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Opioid- Induced Hyperalgesia

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Abstract

Opioids are a fundamental part in the treatment of pain especially within the perioperative setting. While opioids are routinely administered by nurse anesthetists for the treatment of pain, they can be associated with several undesirable side effects including opioid-induced hyperalgesia (OIH). OIH is a complex phenomenon that has a significant impact on the successful treatment of pain in a surgical setting. While there have been many advances in recent years into the topic of OIH, the mechanisms are complex and remain incompletely understood. OIH is believed to occur from changes in both the peripheral and central nervous systems that lead to sensitization of nociceptive pathways. A number of specific mechanisms have been postulated including peripheral second-messenger systems, the release of excitatory amino-acid neurotransmitters from primary afferents and activation of *n*-methyl-d-aspartate receptors (NMDA) receptors, enhanced spinal expression of dynorphin, spinal prostaglandins, and spinal cytokines, and neuroplastic changes to the descending facilitatory pathways within the rostral ventromedial medulla. There is sufficient evidence that OIH exists in humans and that it can develop within the perioperative period. While several opioids have been implicated in causing OIH, remifentanyl is one of the most widely studied opioids in relation to OIH and has been shown to cause OIH at higher doses. This hyperalgesia may extend well beyond the postoperative period and can lead to the development of chronic pain persisting for months. Current recommendations involve using remifentanyl at lower doses, rotating opioids, utilizing alternative analgesics and multimodal analgesia, and utilizing adjuvant therapies to prevent the development of and treat OIH should it occur.

Introduction

Opioid- induced hyperalgesia is a state of nociceptive sensitization to opioids where the administration of opioids causes a paradoxical response and increases pain. Over time, the systems in which opioids work can change leading to enhanced nociception and an increased amount of pain experienced by the patient. The phenomenon of OIH may potentially limit the effectiveness of opioids and has a significant impact on anesthesia providers attempting to prevent and treat pain in a patient undergoing a surgical procedure. Current research suggests that OIH does occur in humans and can make an impact clinically (Angst & Clark, 2006). Emerging studies have changed the way providers respond to potential side effects of opioids, such as tolerance. Clinically, tolerance and opioid- induced hyperalgesia may be difficult to distinguish. It is important for the anesthesia provider to recognize the development of OIH and understand the mechanisms of OIH to provide effective pain relief in the surgical setting. The scope of this paper is to define OIH and discuss the underlying mechanisms of the development of this phenomenon. This paper will discuss the most recent research about OIH, particularly the development of OIH in humans, as well as presenting research about how to prevent and treat opioid- induced hyperalgesia.

Mechanisms of Opioid- Induced Hyperalgesia

The complete mechanisms of OIH are not completely understood and there are several theories to explain this complex phenomenon. The majority of preliminary and early research has been conducted in animals, though more recent studies have begun to investigate this phenomenon in humans. While animal research is not always necessarily translatable to humans, this research has resulted in a model for the mechanisms of OIH. Angst and Clark (2006) published an earlier systematic review of OIH in the literature. According to Angst and Clark

(2006), “the opioid receptor system signals and modulates a multitude of effects, and under certain conditions mediates hyperalgesia rather than analgesia” (p. 582). However, there are conflicts within the existing literature regarding the development of OIH specifically in humans. A systematic review by Fishbain, Cole, Lewis, Gao, and Rosomoff (2009) concluded that there was evidence for the presence of OIH development in humans and that the strongest evidence came from opioid infusions in healthy volunteers. However, this systematic review ultimately found that there were too few studies to definitively conclude that OIH was present in humans. In another review of current research, Chu, Angst, and Clark (2008), report that there is mixed evidence for the development of OIH after perioperative exposure to opioids and that most studies provide indirect evidence. Chu et al. (2008) cite the need for additional high- quality trials to further define the role of perioperative exposure to opioids in the development of OIH. Fletcher and Martinez (2014) compiled a more recent systematic review that adds to the evidence of OIH in humans. This review involved 27 studies and 1,494 patients. Fletcher and Martinez (2014) stated, “our review clearly confirms that high intraoperative doses of remifentanyl results in hyperalgesia in patients after surgery” (p. 997). Fletcher and Martinez (2014) referenced the systematic review conducted by Fishbain et al. (2009) where it was concluded there was insufficient evidence for OIH in humans. According to Fletcher and Martinez (2014), “we can now clearly demonstrate that high- dose intraoperative opioid causes a significant increase in postoperative pain intensity at rest persisting 24h after surgery” (p. 999). The overwhelming body of current research consists of evidence of OIH in humans. Within the existing literature, many of the mechanisms of OIH have been elicited and studies have begun to clarify the specific mechanisms for the development of OIH. Current research finds that OIH has been implicated to occur peripherally as well as centrally via spinal mechanisms and supraspinal mechanisms.

