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Opioid-Induced Hyperalgesia (OIH)

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Summary: Leal PC, Clivatti J, Garcia JBS, Sakata RK – Opioid-Induced Hyperalgesia (OIH).

Background and objectives: Opioids are commonly used for pain control; however, they can cause hyperalgesia. The reason why this can happen is not known. The objective of this review was to describe the mechanisms, factors implicated, and drug modulation.

Contents: The factors implicated in the development of opioid-induced hyperalgesia (OIH), such as duration of use, dose, and type of opioids are described. Mechanisms involved include the glutamatergic system and N-methyl-D-aspartate receptors (NMDA), spinal cyclooxygenase (COX) activation, excitatory amino acids, dynorphin, cytokines and chemokines; prostaglandins, and descending facilitation. Modulation of hyperalgesia could be done through: NMDA receptor antagonists, alpha2-adrenergic agonists, and COX inhibitors.

Conclusions: This is a very complex subject, which involves a series of pathophysiological mechanisms that could contribute for OIH and patient discomfort, bringing disastrous consequences.

Keywords: ANALGESICS, Opioids; COMPLICATIONS: hyperalgesia.

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INTRODUCTION

Opioids are fundamental drugs in the treatment of pain [1,2]. Although they work as analgesics, evidence that opioids cause hyperalgesia does exist. Thus, paradoxically, the drug used to relieve pain makes the patient more sensitive to it [1].

Therefore, initially they have analgesic and anti-hyperalgesic effects, but subsequently they can cause hyperalgesia [1].

OPIOID-INDUCED HYPERALGESIA (OIH)

Opioid-induced hyperalgesia is the increased sensitivity to pain caused by exposure to opioids [2]. This phenomenon has a negative effect in pain treatment [3].

Reports in the literature on the incidence of OIH are lacking; however, since it can affect individuals on opioids, we should be aware of it. The use of opioids is the required condition for the development of OIH, both acute and chronic [1-3]. Administration of large doses of opioids for a prolonged period seems to be associated with a higher incidence of OIH [1,2,4]. Opioid-induced hyperalgesia can also be seen when those drugs are administered for a short period [3].

Opioid-induced hyperalgesia affects animals and humans who receive opioids and drug-addicts on methadone maintenance [1,2,5-7]. In opioid-dependent individuals, a heightened sensitivity to pain is observed, and its interruption causes hyperalgesia. Sensitivity in areas of trauma is observed [1], but the type and location of this pain can be different from the original pain [2,3,7,8]. Opioid-induced hyperalgesia can develop differently for different types of pain [1]. In animals, hyperalgia, which varies according to the different stimuli (mechanical, thermal) is also observed after discontinuation of the opioid [1]. Opioid-dependent patients show sensitivity to cold, but not to electrical and mechanical stimuli [1]. Increased sensitivity to cold and heat without affecting pressure sensitivity can be observed [1]. A difference in chronic oncologic pain and non-oncologic pain was not observed [4].

After acute administration of opioid the anti-nociceptive effect is seen during 1 to 5 hours followed by a reduction of pain threshold for several hours (up to 10 days) [2,4,8,10]. The use of long-acting opioids after surgeries can mask hyperalgesia [4]. With chronic use, an anti-nociceptive effect is seen on the first day followed by the loss of the effect or even progressive hyperalgia [1].

Evaluation of hyperalgesia can be done through the threshold for mechanical stimulus (per-incisional, in the palmar region of the carpus, or in the interior face of the forearm) or with the cold-tolerance test [8,9].

Animals recovering from OIH remain sensitized to the effects of hyperalgesia of opioids with greater vulnerability to pain [1]. This phenomenon is reversible to some extent, but it requires a long period of abstinence [3].

Therefore, any chronic or acute use of opioids can cause hyperalgesia.

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DISCUSSION BETWEEN TOLERANCE AND HYPERALGESIA

Hyperalgesia is associated with central sensitization with reduction in pain threshold, expansion of the receptive field (stimulation of a neuron in the posterior horn of the spinal cord activates a greater peripheral area), and increase in the answer to the nociceptive stimulus. In OIH, the dose/effect curve is deviated downward, i.e., the analgesic effect decreases along time with a specific dose of the opioid, without improvement with an increase in the dose – on the contrary, it can increase the pain [1,2]. The pain is more severe than the original or initial pain, is not well defined in terms of quality and location, and it is associated with a reduction in the threshold and tolerability [5].

