that a multidisciplinary approach to pain rehabilitation, which would incorporate opioid withdrawal, would provide the most effective method of pain relief in chronic-pain patients [24••]. Whether the pain improvement reflected the resolution of OIH, which was previously undiagnosed, is not known. A comparison group where medications were not tapered would have improved the ability to draw more conclusions from this study.

As the human mechanistic underpinnings of OIH are unknown, understanding the clinical ramifications of OIH is thus far impossible. QST is offered as the most appropriate tool for testing analgesic sensitivity in opioid naïve and opioid-maintained patients, which might help diagnostic improvement [25•]. The availability of prospective random control trials for chronic-pain patients on opioid therapy is limited. Ethical considerations mean that chronically administering opioids to healthy human individuals is unfeasible, and so validating whether or not OIH is a clinically meaningful symptom under long-term opioid treatment remains, so far, impossible.

Conclusion

A paucity of corroborating studies exists that either accept or refute the existence of OIH in humans. Prior investigations have evidenced that the strongest and most consistent data regarding the development of hyperalgesia following chronic-morphine dosing come from tests observing secondary hyperalgesia in normal human volunteers receiving acute-morphine infusions. This conclusion was reached in 2006 by Angst and Clark [1], and has been confirmed more rigorously very recently by Fishbain *et al.* [26••] who used Agency for Healthcare Policy and Research (AHCPR) criteria to determine quality scores for the investigations undertaken. The need for a prospective experimental set up which addresses the issues of selection bias and allows us to compare outcomes with patients who do not undergo opioid withdrawal has never been greater. Retrospective studies ultimately involve cohorts already exposed to opioids, disallowing the establishment of proof of a causal relationship between opioid usage and the development of OIH.

Until the existence of OIH is fully recognized and understood, both mechanistically and by the clinician, the usefulness of opioids could be suboptimal, and alternative methods of pain relief will continue to be sought. However, until an analgesic is found with comparably effective pain-relieving capabilities as the opioids, morphine will remain the gold standard against which other analgesics are judged and prescribed.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 46–47).

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