

## Review Article

# Neuraxial opioid-induced pruritus: An update

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### Abstract

Pruritus is a troublesome side-effect of neuraxial (epidural and intrathecal) opioids. Sometimes it may be more unpleasant than pain itself. The prevention and treatment still remains a challenge. A variety of medications with different mechanisms of action have been used for the prevention and treatment of opioid-induced pruritus, with mixed results. The aim of this article is to review the current body of literature and summarize the current understanding of the mechanisms and the pharmacological therapies available to manage opioid-induced pruritus. The literature source of this review was obtained via PubMed, Medline and Cochrane Database of Systematic Reviews until 2012. The search results were limited to the randomized controlled trials, systemic reviews and non-systemic reviews.

**Key words:** Complications, epidural, itching, neuraxial opioids, post-operative, pruritus, spinal

### Introduction

Neuraxial opioids are one of the most frequently used methods of analgesia after cesarean delivery and other surgical procedures. The beneficial effect of neuraxial opioids used either alone or in combination with the local anesthetics is to augment and prolong intraoperative and postoperative analgesia. A wide range of side-effects has been reported, out of which one is pruritus.<sup>[1]</sup>

Pruritus, a subjective unpleasant and irritating sensation that provokes an urge to scratch and the symptoms typically start at the trunk, nose, around the eyes and is usually localized to facial areas, innervated by the trigeminal nerve.<sup>[2]</sup> The spinal nucleus of the trigeminal nerve is rich in opioid receptors and is continuous with the substantia gelatinosa and Lissauer tract at C3-C4.<sup>[3]</sup> The ophthalmic division of the spinal sensory nucleus of the trigeminal nerve is most inferior; thus, supporting the observation that the pruritus following neuraxial opioid administration is typically in the nose and upper part of the face.<sup>[3]</sup>

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The objective of this review is to understand the pathophysiology and mechanism of opioid-induced pruritus and review the current body of literature for evidence available for pharmacological therapies to manage opioid-induced pruritus.

### Incidence and prevalence

The incidence of pruritus is 83% in postpartum patients and 69% in non-pregnant patients including males and females.<sup>[4-7]</sup> Pregnant women seem to be more susceptible to pruritus after neuraxial opioid administration than other populations, with incidence of 60-100%.<sup>[2,8,9]</sup> In contrast, after orthopedic surgery, the incidence of pruritus after intrathecal opioid ranged from 30% to 60%.<sup>[10-12]</sup> This increased incidence may be due to an interaction of estrogen with opioid receptors.<sup>[13,14]</sup>

Pruritus begins shortly after analgesia, with the onset depending on the type, route and dosage of opioid used. Pruritus invoked by lipid-soluble opioids such as fentanyl and sufentanil is of shorter duration, and the use of the minimum effective dose and addition of local anesthetics seems to decrease the prevalence and the severity of itching. Pruritus invoked by intrathecal morphine is of longer duration and is difficult to treat.<sup>[15]</sup> Intrathecal administration, of opioids reach peak concentrations in the cerebrospinal fluid almost immediately.<sup>[16,17]</sup> After epidural administration, there is a delay in the rise to peak concentration (10-20 min with fentanyl and 1-4 h with morphine).<sup>[17,18]</sup> Co-administration of epinephrine may have an influence on spinal and epidural opioid-induced side-effects, including pruritus. As a vasoconstrictor agent, epinephrine decreases the vascular uptake of the opioid from the spinal and epidural space,

increasing opioid concentrations within the cerebrospinal fluid and therefore, possibly increasing the severity of side-effects.<sup>[1,2]</sup>

### Mechanism of neuraxial opioid-induced pruritus

The exact mechanism of neuraxial opioid-induced pruritus is unclear. Many mechanisms have been postulated, but no single mechanism can explain all instances.

Postulated mechanisms include:<sup>[15,16,19-23]</sup>

- The presence of “itch center” in the central nervous system
- Medullary dorsal horn activation and antagonism of inhibitory transmitters
- Modulation of the serotonergic pathway
- Theory linking pain and pruritus.

