Review Article

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Opioid induced hyperalgesia in anesthetic settings

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Pain is difficult to investigate and difficult to treat, in part, because of problems in quantification and assessment. The use of opioids, combined with classic anesthetics to maintain hemodynamic stability by controlling responses to intraoperative painful events has gained significant popularity in the anesthetic field. However, several side effects profiles concerning perioperative use of opioid have been published. Over the past two decades, many concerns have arisen with respect to opioid-induced hyperalgesia (OIH), which is the paradoxical effect wherein opioid usage may decrease pain thresholds and increase atypical pain unrelated to the original, preexisting pain. This brief review focuses on the evidence, mechanisms, and modulatory and pharmacologic management of OIH in order to elaborate on the clinical implication of OIH. (Korean J Anesthesiol 2014; 67: 299-304)

Key Words: Hyperalgesia, Opioid Analgesics, Postoperative pain.

Introduction

Opioids have been increasing in usage and play an important role in every aspect of modern anesthesia. Among opioids, fentanyl, alfentanil, sufentanil, and remifentanil are commonly chosen for analgesia, sedation, hemodynamic stability, as well as attenuation of stress response during anesthesia. However, the administration of opioids has sometimes been found to induce unanticipated pain sensitivity changes, such as opioid-induced hyperalgesia (OIH) or tolerance. Hyperalgesia is defined as enhanced pain response to a noxious stimulus, in this case induced by opiate use. Although still being debated, the presence of OIH would be a clinical challenge not only in chronic cancer pain management, but also perioperative pain. In addition to OIH, administration of opioids may also tolerance, defined as a decreased response to the drug's analgesic effects over time, followed by loss of analgesic efficacy.

Although OIH is frequently conflated with opioid tolerance in the literature as the clinical features are similar, in fact they are different phenomena; Increasing opioid dose aggravates pain in OIH, whereas tolerance does not [1]. Thus, although the mechanisms underlying these two phenomena are likely distinct, they are clearly related and on the same continuum of pain sensitization processes.

The prevalence of OIH and tolerance related with opioids remains unknown, however, these states appear to occur have increased in frequency with the growing use of remifentanil [2]. Moreover, the clinical significance of occurrence of OIH or

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tolerance after perioperative use of opioid is been still under debate.

The aim of this review is to present a brief overview of OIH in the setting of surgical anesthesia. An understanding of current knowledge of potential OH mechanisms underlying OIH as well as the clinical implication should be helpful to clinical anesthesiologists in helping to plan better perioperative pain control strategies.

Evidence

Andrews [3] first reported reduced pain thresholds after morphine administration in opioid addicts in 1943. Similarly, Tilson et al. [4] first demonstrated that abrupt cessation of opioids induced decreased pain thresholds in rats and showed that this enhanced pain sensitivity was highly correlated with the administered dose of opioid. Other animal studies followed, [2,5-7] all supporting the occurrence of OIH. Consistent with these animal results, clinical investigators demonstrated the occurrence of OIH after intraoperative remifentanil infusion, characterized by increased pain, combined with increased consumption of postoperative opioid, which in turn, resulted in decreased opioid efficacy [8]. Moreover, significant pain reduction was observed after detoxification from high dose opioids which was observed in surgical patients also supports the existence of perioperative OIH [9]. Although there have also been numerous experimental studies in human and animals on OIH or opioid tolerance, the differentiation between them has been indistinct. Both OIH and tolerance are more evident in patients receiving a high rather that low intraoperative opioid doses. Pharmacologically, tolerance is characterized by a loss of drug potency, likely by means of a desensitization of the antinociceptive pathways to opioids, while OIH is characterized by increased pain sensitivity and involves sensitization of pronociceptive pathways, both phenomena resulting in increased dose requirements [10]. In despite of these clear differences in definition and mechanism, it is very complicated to differentiate them in clinically because the symptoms of both are somewhat relieved by increased doses of opioid. Quantitative sensory testing (QST) has been shown to be the most accurate means of differentiating OIH and tolerance, but the complexity of time-consuming process of QST limits its wide spread use [11].

Mechanism

The neurobiology of OIH is complex and several mechanisms for OIH have been proposed [8,12-14]. To date, activation of central glutaminergic pathways, mainly via N-methyl D-aspartate (NMDA) receptor, have been regarded as a key pronociceptive mechanism for inducing OIH. In an early study, Mao et al. [13,15] proposed that an increase in responsiveness of the NMDA receptor contributes to the development of opioid tolerance and hyperalgesia, as evidenced by his finding that the NMDA antagonist MK-801 prevented the development of OIH in rats. These concepts also supported by the finding that Ketamine, a clinically-used NMDA receptor antagonist, reduced fentanyl-induced hyperalgesia [12,16].