The phenomenon in which exposure to opioids leads to a reduction on its effect, requiring larger doses to maintain it, is called tolerance, i.e., the tolerant organism is less susceptible to the pharmacologic effect of a drug [11]. It reflects the reduction in the sensitivity to opioids, which is due to desensitization of the anti-nociceptive pathway [3]. In desensitization of the anti-nociceptive pathway, G-protein receptors are incapable of reducing intracellular cyclic AMP and, consequently, the inward movement of sodium and calcium. A reduction in membrane receptors by internalization is another reason for tolerance [3]. A shift of the dose/effect curve to the right is seen in tolerance [1,2]. It is characterized by a reduction of the analgesic potency and it improves with an increase in the dose of the medication or changing of the opioid [1]. Pharmacologically, they are distinct phenomena [2]. They can involve opposite cellular mechanisms, with desensitization (tolerance) and sensitization (OIH) [6]. In clinical practice it is difficult, and even impossible to distinguish the two phenomena. Hyperalgesia can mask anti-nociception producing the impression of tolerance [7]. Both conditions probably coexist and evidence that tolerance and hyperalgesia share several cellular mechanisms and some neurotransmitters and receptors systems, including dynorphin, protein kinase-C, NMDA receptors, nitric oxide synthase, heme oxigenase, and others exists [1]. Other cellular mechanisms differ in tolerance and hyperalgesia [3]. However, the mechanisms might not contribute in the same proportion for the loss of the analgesic effect. The expression of both phenomena may vary, depending on the treatment protocol and type of study [1].

MECHANISMS OF OIH

Most likely, multiple factors and mechanisms contribute for IOH, such as: anti-analgesic system, changes in NMDA receptors and intracellular second messengers, spinal COX activation, release of excitatory amino acids, reduction if inhibitory neurotransmitters, increased in phosphorylation, and descending facilitation [1,2,6,7,10,11]. Neuroplastic changes can be seen in the central and peripheral nervous system, with sensitization of pro-nociceptive pathways [2]. Cellular changes are seen in several anatomical sites, such as afferent neurons and spinal cord, glia, encephalic nuclei, and descending modulation pathways [2,3]. Changes can be seen in receptors and channels, as well as peripheral and central sensitization [9,11-13].

Activation of NMDA receptors

Activation of NMDA receptors by glutamate is implicated in the mechanism of OIH [1,3,6]. The increase in the release of glutamate in the dorsal horn of the spinal cord and the sustained increase in the response of NMDA receptors through protein kinase-C-mediated manganese removal, seem to be the main mechanisms implicated in OIH [5,10]. NMDA receptors can be activated by opioids, which behave as excitatory neurotransmitters, causing the inward flow of calcium and central sensitization. The inward flow of calcium increases the activity of protein kinase–C, phosphorylation, and inactivation of opioid receptors, besides causing an increase of nitric oxide synthase [10]. The inactivation of protein kinase-C causes phosphorylation of NMDA receptors, with the removal of magnesium from the channels and an increase in the inward flow of calcium.

Increase of anti-opioid peptides

Excitatory amino acids are implicated in the process of hyperalgesia [1]. Opioid-induced hyperalgesia has been associated to the increase in cholecystokinin, a peptide related to the calcitonin gene (CGRP), substance-P, and nociceptin in the rostral ventromedial medulla due to an increase in the expression of excitatory opioid receptors in detriment of inhibitory opioid receptors [6,14,15].

Descending facilitation

Another mechanism involves descending facilitation pathways, which are mediated by opioids in on-cells located in the rostral ventromedial medulla [16]. Exposure to morphine causes neuroplastic changes in the rostral ventromedial medulla, descending facilitation through on-cells, with increase in dynorphin, and release of neurotransmitters in primary afferent fibers [2,7].

Dynorphin function

Administration of opioids provokes an increase in dynorphin, which might be one of the responsible factors for OIH [6,7]. Spinal dynorphin is pro-nociceptive and there is evidence that it causes the release of excitatory neurotransmitters from primary afferent neurons, suggesting positive retro-feeding that amplifies sensorial afference [7].