Peripheral Mechanisms

Tolerance and hyperalgesia with peripheral injections were demonstrated utilizing research in rats. It is not required that opioids reach the central nervous system for hyperalgesia to occur. This is possible because μ - opioid receptors are found peripherally on the terminals of primary afferent neurons and injections can cause changes to occur within these systems.

Additionally, a number of intracellular mechanisms and second- messenger systems have been shown to play a role in the development of hyperalgesia and tolerance. According to Aley and Levine (1997), “the mu- opioid [D-Ala², N-Me-Phe⁴, Gly-ol⁵] -enkephalin (DAMGO) exerts an antinociceptive effect against prostaglandin E₂ (PGE₂)- induced hyperalgesia in the hindpaw of the rat” (p. 8018). This tolerance was prevented by a nitric oxide synthase inhibitor (NMLA), but not a protein kinase C (PKC) inhibitor or the adenylyl cyclase inhibitor, revealing a role for these second messenger systems in peripheral development of OIH (Aley & Levine, 1997).

Spinal Mechanisms

Spinal cord mechanisms have also been implicated in the development of OIH, with both the systemic and intrathecal injection of opioids. According to Chu et al. (2008), “... additional biochemical and behavioral observations suggest that the dorsal horn of the spinal cord is central to many mechanisms converging to support OIH” (p. 484). An early study involving the injection of opioids intrathecally in rats demonstrated decreased analgesia on day eight of injection as compared to day one (Mao, Price, & Mayer, 1994). Mao et al. (1994) proved that thermal hyperalgesia develops in combination with morphine tolerance. Additionally, their results indicated a critically important role of central NMDA antagonists and intracellular PKC activation in both prevention of and reversal of thermal hyperalgesia (Mao et al., 1994). The authors hypothesized that there could be a configurational similarity between the opiate receptor

and the NMDA receptor and that exogenous morphine could activate the NMDA receptors to some degree. Remifentanyl has, in fact, been shown to stimulate different NMDA receptor subunits (Joly et al., 2005). An additional hypothesis by Mao et al. (1994) is that NMDA receptors are activated by endogenous agonists over the period of morphine administration leading to these changes.

Regardless of the mechanism, it is clear that the excitatory amino acid neurotransmitter and receptor system has been implicated. The co-administration of NMDA antagonist MK- 801 blocked the development of OIH (Mao, 1994). The role for PKC was suggested because the use of GM1 ganglioside, a PKC inhibitor, prevented the development of tolerance and OIH (Mao et al., 1994). The excitatory amino acid glutamate and also the neurokinin-1 agonist substance P in mice have been proven to provoke an exaggerated pain response. Additionally, enhanced spinal expression of dynorphin and spinal prostaglandins as well as spinal cytokines have been shown to propagate the development of OIH (Chu et al., 2008). An increase in spinal dynorphin levels has been shown with continuous morphine infusion (Lee, Silverman, Hansen, Patel, & Manchikanti, 2011). According to Lee et al. (2011), "OIH is therefore a pro- nociceptive process facilitated by increasing the synthesis of excitatory neuropeptides and their release upon peripheral nociceptive stimulation" (p. 148).