It appears pain and pruritus are transmitted by the same population of sensory neurons, namely small un-myelinated nerve fibers (C-fibers) and the release of prostaglandins (PGE1 and PGE2) enhance C-fiber transmission to the central nervous system, which potentiates pruritus.<sup>[24]</sup>

A high density of 5-hydroxytryptamine subtype 3 (5-HT<sub>3</sub>) receptor and  $\mu$  receptors are present in the superficial layers of the dorsal horn and in the nucleus of the spinal tract of the trigeminal nerve in the medulla. The spinal trigeminal nucleus located superficially in the medulla is an integrative center for sensory input from the face and an area known as the “itch center.” The Cephalic migration of neuraxial opioids toward this “itch center and activation of 5-HT<sub>3</sub> receptors by opioids may play a role in the generation of neuraxial opioid-induced pruritus.<sup>[25,26]</sup>

Opioids can also induce itching at the spinal level by “itch-selective” secondary neurons in the lamina I spino-thalamic tract of the dorsal horn. The active wide dynamic range or nociception-specific neurons of the dorsal horn inhibit these spinal itch neurons. If this inhibition is weakened by opioids, the disinhibited itch neurons become active and mediate itching, without stimulation of the primary afferent peripheral nerves.<sup>[26]</sup> Spinal triggering of itching is observed in particular by activation of  $\mu$ -opioid receptors (MOR) although  $\kappa$ -opioid receptors (KOR) suppress itch.<sup>[26-28]</sup>

### Prevention and treatment of opioid-induced pruritus

Treatment of neuraxial opioid-induced pruritus remains a challenge. It is often difficult to treat and is refractory to conventional antipruritic treatment. Several drugs have been tried with some evidence of efficacy. The pharmacological therapies including antihistamines, 5-HT<sub>3</sub>-receptor antagonists, opiate-antagonists, propofol, non-steroidal

anti-inflammatory drugs (NSAIDs), and droperidol have been studied.

### 5-HT<sub>3</sub> receptor antagonist

5-HT<sub>3</sub> receptors are abundant in the dorsal horn of the spinal cord and the spinal tract of the trigeminal nerve in the medulla. The interaction between opioids and 5-HT<sub>3</sub> receptors may play a role in the generation of neuraxial opioid-induced pruritus.<sup>[7,8,29]</sup> 5-HT<sub>3</sub> antagonists, such as ondansetron, granisetron, and dolasetron have been used to prevent the neuraxial opioid-induced pruritus.

Systematic review of 15 randomized controlled trials (RCTs) indicates that prophylactic treatment with a single i.v. bolus of 5-HT<sub>3</sub> receptor antagonists may provide a significant decrease in the incidence and the intensity score of pruritus after neuraxial opioid administration, particularly when morphine is used. It also suggested a significant decrease in the requirement for treatment of pruritus.<sup>[7]</sup> Dosage for the 5-HT<sub>3</sub> receptor antagonists used were ondansetron four, and 8 mg, or 0.1 mg kg.<sup>[30]</sup> The other 5-HT<sub>3</sub> receptor antagonists studied are Tropisetron (5 mg), granisetron (3 mg), and dolasetron (12.5 mg).

5-HT<sub>3</sub> receptor antagonists reduced the incidence of pruritus after neuraxial morphine injection but not after neuraxial lipid-soluble opioids injection. One of the postulated mechanism is Morphine is less lipid-soluble and slow in the onset of analgesia, which gives higher residual opioid concentration in the cerebrospinal fluid and a greater cephalic migration.<sup>[31]</sup> As the peak concentration of ondansetron, occurs around 15 min, 5-HT<sub>3</sub> antagonists may reach 5-HT<sub>3</sub> receptors in the spinal cord before morphine, but not after the lipid-soluble drugs.<sup>[32,33]</sup>