Other mechanisms

Prostaglandins might be important. Cytokines and chemokines might also be relevant for the development of OIH [1,2].

Opioids facilitate the release of cytokines [1,2,17]. An increase in C-fos protein is seen in sensorial neurons in the spinal cord [1,2]. The nitric oxide synthase system and heme oxigenase might be involved in OIH. The reduction of inhibitory glycinergic control is a possible mechanism [1].

HYPERALGESIA-RELATED FACTORS

Dose

Exposure to large doses of opioids seems to be associated with OIH [1,4,7,9,10,18]. Studies have demonstrated that large doses of intraoperative remifentanil cause an increase in postoperative pain [2,4,5,8,9]. However, OIH was observed after interruption of an infusion of 3.1 ng.mL^{-1} of remifentanil [19]. On the other hand, a study failed to demonstrate an increase in postoperative opioid consumption after the use of large doses of remifentanil [20].

Large or repetitive doses of intraoperative fentanyl also have induced an increase in postoperative pain [5,21]. However, OIH has also been observed with small doses of fentanyl during maintenance of a dependent individual [2]. The case of a patient using a fentanyl adhesive (75 µg.day^{-1}) for chronic pain, who underwent general anesthesia with remifentanil and developed more severe pain postoperatively has also been reported [22].

Hyperalgia was observed with oral oxycodone (2,400 mg.day^{-1}), oral methadone (675 mg.day^{-1}), and intravenous methadone (30 mg.h^{-1}) [23]. Methadone 62 mg.day^{-1} also caused hyperalgesia [24].

Type of opioid

The authors of a study have reported that some conditions of the molecule, such as the structure of fenantrene, hydrogen in position 14, ether binding, one or no methyl group bound to nitrogen, and free OH in position 3 free or conjugated with glucuronide/sulfate are necessary for the development of OIH [25]. Thus, the molecular formula seems to be important in inducing OIH [1]. However, OIH developed even with piperidine derivatives like fentanyl [1].

It seems that the action on µ receptors is relevant [1,2]; however, it is possible that opioids with action on kappa receptors also can cause OIH [1].

Another factor implicated seems to be the short duration of action of opioids, such as remifentanil [5,9,21,26-30]. On the other hand, in most studies on OIH involving chronic pain, morphine seems to be implicated raising the possibility that the metabolite morphine-3-glucuronide has a contribution [2]. Opioid-induced hyperalgesia has been observed in four weeks after exposure to moderate doses of morphine (75 mg.day^{-1}) [2].

Some opioids can be associated to a higher possibility of inducing OIH. Besides, crossed sensitization with other opioids has been observed [6].

Duration of use and of hyperalgesia

Opioid-induced hyperalgesia is more evident with prolonged use [3,6,14]. Chronic use of oral morphine for 4 weeks was associated with hyperalgesia [2]. However, a study demonstrated the presence of hyperalgia in patients who used only opioids intraoperatively [8].

Studies in rats treated with large doses of intravenous morphine and fentanyl during one hour demonstrated that hyperalgesia had a duration of 2 to 3 hours [3,6,18]. However, hyperalgesia can last anywhere from 2 to 10 days [10,31].

Type and route of administration

Several routes of administration are implicated in OIH [21,32,33]. Pain can be seen during continuous infusion of opioids, going against the hypothesis that the sensorial change is associated with suspension of the opioid [2,5,7].

MODULATION OF OIH

Several drugs have been used in an attempt to reduce the development of OIH [1,2,15,34].

NMDA receptor blockers can prevent or reduce the development of OIH [5]. Evidence that low dose ketamine can modulate OIH exists [2,9,10,28,35,36].

Ketamine, 0.15 mg.kg^{-1}, followed by the intraoperative infusion of 5 µg.kg.min^{-1} reduced morphine consumption and pain scores, delaying the time for the first complementation [36]. In another study low dose ketamine (0.5 mg.kg^{-1}) for induction, and infusion of 5 µg.kg^{-1}.min^{-1}, prevented remifentanil-induced hyperalgesia[9]. However, in rather another study ketamine did not prevent the development of OIH [37].