Systemic Mechanisms

The results from studies involving the systemic administration of opioids have been consistent with those investigating spinal mechanisms. Systemic administration of opioids has been the most studied in the literature (Angst & Clark, 2006). The central glutaminergic system is the most commonly implicated system in the literature that explains the mechanisms of OIH (Lee et al., 2011). Angst and Clark (2006) conducted a qualitative systematic review regarding

OIH mechanisms and recommendations and investigated numerous studies. According to Angst and Clark (2006), “the systemic administration of the NMDA receptor antagonist MK-801, or ketamine, reduced opioid- induced thermal and mechanical hyperalgesia after acute (one injection or multiple injections on a single day) and chronic opioid administration (5 days continuously)” (p. 577). Specifically, the μ - opioid receptor is relevant in the development of OIH. This can be explained by a study utilizing a specific strain of mice, CXBK mice. This particular strain of mice expresses low levels of μ - opioid receptors and it has been shown that the development of OIH did not occur in these mice compared to other strains of mice (Li, Angst, & Clark, 2001). Additionally, κ - receptors have also been implicated in the development of OIH and likely play a role along with μ - opioid receptors (Angst & Clark, 2006).

Neuroplastic changes to the rostral ventromedial medulla (RVM), a group of neurons located on the floor of the medulla oblongata, is also key to the development of OIH. These neurons have been implicated to act both as descending facilitatory and inhibitory pathways utilizing neurons classified as either “on” or “off” cells. The “on” cells contribute to nociception, whereas the “off” cells inhibit nociception. These cells can undergo neuroplastic changes in their expression, which help to explain opioid hyperalgesia and opioid- induced pain (Longnecker, Brown, Newman, & Zapol, 2012). Morphine and other μ -agonist opioids decrease firing of the “on” cells and increase activity of the “off” cells providing pain relief (Longnecker et al., 2012). Descending pain facilitation within the RVM is necessary for opioid- induced hyperalgesia to occur (Xie et al., 2005). This hyperalgesia has been shown to be able to be reversed by lidocaine administration in the RVM or by creating a lesion in the dorsolateral funiculus, which is a neuronal tract of descending modulation. Cholecystinin (CCK) has been shown to be an important neurotransmitter that acts within the RVM to decrease opioid antinociception (Xie et

al., 2005). Additionally, it has been demonstrated that opioid tolerance coincides with CCK up-regulation. In their experiments utilizing rats, Xie et al. (2005) discovered that morphine administration was associated with elevated levels of CCK in the RVM. This study helped to confirm the RVM role in mediating opioid- induced hypersensitivity. Further, according to Xie et al. (2005), “CCK in the RVM inhibits the antinociceptive effect of systemic morphine by preventing the morphine- induced increase in the firing of the RVM “off” cells” (p. 414). It has also been suggested that CCK can induce firing of the “on” cells, creating a pathway of descending pain facilitation.

Additionally, spinal dynorphins have also been implicated in playing a role in opioid-induced hyperalgesia via these descending facilitatory pathways. Gardell et al. (2002) found that morphine exposure up-regulates spinal dynorphin. The dynorphin causes release of excitatory peptides like calcitonin gene- related peptide (CGRP) and substance P at dorsal root ganglia primary afferents (Gardell et al., 2002). These mechanisms are important factors that underlie the phenomenon of opioid- induced hyperalgesia.

Evidence of Opioid- Induced Hyperalgesia in Humans

Animal models have not only demonstrated the evidence for opioid- induced hyperalgesia but have also given a framework with which to develop studies in humans. Recently, there has been an effort to investigate OIH in humans and studies have been done both in the clinical environment and in volunteers.

Acute Opioid Exposure in Healthy Volunteers

Opioid- induced hyperalgesia has been studied in volunteers. Hood, Curry, and Eisenach (2003) conducted a study to test whether opioid infusion produces hyperalgesia in human volunteers. After capsaicin application, a remifentanil infusion was started to reduce pain by

70% and infused for 60- 100 minutes. According to Hood et al. (2003), “the area of hyperalgesia progressively enlarged after termination of the remifentanil infusion and was significantly larger compared with the baseline measurement at the 200 and 240-minute postinfusion assessments” (p. 813). Areas of allodynia also increased after the discontinuation of the infusion. Hyperalgesia was also still present at the 24- hour assessment (Hood et al., 2003). The data in this study does agree with others that even acute exposure to opioids can cause a prolonged period of hyperalgesia (Hood et al., 2003). This study does offer direct evidence of hyperalgesia development in humans. The design of the study is advantageous because heat- induced hyperalgesia can mimic the pain experienced by post- operative patients. According to Joly et al. (2005), “Mechanical hyperalgesia surrounding the wound in postoperative patients shares the same central neuronal mechanism as heat-induced secondary hyperalgesia and confirms a degree of central sensitization” (p. 147). Unfortunately, there were several limitations to the study including a small sample size and lack of a control group. Additionally, the researchers were not blinded. Regardless, these results indicate that even acute exposure to opioids can induce hyperalgesia and allodynia for a long period of time.