Descending spinal facilitation mediated via changes in activity of on- and off- cells within the rostro-ventral medulla (RVM) involving NMDA system comprises another suggested mechanism to explain OIH. These neurons, which project to the spinal cord and display changes in activity in response to noxious stimuli facilitate or inhibit nociceptive transmission respectively. Administration of μ-opioid receptor (MOR) ligands changes the circuit into the off-cell state, whereas the presence of a prolonged noxious stimulus changes it into an on-cell state [17]. Globally, OIH may partly result from an unbalanced activity of the off- and on-cells underlying the apparent development of tolerance. In support of this theory, Vanderah et al. [18] demonstrated that injection of lidocaine into the RVM or bilateral lesions of the dorsolateral funiculus blocked opioid-induced hyperalgesia and restored antinociceptive morphine potency.

The opioid receptor family, part of the large G-protein-coupled receptor (GPCR) family, consists of 4 different distinct receptors: μ, δ (DOR/OPRD), κ (KOR/OPRK1) and opioid receptor-like (ORL1/OPRL) receptor [19], all of which are present in nuclei of the pain modulation circuit [20]. MOR and DOR postsynaptically inhibit on-cells excitation [21]. In contrast, KOR agonists act presynaptically and ORL1 agonists act postsynaptically to inhibit both on- and off-cells in the RVM. When morphine is administered systemically or into the periaqueductal grey matter, the on-cells become silent and the off-cells fire continuously. In this off-cell state, dorsal horn neurons and withdrawal reflexes are inhibited. This inhibition is reversed by inactivation of the RVM or selective inhibition of off-cell firing. In the off-cell activated state, microinjection of either an ORL1 or a KOR agonist will inhibit off-cells and has anti-analgesic action.

Adrenergic and opioid receptors both belong to the GPCR family, couple to analogous signal transduction pathways, and affect the nociceptive system. Various biochemical studies have proposed the existence of GPCR dimerization, which may facilitate transport of receptors to the cell surface and G protein coupling and activation. A heterodimer formation between MOR and α-adrenoceptor units (α2AR) enhances MOR signaling in response to morphine [22] but severely decreases the opioid response following the simultaneous addition of morphine and α2AR agonist [23]. Vilardaga et al. [24] proposed a model in which morphine binding to the MOR rapidly changes conformation of the activated α2AR, and this transconformational

change permits direct inactivation of a Gi protein. The direct conformational switching of one receptor by the other that enables inhibition of receptor activation is likely a means of rapidly preventing overstimulation of signaling pathways and may contribute to OIH.

Some neuropeptides, which oppose anti-opioid peptides has been investigated and shown convincing results. The administration of neuropeptide cholecystokinin [25], the neuropeptide FF [26], and orphanin FQ/nociception [27] have all demonstrated anti-hyperalgesic effect.

As a possible third mechanism, spinal dynorphin, an endogenous κ opioid ligand, may also play an important role in the development of OIH. Increased concentration dynorphin in spinal cord and primary afferents after noxious stimuli stimulates the release of calcitonin gene-related peptide and thus increase stimulus-evoked spinal excitation.

Based on the fact that there exists individual difference in the occurrence of OIH, there may well be a genetic predisposition of OIH among the patients. Consistent with this hypothesis, Jensen et al. [28] found that polymorphisms of the catechol-O-methyl transferase gene were more prevalent in patients demonstrating OIH and pain sensitization. Finally, beyond the physiological mechanisms discussed here, psychological factors including anxiety and catastrophizing about pain could be modulating factors in the development of OIH.

Célèrier [12] proposed a model of neuroadaptative changes linking OIH. Before the first exposure to opioid, an initial equilibrium is associated with a low level balance between opioid-dependent analgesic systems (pain inhibitory) and NMDA-dependent pronociceptive systems (pain excitatory). Repeated opioid administrations induces a gradual decrease in the nociceptive threshold (*Pronociceptive systems sensitization*) leading to hyperalgesic state. This progressively shifts the unchanged analgesic response, giving the impression of less analgesia (apparent tolerance). After withdrawal of opioid, counter-adaptation of opioid-dependent analgesic systems is built by changes in the endogenous opioidergic system, and thus a new equilibrium between opioid-dependent analgesic systems and NMDA-dependent pronociceptive systems is established. This new, reset equilibrium (*allostasis*) balance leads to long-term pain vulnerability.

Clinical Aspects and Modulatory Factors of OIH

OIH has been studied mainly after opioid-based anesthesia and during postoperative analgesia. For several decades, most of these studies were conducted with remifentanil, but few studies with fentanyl. Importantly, a meta-analysis of studies demonstrated that while OIH is consistently present in patients given remifentanil, it's occurrence with fentanyl administration has not been established [29]. Thus, this review deals mainly with literature reports of clinical manifestation and modulatory factors associated with remifentanil infusion: dose, infusion duration, speed of withdrawal, and other combined anesthetic drugs.

OIH manifests itself by increased sensitivity to painful stimulation which extends to throughout the entire body from the site of preexisting pain. Thus, OIH exacerbates preexisting painful conditions and therefore can further progress a painful disease state [15].