Methadone is a weak NMDA receptor antagonist and, when hyperalgesia caused by another opioid is suspected, it can be switched to methadone [2]. However, methadone can be associated with states of heightened pain [2]. Therefore, opioids should be changed to methadone keeping in mind that it can also activate pro-nociceptive pathways [23]. Dextrorphan is an antitussive with non-competitive NMDA receptor antagonist and controversial effects on OIH[2]. Memantine is a MNDA receptor antagonist used in patients with Alzheimer's that needs more evaluation [38].

It has been proposed that propofol can be used as an anti-hyperalgesic due to its action in gamma-aminobutyric acid receptors on the supraspinal level [2,30]. In a study, 1.5 µg.mL^{-1} of propofol delayed the hyperalgesic effect of remifentanil; however, an increase in hyperalgesia was observed after the discontinuation of the drug and one should be aware to the possible affect of activating pro-nociceptive pathways [34].

COX-2 inhibitors seem to have a relevant role in inhibiting hyperalgesia by stimulating the reuptake of glutamate in the dorsal horn of the spinal cord besides blocking NMDA receptors [2]. In volunteers, the prior administration of parecoxib, 40 mg IV, reduced remifentanil-induced hyperalgesia

(0.1 μg.kg^{-1}.min^{-1}). However, when parecoxib was administered in parallel with remifentanil this effect was not observed [39].

In volunteers, clonidine, 2 μg.kg^{-1}, reduced pain scores caused by remifentanil (0.1 μg.kg^{-1}.min^{-1}) [40].

CLINICAL IMPLICATIONS

It is often difficult to determine whether OIH developed after the administration of opioids. The reduction in analgesic efficacy could be due to tolerance, OIH, or both [6].

One should consider the presence of opioid-induced hyperalgesia when repetitive increases in dose fails to promote analgesia, causes exacerbation of the pain, causes an unexplainable decrease in the effects of the opioid, or diffuse allodynia not associated to the previous pain is observed, and other causes, such as progression of the disease or acute lesion were ruled out [2,3].

More effective treatment can be obtained when those conditions are recognized [3].

Opioid sparing or changing the opioid represents strategies adopted to prevent or treat OIH, although convincing evidence for those conducts does not exist [3]. The concomitant use of low doses of opioid antagonists or the use of cholecystokinin or NMDA receptor antagonists are other strategies that could be used [1,3].

The concomitant use of other analgesics, besides non-pharmacologic treatment, is the strategy used more often to avoid tolerance and opioid-induced hyperalgesia [3,6].

In general, the reduction of the analgesic effect of the opioid during treatment is considered tolerance to the opioid, which leads to an increase in the dose. On the other hand, OIH can be aggravated by the increase in the dose of the opioid [1,6]. Opioid-induced hyperalgesia should be treated with a reduction in dose, changing of the opioid, or with the association of other analgesics [3].

However, the mixture of tolerance and hyperalgesia could be produced by exposure to large doses of opioids [4].

CONCLUSION

Opioid-induced hyperalgesia is very complex, involving a series of mechanisms that could contribute for patient discomfort, bringing harmful consequences when they are not diagnosed.

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Resumen: Leal PC, Clivatti J, Garcia JBS, Sakata RK – Hiperalgesia Inducida por Opioides (HIO).

Justificativa y objetivos: Los opioides son medicamentos a menudo usados para el control del dolor y que sin embargo pueden causar hiperalgesia. La circunstancia por la cual ese fenómeno puede ocurrir no está totalmente aclarada. El objetivo de esta revisión es describir los mecanismos, los factores que están involucrados y la modulación por medicamentos.

Contenido: Fueron descritos los factores involucrados en el desarrollo de la hiperalgia inducida por opioides (HIO), como la duración en el uso, la dosis y el tipo de opioide. Los mecanismos incluyen los sistemas glutamatérgico y los receptores N-metil-D-aspartato (NMDA), activación de ciclo-oxigenasa (COX) espinal, aminoácidos excitatorios, dinorfina, citocinas y quimocinas; prostaglandinas y facilitación descendiente. La modulación de la hiperalgesia se puede lograr con los antagonistas de receptores NMDA, los agonistas adrenérgicos--alfa2 y con los inhibidores de (COX).

Conclusiones: El tema es bastante complejo, e involucra una serie de mecanismos fisiopatológicos que pueden contribuir para la HIO y la incomodidad del paciente, con consecuencias dañinas para la salud.