Perioperative Exposure to Opioids

Numerous studies have been conducted in the clinical setting regarding hyperalgesia as well as whether small- dose ketamine prevents this hyperalgesia. These studies are advantageous because peri-incisional hyperalgesia and allodynia can be measured objectively. Joly et al. (2005) conducted a study testing the hypothesis that increased pain sensitivity assessed by peri-incisional allodynia and hyperalgesia can occur after relatively large- dose intraoperative remifentanil. In this double- blinded study, 75 patients undergoing major abdominal surgery received either remifentanil at 0.05mcg/kg/min, remifentanil at 0.4mcg/kg/min, or remifentanil at

0.4mcg/kg/min and ketamine 0.5mg/kg just after induction followed by ketamine infusion of 5mcg/kg/min until skin closure then 2mcg/kg/min until 48 hours postoperatively. Joly et al. (2005) confirmed that large- dose remifentanyl increases pain sensitivity throughout both studied postoperative days and is associated with an increase in morphine administration postoperatively. Large doses of remifentanyl without the use of small- dose ketamine may predispose patients at risk for chronic pain. Though this study was well- designed, it provides indirect evidence of OIH from the perioperative administration of opioids.

While further studies are needed to determine whether peri-incisional hyperalgesia is a prognostic factor for development of chronic pain, several studies have shown this hyperalgesia to persist for at least several months. Hyperalgesia proximal to the surgical wound was found to be present three months after surgery in patients who underwent abdominal hysterectomy (Ilkjaer, Bach, Nielsen, & Wernberg, 2000). Similarly, another study found that high- dose remifentanyl in a patient undergoing thoracotomy without epidural analgesia is associated with allodynia. This study involved 38 patients randomized to receive either a low or high dose of remifentanyl with blinded recorders or postoperative pain scores. The area of allodynia experienced was found to be three times larger than the allodynia experienced in a patient utilizing a low- dose infusion of remifentanyl (Salengros et al., 2010). Most interestingly, this study followed up with patients at intervals of one, three, and six months. It was concluded that patients who received the larger dose of remifentanyl developed a much higher incidence of chronic pain that the authors concluded resembled neuropathic pain (Salengros et al., 2010). Therefore, in patients in which hyperalgesia is experienced, long- term consequences may develop and persist, resulting in chronic pain in these patients. However, in contrast to these results, Fletcher and Martinez (2014) report that the hyperalgesia from high- dose remifentanyl

persists only in the immediate postoperative period. While this increased pain is associated with a substantial increase in postoperative morphine consumption, there were no increased side effects such as nausea and vomiting from the additional morphine (Fletcher & Martinez, 2014). It is clear that further studies need to be conducted regarding the clinical implications of opioid-induced hyperalgesia in humans and how long these effects should be expected to persist.

As referenced in previous studies, remifentanyl at 0.05mcg/kg/min has not been shown to induce hyperalgesia in volunteers in previous studies. However, remifentanyl at a rate of at least 0.1mcg/kg/min does induce hyperalgesia (Koppert et al., 2003). Therefore, the dose of remifentanyl administered in the intraoperative period is important and may cause some patients to experience hyperalgesia and allodynia while others do not. The study by Koppert et al. (2003) does provide direct evidence of the development of hyperalgesia after exposure to remifentanyl infusion. However, this study does not distinguish tolerance from hyperalgesia and in a clinical setting this may be difficult to determine.