### Opioid receptor antagonist

The  $\mu$  receptor is responsible for pain modulation and some side-effects, especially pruritus and nausea or vomiting. Pre-treatment with clocinamox, a selective MOR antagonist inhibited intrathecal morphine-induced scratching in primates, but neither  $\kappa$ -opioid (binaltorphimine) nor  $\delta$ -opioid receptor antagonists (naltrindole) produced this effect. This explained the antipruritic effect of  $\mu$  receptor antagonists.<sup>[34]</sup> Several studies have evaluated the effectiveness of naloxone, naltrexone and methyl naltrexone in the prevention of opioid induced pruritus, but mixed results were seen. Based on the existing data, a low dose, continuous i.v. infusion of naloxone has the largest body of evidence supporting its use for prevention of opioid induced pruritus in adult. A continuous infusion produces less fluctuation of naloxone concentrations than bolus injections and compensates for naloxone’s relatively short half-life. It appears that an intravenous dose of 0.25-1  $\mu$ g/kg/h is the most effective without affecting analgesia.<sup>[35]</sup> A systematic review by Kjellberg and Tramer<sup>[36]</sup> concluded that doses above

2 µg/kg/h. are more likely to lead to reversal of analgesia and thus are not recommended.

### Mixed agonist – antagonist opioid

Mixed agonist – antagonist opioid has a potential to attenuate the µ-opioid effects and to enhance the κ-opioid effects. There is experimental evidence suggesting that activation of KOR attenuated morphine-induced itching without interfering with nociception in monkeys.<sup>[37]</sup> Studies have demonstrated that both MOR antagonists and κ-KOR agonists are effective in alleviating intrathecal morphine induced itch in primates.<sup>[38,39]</sup> Effectiveness of nalbuphine, butorphanol, and pentazocine has also been studied with positive results.<sup>[6,40-42]</sup>

Tamdee *et al.* performed a randomized trial to study the efficacy of pentazocine for the treatment of pruritus associated with intrathecal injection of morphine and concluded that pentazocine 15 mg is superior to ondansetron 4 mg for the treatment of intrathecal morphine-induced pruritus.<sup>[42]</sup>

Mixed agonist – antagonist opioid effectively prevents and treats opioid-induced pruritus without increasing pain, but the treatment may be complicated by increased drowsiness.<sup>[43]</sup> However, a recent study suggested that nalbuphine is not effective in the treatment of post-operative opioid-induced pruritus in the pediatric patients.<sup>[44]</sup>

### NSAIDs

NSAIDs have a well-recognized role in the relief of postoperative pain. They inhibit cyclooxygenases and decrease the formation of prostaglandins.

Tenoxicam and diclofenac have been shown to have anti-pruritic effects in patients receiving neuraxial opioids.<sup>[10,45]</sup> However, Gulhas *et al.*<sup>[24]</sup> found no decrease in pruritus with the use of Lornoxicam following intrathecal fentanyl administration. Celecoxib have shown mixed results in having anti-pruritic effects. Lee *et al.*<sup>[46]</sup> found no reduction of pruritus with the use of celecoxib following intrathecal morphine administration. Their study failed to demonstrate any significant antipruritic or analgesic effects of celecoxib in a single dose of 200 mg (administered after delivery of baby) within the first 24 h post-operatively but Samimi *et al.*<sup>[47]</sup> used 400 mg celecoxib orally 1 h before surgery and showed the effectiveness of celecoxib in decreasing the incidence of Intrathecal morphine-induced pruritus.

### Antihistamines

H1 blockers have little or no effect on centrally induced pruritus; although, first-generation H1 receptor antagonists such as diphenhydramine or hydroxyzine may produce a sedative effect, which could sometimes, be helpful in patients

with pruritus. They primarily interrupt the itch-scratch cycle by providing needed sleep but are not really effective at reducing the severity of the itch.<sup>[13]</sup>

### Propofol

Propofol has been used for the treatment and prevention of pruritus. It exerts its antipruritic action through the inhibition of the posterior horn transmission in the spinal cord.<sup>[11,48-54]</sup> Many studies have been carried out with the sub-hypnotic propofol doses ranging from 10 mg bolus to 30 mg over 24 h, but results were conflicting.<sup>[5,11,25]</sup>