Through the literature, high doses of remifentanil have been regarded as an important factor of OIH [30]: Most trials show that OIH is most likely to occur at infusion rates of > 0.32 ug/kg/min [29]. This dose dependency in inducing OIH has been demonstrated both in animal and human study. In rats, a decrease in both thermal threshold and mechanical thresholds are directly proportional to the administered dose of remifentanil [31]. Similarly, in surgical patients, postoperative pain scores and cumulative morphine consumption have been shown to be enhanced more in patients receiving high dose remifentanil [32].

A potential mechanism underlying this dose dependence was demonstrated in vitro in a patch clamp single-cell electrophysiologic study [33] which demonstrated cumulative dose, duration of administration, and modality of withdrawal could all influence the extent of OIH. Bolus only or shorter infusion of remifentanils led to long-term potentiation but with lower incidence. Moreover, tapered withdrawal more than 30 minutes after 1 hr infusion prevented long-term potentiation compared with abrupt withdrawal.

The effect of combined anesthetics with remifentanil could also affect OIH. Co-administration of N_2O [34] or propofol [32,35] with remifentanil decreases OIH development and consumption of analgesics. However, more human studies are needed to confirm those modulatory effects on OIH. All of these factors could be an auxiliary method to minimize the pronociceptive effects of opioids.

To date, possible treatment pharmacologic regimens for OIH include partial MOR agonist (buprenorphine) NMDA receptor antagonists (ketamine and dextromethorphan), cyclooxygenase (COX) inhibitors (nonsteroidal anti-inflammatory drugs), and α2 receptor agonists. Buprenorhine, a partial MOR agonist and δ- and κ- receptor antagonist [36], has a unique property: its antihyperalgesic effects lasted longer than its analgesic effects (2.6 times and 1.9 times for i.v. and s.c., respectively). This effect may be mediated through the blockade of κ -receptors, as agonists at this receptor are known to promote hyperalgesia mediated by descending facilitation [37]. Methadone also has an antihyperalgesic action, and has the potential to be widely used in the clinical setting to reduce OIH [38].

Spinal NMDA receptors appear to contribute to the development and maintenance of OIH. Numerous animal and human

studies have demonstrated that the NMDA receptor antagonist ketamine can inhibit OIH. These studies have shown beneficial effects of supplementation of opioid treatment with ketamine: higher pain thresholds and lessened hyperalgesia in animals [39] and better pain control scores and less use of postoperative morphine in humans [2]. Another NMDA receptor antagonist, dextromethorphan, has not been widely studied as a means of modulation of OIH, likely due to its lack of antihyperalgesic action [40].

Prostaglandins, including PGE2, can stimulate glutamate release in the spinal cord resulting in activation of NMDA receptors [41]. Thus, COX inhibitors could antagonize this NMDA activation and further inhibit OIH. Thus, coadministration of the COX inhibitors parecoxib and ketorolac significantly decreased the area of pinprick hyperalgesia during remifentanil, however, pretreatment prior to remifentanil infusion was without effect. These results suggest that the timing of COX inhibition may be critical in preventing OIH. Further study of this promising treatment is needed to guide COX inhibitor use in preventing OIH.

Several studies have provided biochemical evidence for the physical association of α2AR with MORs [24] and have identified that functional MOR-α2AR complexes can form in brain and spinal cord neurons. Although the significance and function of such a receptor complex are not fully understood, the effect of α2AR antagonist on OIH could be accomplished by interactions with this heterodimer complex [36]. Clinical and laboratory observations also indicate that α2-adrenoceptor agonists may deter the development of OIH [36] as well as alleviate the symptoms of opioid-withdrawal [42]. For example, coadministration of clonidine with morphine in rats wherein OIH had been induced [43] normalized both mechanical and thermal thresholds to baseline sensitivities. Clinically, a case report presented the experience of administering dexmedetomidine [44], an α2AR agonist, during opioid dose reduction in patients with OIH, allowed normalization of nociceptive and antinociceptive responses.

When compared to the chronic pain management setting, OIH is less well recognized and the clinical implications less well understood in perioperative settings, despite the fact that there multiple articles have been published establishing this side effect of perioperative opioid administration. Several clinical trials of OIH have reported increased postoperative pain and morphine consumption. However, those changes are typically controlled acutely without severe side effects by increased morphine consumption. Anesthesiologist should however improve their armamentarium in dealing with OIH, using some modulatory or pharmacologic approaches to OIH which should be helpful both in terms of eliciting fewer and less severe acute side effects but also limiting the lasting consequences of OIH.

Conclusion

Clinical anesthesiologists need to better understand OIH and its implications for pain control and opioid usage during the perioperative period. Although the clinical implication of OIH is not fully established, we need to understand that OIH could be a starting point of pain sensitization and pain chronicification. Therefore, anesthesiologists should endeavor to prevent or treat OIH through modulatory or pharmacologic means based on and understanding of the likely mechanisms underlying OIH and these treatment means.

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