Other studies have also concluded that remifentanyl has been associated with hyperalgesia. Guignard et al. (2000) concluded that large- dose remifentanyl caused increased postoperative pain scores and also increased postoperative morphine consumption. This study included 50 patients undergoing major abdominal surgery utilizing desflurane and remifentanyl as the anesthetic agents. The patients were randomized to receive either half minimum alveolar concentration (MAC) of desflurane with remifentanyl titrated to autonomic responses or 0.1mcg/kg/min of remifentanyl with desflurane titrated to autonomic responses. Additionally, the systematic review conducted by Fletcher and Martinez (2014) found that in patients who received higher doses of remifentanyl there was a higher morphine use postoperatively. It was

estimated that an additional 18mg of morphine was given in groups that received high- dose remifentanyl intraoperatively in order to control postoperative pain (Fletcher & Martinez, 2014).

Opioids that Induce Hyperalgesia

It is possible that not all opioids produce a hyperalgesic or allodynic response when given at high doses. One experiment found that it existed only with morphine and that switching to piperidine derivatives like fentanyl abolished the response (Angst & Clark, 2006). Remifentanyl has been found to stimulate different NMDA receptor subunits called NR1A/2A and NR1A/2B (Joly et al., 2005). In the systematic review conducted by Fletcher and Martinez (2014) it was concluded that high intraoperative doses of remifentanyl caused hyperalgesia in patients after surgery. These authors found insufficient evidence of hyperalgesia when alternative opioids were administered. Additionally, Fletcher and Martinez (2014) state, "... our analyses suggest that high doses of fentanyl cause no significant modifications to the pain score at rest" (p. 999). According to Fletcher and Martinez (2014) there is no evidence that fentanyl or sufentanyl cause hyperalgesia, unlike remifentanyl.

Recommendations

There are many recommendations to treat and prevent the development of OIH within the existing body of literature. It is most important for nurse anesthetists to understand how to properly prevent and treat the development of OIH should it occur. The classic symptom of OIH is a lack of effectiveness with administration of opioids. Though it is often difficult to distinguish between tolerance and OIH, practitioners must be able to differentiate OIH from other causes of increased pain such as disease progression, additional injuries, and exacerbation of pre-existing pain (Lee et al., 2011). There are clinical features that differentiate OIH from other processes. According to Lee et al. (2011), "In contrast, OIH typically produces diffuse pain, less defined in

quality, which extends to other areas of distribution from preexisting pain” (p. 152). OIH does mimic the signs of opioid withdrawal because both have similar pathophysiological processes. It can be helpful to administer opioids initially because if the pain is simply undertreated or there is an opioid tolerance a response will occur to opioid administration. A patient experiencing OIH would have an increase in symptoms with additional opioid administration (Lee et al., 2011). Additionally, having a high index of suspicion for the disease process of OIH, especially in the setting of remifentanyl administration intraoperatively, can assist the practitioner in identifying OIH in patients.

Clinically, reducing the dosage of opioids can be difficult in a patient experiencing and reporting pain. Many strategies have been shown to effectively treat and reduce the symptoms of OIH. There has been evidence that shows remifentanyl anesthesia in combination with propofol-based anesthesia prevents the development of OIH. Propofol has been shown in some studies to prevent hyperalgesia in volunteers, whereas inhalational anesthesia has not shown these same properties (Fletcher & Martinez, 2014). According to Fletcher and Martinez (2014), “... we suggest that remifentanyl may be administered, preferentially, at the lowest possible dose and associated with propofol anaesthesia” (p. 1002). Additionally, many studies implicate the glutaminergic system in OIH, thus many of the treatment recommendations also relate to this system. Numerous studies have shown a benefit in using adjuvant therapies to modulate and reduce the symptoms of OIH. Specifically, the use of NMDA receptor antagonist medications, alpha-2 agonist medications, and cyclooxygenase-2 (COX-2) inhibitors have been implicated to both directly and indirectly manipulate the glutaminergic system. Utilizing these therapies can be beneficial in the treatment of OIH symptoms.