### Mirtazapine

Mirtazapine is a new antidepressant that selectively blocks 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors. Mirtazapine has a unique pharmacological profile apart from increasing noradrenergic and serotonergic neurotransmission; mirtazapine can exert its antidepressant and anti-nociception action through the κ-opioid system.<sup>[51,52]</sup> Its antipruritic activity was first reported by Davis *et al.*<sup>[53]</sup> Sheen *et al.* studied Mirtazapine to reduce intrathecal morphine-induced pruritus.<sup>[54]</sup> They concluded that pre-operative oral mirtazapine 30 mg decreased the incidence, delayed the onset time, decreased the severity, and shortened the duration of pruritus. Mirtazapine could exert its antipruritic effect through activating the κ-opioid system. Secondly, mirtazapine can work on the cerebral cortex to reduce the perception of pruritus. Thirdly, mirtazapine had strong antihistamine effect. From the pharmacokinetic viewpoint, mirtazapine has another advantage over the first-generation 5-HT<sub>3</sub> receptor antagonists. The peak concentration of mirtazapine is reached 2 h. after a single dose and the elimination half-life ranges from 20 h to 40 h.<sup>[55]</sup> allowing the drug to cover the onset and duration of pruritus.

### Dopamine D2 receptor antagonist

Droperidol and alizapride has also been used for the treatment of opioid-induced pruritus. Both are potent dopamine D<sub>2</sub> receptor antagonist. Droperidol is also having weak anti-5-HT<sub>3</sub> activity. In the study by Horta *et al.*<sup>[50]</sup> involving 300 women undergoing cesarean section, the intravenous droperidol subgroup showed the lowest prevalence of pruritus compared with placebo and also compared with propofol, alizapride, and promethazine. Metoclopramide, another dopamine D<sub>2</sub> receptor antagonist has been shown to be ineffective in this regard.<sup>[56]</sup>

### Gabapentin

Gabapentin is an anticonvulsant, a structural analog of γ-amino butyric acid. Several studies have shown gabapentin to be effective in many chronic pruritus conditions.<sup>[57-61]</sup> Sheen *et al.* studied the role of gabapentin in the management of intrathecal morphine-induced pruritus.<sup>[62]</sup> They concluded that

pre-operative gabapentin 1200 mg decreased the incidence, delayed the onset time, decreased the severity, and shortened the duration of intrathecal morphine pruritus and it may be due to the multimodal anti pruritic action of gabapentin that includes central reduction of itch perception,<sup>[63]</sup> modulatory action on transmitter release,<sup>[64]</sup> which reduce the excitability of spinal and supraspinal neurons during itch transmission and spinal-supraspinal inhibition of serotonergic circuits.<sup>[65]</sup> Recently, Chiravanich *et al.* has carried out RCT on single dose of gabapentin as prophylaxis for intrathecal morphine-induced pruritus in orthopedic surgery.<sup>[66]</sup> They Concluded that pre-operative gabapentin 600 mg did not significantly reduces the post-operative intrathecal morphine-induced pruritus. Therefore, the effectiveness of antipruritic dosage and the other pharmacological mechanisms of gabapentin need further study.

## Prevention

The treatment of neuraxial opioid-induced pruritus is complex even after, significant research in these fields. We yet fail to describe a definitive treatment. Believing that prevention is better than cure and we suggest the use of minimal analgesic doses of neuraxial opioids, use of neuraxial opioids in combination with a local anesthetic, which offers satisfactory analgesia with a very low incidence of pruritus.<sup>[4]</sup> Drugs such as Tenoxicam, rectal diclofenac, pre-operative oral gabapentin, intravenous 5-HT<sub>3</sub> antagonists, droperidol and subhypnotic dose of propofol have shown positive results for prevention of neuraxial opioid-induced pruritus and therefore, may be considered as possible prophylactic therapy.

## Conclusion

Pruritus is a well-recognized adverse effect of neuraxial opioids. It may have an impact on patient comfort, quality of life, and willingness to continue opioid therapy. Mechanism of intrathecal opioid-induced pruritus is complex and the literature data on the pathogenesis is still not clear. Many treatments have been tried, but to date, the data are conflicting and only limited studies have confirmed their efficacy. MOR antagonists, mixed opioid receptor agonist-antagonists, serotonin 5-HT<sub>3</sub> receptor antagonists, and D<sub>2</sub> receptor antagonists have been demonstrated most consistent in terms of attenuating opioid-induced pruritus.

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