NMDA receptor antagonists

NMDA antagonist medications directly modulate the glutaminergic system. NMDA antagonists inhibit central sensitization and have been found to prevent hyperalgesia. Ketamine, a dissociative anesthetic agent, binds to many different receptor sites and is an NMDA receptor antagonist. In the study conducted by Joly et al. (2005), it was demonstrated that the use of small- dose ketamine effectively prevented the development of hyperalgesia. This study included patients who received small- dose remifentanyl infusion, large- dose remifentanyl infusion, and large- dose remifentanyl infusion with the addition of ketamine at 0.5mg/kg, followed by 5 mcg/kg/min until skin closure, then 2 mcg/kg/min until 48 hours post-operatively. The ketamine doses used in this study were calculated using published pharmacokinetics to achieve target plasma concentrations of 250 ng/ml intraoperatively and 100 ng/ml postoperatively (Joly et al., 2005). According to Joly et al. (2005), “These ketamine concentrations, especially 100 ng/ml, are in the range known to counteract hyperalgesia while producing minimal side effects” (p. 148). As previously discussed, the group of patients receiving the large- dose remifentanyl developed a larger area of allodynia to von Frey hair stimulation, while the group receiving the small- dose remifentanyl and the group receiving the large- dose remifentanyl with ketamine developed a much smaller area of allodynia. This area was comparable between the two groups. Ketamine effectively prohibited the increase in pain sensitivity postoperatively and was associated with a lower morphine consumption postoperatively (Joly et al., 2005). Interestingly, in this study one patient that received the ketamine reported hallucinations and one patient reported altered color perception and dizziness. Therefore, utilizing the ketamine to prevent hyperalgesia is not without certain side effects

associated with this anesthetic agent. There is also some evidence for the use of memantine, an oral NMDA receptor antagonist (Chu et al., 2008).

Cyclooxygenase-2 inhibitors

These medications have been shown to antagonize NMDA receptor function within the central nervous system though the main mechanism by which COX-2 inhibitors reduce symptoms of OIH is by inhibition of prostaglandin synthesis. Prostaglandins have been implicated in the stimulation of glutamate release from the spinal cord dorsal horns (Lenz et al., 2011). There has been evidence in animals that their use can reduce the expression of OIH (Chu et al., 2008). Though these medications may be useful, they likely have a less significant clinical impact than the NMDA antagonist medications (Lee et al., 2011). Lenz et al. (2011) demonstrated that pre-treatment with either parecoxib (a relatively selective COX-2 inhibitor) or ketorolac (a COX-1 inhibitor) reduced an area of post-infusion hyperalgesia after remifentanil infusion in healthy volunteers. Parecoxib was found to completely prevent the development of post-infusion hyperalgesia, whereas ketorolac was found to reduce the area of hyperalgesia, but to a much lower extent than parecoxib.

Esmolol

Esmolol infusion has also been implicated in numerous studies to have an opioid- sparing effect. Collard et al. (2007) found that an esmolol infusion reduced the amount of fentanyl required in the post- anesthesia care unit in patients undergoing laparoscopic cholecystectomy. This observer- blinded study involved 90 patients who were randomized to one of three groups. One group received doses of fentanyl intraoperatively, one group received an esmolol infusion of 5- 15mcg/kg/min without supplemental opioids intraoperatively, and one group received a remifentanil infusion of 0.1- 0.5mcg/kg/min intraoperatively. The group that required the most

fentanyl postoperatively was the remifentanil group. Additionally, the patients in the esmolol infusion group experienced a lower incidence of post-operative nausea and vomiting. The incidence of nausea in the group that received fentanyl and the group that received remifentanil were similar, at 66.7% and 67.9%, respectively. The incidence of nausea in the group that received an esmolol infusion was 30% (Collard et al., 2007). The group that received the esmolol infusion also met discharge criteria and left the hospital 45- 60 minutes earlier than the other two groups (Collard et al., 2007). One major disadvantage to this study is that it involved such a specific group of patients all undergoing the same surgical procedure and may not be translatable to other procedures. According to Collard et al. (2007), “acute pain after laparoscopic cholecystectomy has some characteristics not shared by other laparoscopic procedures” (p. 1255). The mechanism behind which beta- blockers, such as esmolol, work is postulated to be by beta- receptor blockade within the hippocampus. According to Collard et al. (2007), “the hippocampus plays a role in nociception, a role predicated, at least in part on *n*-methyl-d-aspartate receptors” (p. 1261). Therefore, blocking the beta- receptors within the hippocampus could modulate the nociceptive process and result in lower perceived pain.

Alpha- 2 Agonists

Some studies have suggested that there is a role for alpha- 2 agonists in the modulation of OIH. Human studies provide support for the use of the medications in the setting of acute opioid exposure. Koppert et al. (2003) concluded that ketamine infusion combined with remifentanil initially resulted in reduced pain but after discontinuation of both in the postoperative period pain levels reached comparable levels in a group that received remifentanil infusion without ketamine. They found that clonidine but not ketamine reduced the post-infusion pain, which suggests a modulating effect of the alpha- 2 receptor agonist clonidine.

Opioid Dose Reduction and Rotation of Different Opioids

Many reports have found an association with high- dose opioids and the development of hyperalgesia. According to Angst & Clark (2006), “as soon as a high-dose, opioid-induced allodynic/ hyperalgesic state is suspected, dose reduction of the causative agent and/or substitution of the causative agent with an opioid agonist less likely to cause such symptoms are appropriate next steps aiming at attenuating or eliminating these symptoms” (p. 581). It is recommended not only to lower the doses of the causative agents but also to switch or rotate to different opioids as it is possible that not all opioids are implicated in inciting this hyperalgesic response (Angst & Clark, 2006; Chu et al., 2008).

Additionally, in the treatment of chronic OIH, it is recommended to start the patient on methadone. Methadone has been shown to have an efficacy in reducing OIH because of its weak NMDA receptor affinity. Chu et al. (2008) asserted that opioid rotation to methadone significantly reduced the symptoms of OIH and began to resolve the suspected hyperalgesia. While the use of methadone may be less applicable in the short- term clinical period, its possible use in the treatment of OIH should be discussed. It has been shown to reduce high- dose opioid OIH and can be included in opioid rotation strategies to improve the symptoms of OIH. According to Lee et al. (2011), “methadone offers several advantages for opioid switching or rotation, including incomplete cross- tolerance with opioid receptors and NMDA receptor antagonism” (p. 153). Some major disadvantages of methadone include its possibility of undesirable side effects such as Torsades de Points at higher doses, and the possibility that it may activate pronociceptive pathways and leads to increased pain states in patients with chronic pain (Lee et al., 2011). Some articles have shown conflicting evidence for methadone in the treatment of OIH, with one article reporting an increase in the symptoms of OIH.

Conclusion

While many advances have been made recently in the area of opioid- induced hyperalgesia, additional studies are needed to fully understand the anesthetic implications of this complex phenomenon. According to Angst & Clark (2006), “existing data suggest that peripheral, spinal cord, and higher central nervous system structures may be involved in OIH, but many specifics are missing from our understanding. Such topics include the sensitization of primary afferents, the over- all understanding of the neurotransmitter systems involved, the participating intracellular second messenger systems, and the genetic susceptibility to OIH” (p. 583). Future studies should continue to clarify and expand out understanding of the mechanisms of opioid- induced hyperalgesia in humans. More larger- scale studies should attempt to elicit specifically which opioids are implicated in causing hyperalgesia and additional research should be conducted to determine the most effective ways at preventing its development. Future research should also focus on the development of agents that antagonize CCK activity in the RVM or prevent the development of spinal dynorphins, which lead to the development of descending pain facilitation. Finally, the clinical significance of this phenomenon should be determined in future studies, especially with regard to the development of chronic pain in the setting of OIH. This research will help with the recognition of OIH within the perioperative setting and lead to more definitive treatment recommendations.

References

- Aley, D. & Levine, J. (1997). Different mechanisms mediate development and expression of tolerance and dependence for peripheral μ - opioid antinociception in rat. *The Journal of Neuroscience*, 17(20), 8018- 8023.
- Angst, M. & Clark, D. (2006). Opioid- induced hyperalgesia: a qualitative systematic review. *Anesthesiology*, 104(3), 570-587.
- Chu L., Angst M., & Clark, D. (2008). Opioid- induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clinical Journal of Pain*, 24(6), 479–496.
- Collard, V., Mistraletti, G., Taqi, A., Asenjo, J., Feldman, L., Fried, G., & Carli, F. (2007). Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing laparoscopic cholecystectomy. *Anesthesia & Analgesia*, 105(5), 1255-1262.
- Fishbain D., Cole B., Lewis J., Gao J., & Rosomoff, R. (2009). Do opioids induce hyperalgesia in humans? An evidence- based structured review. *Pain Medicine*, 10(5), 829- 839.
- Fletcher, D. & Martinez, V. (2014). Opioid- induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *The British Journal of Anaesthesia*, 112(6), 991- 1004.
- Gardell, L., Wang, R., Burgess, S., Ossipov, M., Vanderah, T., Malan, T., Lai, J., & Porreca, F. (2002). Sustained morphine exposure induces a spinal dynorphin- dependent enhancement of excitatory transmitter release from primary afferent fibers. *The Journal of Neuroscience*, 22(15), 6747- 6755.

- Guignard B., Bossard, A., Coste, C., Sessler, D., Lebrault, C., Alfonsi, P., Fletcher, D., Chauvin M. (2000). Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology*, *93*(2), 409- 417.
- Hood, D., Curry, R., & Eisenach, J. (2003). Intravenous remifentanil produces withdrawal hyperalgesia in volunteers with capsaicin- induced hyperalgesia. *Anesthesia and Analgesia*, *97*(3), 810–815.
- Ilkjaer, S., Bach, L., Nielsen, P., Wernberg, M., & Dahl, J. (2000). Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy. *Pain*, *86*(1-2), 19–24.
- Joly V., Richebe P., Guignard B., Fletcher, D., Maurette, P., Sessler, D., & Chauvin, M. (2005). Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology*, *103*(1), 147–155.
- Koppert, W., Angst, M., Alsheimer, M., Sittl, R., Albrecht, S., Schüttler, J., & Schmelz, M. (2003), Naloxone provokes similar pain facilitation as observed after short-term infusion of remifentanil in humans. *Pain*, *106*(1-2), 91–99.
- Koppert, W., Sittl, R., Scheuber, K., Alsheimer, M., Schmelz, M., Schüttler, J. (2003). Differential modulation of remifentanil- induced analgesia and postinfusion hyperalgesia by s-ketamine and clonidine in humans. *Anesthesiology*, *99*(1), 152-159.
- Lee, M., Silverman, S., Hansen, H., Patel, V., & Manchikanti, L. (2011). A comprehensive review of opioid induced hyperalgesia, *Pain Physician*, *14*(2), 145-161.
- Lenz, H., Raeder, J., Draegni, T., Heyerdahl, F., Schmelz, M., & Stubhaug, A. (2011). Effects of COX inhibition on experimental pain and hyperalgesia during and after remifentanil infusion in humans. *Pain*, *152*(6), 1289-1297. doi: 10.1016/j.pain.2011.02.007.

- Li, X., Angst, M., & Clark, D. (2001). A murine model of opioid- induced hyperalgesia. *Molecular Brain Research, 86*(1-2), 56-62.
- Longnecker, D., Brown, D., Newman, M. & Zapol, W. (2012). *Anesthesiology* (2nd ed.). New York, NY: McGraw-Hill.
- Mao, J., Price, D., & Mayer, D. (1994). Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C. *The Journal of Neuroscience, 14*(4), 2301-2302.
- Salengros, J., Huybrechts, I., Ducart, A., Faraoni, D., Marsala, C., Barvais, L., Cappello, M., & Engelman, E. (2010). Different anesthetic techniques associated with different incidences of chronic post- thoracotomy pain: low- dose remifentanil plus presurgical epidural analgesia is preferable to high- dose remifentanil with postsurgical epidural analgesia. *Journal of Cardiothoracic and Vascular Anesthesia, 24*(4), 608-616.
- Xie, J., Herman, D., Stiller, C., Gardell, L., Ossipov, M., Lai, J., Porreca, F., & Vanderah, T. (2005). Cholecystokinin in the rostral ventromedial medulla mediates opioid- induced hyperalgesia and antinociceptive tolerance. *The Journal of Neuroscience, 25*(2), 409-416.