Neuraxial Opioid-Induced Pruritus: A Review

Szilvia Szarvas, MB,* Dominic Harmon, MMedSci, FCARCSI,† Damian Murphy, MD, FFARCSI‡

Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital, Wilton Road, Cork, Ireland

When intrathecal and epidural opioids are administered, pruritus occurs as an unwanted and troublesome side effect. The reported incidence varies between 30% and 100%. The exact mechanisms of neuraxial opioid-induced pruritus remain unclear. Postulated mechanisms include the presence of an “itch center” in the central nervous system, medullary dorsal horn activation, and antagonism of inhibitory transmitters. The treatment of intrathecal opioid-induced pruritus remains a challenge. Many pharmacological therapies, including antihistamines, 5-HT3-receptor antagonists, opiate-antagonists, propofol, nonsteroid antiinflammatory drugs, and droperidol, have been studied. In this review, we will summarize pathophysiological and pharmacological advances that will improve understanding and ultimately the management of this troublesome problem.

Keywords: Itching; opioids: epidural, spinal.

Introduction

Antinociception without side effects has been a difficult problem in the history of medical science. In the 1970s, highly specific opioid receptors were discovered in the central nervous system (CNS), including the spinal cord, and it seemed to bring physicians closer to finding a solution to the problem. This, however, has not been achieved. Intrathecal and epidural anesthesia is common in anesthetic practice, providing successful analgesia. The beneficial effect of intrathecal morphine used either alone or in combination with local anesthetics is to augment and prolong intraoperative and postoperative analgesia. However, a wide variety of clinically relevant side effects have been reported. One of these side effects is pruritus, which is a common sensation after the administration of opioids. Itch is by definition a sensation that provokes the desire to scratch and can be aroused by variety of mechanical, electrical, and chemical stimuli.1 It is bothersome to the patient and sometimes may be more unpleasant than pain itself for the patient.1

The reported incidence of pruritus after neuraxial opioid administration varies from 30% to 100%.2–7 Parturients appear to be the most susceptible. The incidence of neuraxial opioid-induced pruritus in parturients has been reported to be between 60% and 100%,4,6,8 and appears to be dose-dependent.1,6,8–10 This increased incidence may be due to an interaction of estrogen with opioid receptors.11,12 Following major orthopedic surgery, the incidence of pruritus after intrathecal opioids is less, with an incidence of between 30% and 60%.13–16
The exact mechanism of neuraxial opioid-induced pruritus is unclear. Postulated mechanisms include the presence of an “itch center” in the CNS, medullary dorsal horn activation, and antagonism of inhibitory neurotransmitters. Modulation of the serotonergic pathway and involvement of prostaglandins may also be important in the etiology of neuraxial opioid-induced pruritus.

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. The evidence regarding an influence of co-administered epinephrine on neuraxial opioid induced pruritus is conflicting.

The treatment of intrathecal opioid-induced pruritus remains a challenge. Many pharmacological therapies including antihistamines, 5-HT3-receptor antagonists, opioid agonists, and propofol, nonsteroidal antiinflammatory drugs (NSAIDs), and droperidol have been studied. In this review we will summarize pathophysiological and pharmacological advances that will improve understanding and ultimately the management of this troublesome problem.

Pathophysiology of Neuraxial Opioid-Induced Pruritus

The wide range in the reported incidence of neuraxial opioid-induced pruritus suggests that there may be individual patient differences that influence itch perception. This concept is further supported by the lack of association between the dose of opioids administered neuraxially and the intensity with which pruritus is perceived by patients, and by the absence of the symptom in some patients receiving neuraxial opioids. More than one mechanism may participate in the development of neuraxial-opioid induced pruritus.

Receptors in the Skin

The sensation of itch arises from the superficial layers of the skin, the mucous membranes, and the conjunctivae. Based on microstimulation studies, the current view is that nerve endings in the subepidermal area cluster densely around “itch points” that correspond to areas that are very sensitive to pruritogenic stimuli in humans. Schmelz and colleagues in 1997 identified a new class of afferent C fibers with particularly thin axons using a computer-assisted marking technique. This group postulated that this type of C fiber may represent the afferent units mediating itch sensation.

Mediators

Serotonin

Morphine produces part of its analgesic effect through the release of serotonin. There are dense concentrations of serotonin receptors in the dorsal part of spinal cord and the nucleus of the spinal tract of the trigeminal nerve in the medulla, in which opioid receptor density is also high. These observations suggest that the 5-HT3 receptor may be implicated in the development of the pruritus associated with administration of neuraxial opioids. Ondansetron, a specific 5-HT3 antagonist, has been shown to decrease the incidence of pruritus following intrathecal morphine injection associated with elective cesarean section.

Prostaglandins

It has also been suggested that prostaglandin (PGE1 and PGE2) release may be associated with neuraxial opioid-induced pruritus. Colbert and colleagues have reported that tenoxicam and diclofenac had antipruritic effects in patients after intrathecal and epidural opioid administration, respectively. Prostaglandins (PGE1 and PGE2) enhance C fiber transmission to the CNS. They are also known to release histamine and to potentiate pruritus induced by histamine. Colbert and colleagues assumed that the antipruritic effects of NSAIDs in patients following intrathecal and epidural opioids may have been largely due to their analgesic effects.

Pruritus Associated with Liver Disease

Similarities of pruritus of liver disease and that associated with intrathecal opiates implicate the encephalins. Observations in clinical trials that pruritus associated with both intrathecal morphine administration and cholestatic liver disease can be treated successfully with the same antipruritic agents (specific opioid-antagonists, ondansetron, and propofol) suggests that a common causal pathway exists between the two clinical syndromes. Jones and colleagues have postulated that opioidergic neurotransmission/neuromodulation in the CNS contributes to the pruritus of cholestasis. The concentration of endogenous opioid (metenkephalin and leu-enkephalin) agonists are elevated in the plasma of rats with acute cholestasis and patients with chronic cholestasis. Furthermore, both intrathecal morphine (1 to 32 μg administration and microinjection of morphine and opioid agonist ligand [(D-Ala2-N-Me-Phe4,Gly-ol)-enkephalin] into the medullary dorsal horn of monkeys induces dose-dependent facial scratching activity, which is reversed by naloxone and naloxone. Therefore, it is likely that in cholestasis, the elevated plasma level of endogenous opioid contributes to pruritus but the specification of this endogenous opioid receptor ligand and the site of synthesis of endogenous opioids involved has not yet been confirmed.

Central Mechanisms of Spinal Opioid-Induced Itch

The reported incidence of pruritus after intrathecal morphine is 62% to 85%, after epidural morphine the incidence is 65% to 70%, after intrathecal fentanyl 67% to 100%, after epidural fentanyl 67%, after intrathecal sufentanil 80%, and after epidural sufentanil 55%. After
intrathecal administration, opioids reach peak concentrations in the cerebrospinal fluid almost immediately. After epidural administration there is a delay in rise to peak concentration (10 to 20 min with fentanyl and 1 to 4 hours with morphine). Neuraxial opioids administered in the lumbar region reach their peak cerebrospinal fluid concentration at the level of cisterna magna after 1 to 2 hours (also the level of nucleus trigeminus). In 181 parturients undergoing elective cesarean section, who received 0.2 mg intrathecal morphine, the onset of pruritus occurred between 25 and 180 minutes following the neuraxial administration of morphine. It is noteworthy that the time course of pruritus occurs within 1 to 3 hours of morphine administration in healthy human volunteers as well as in clinical trials in which authors examined the association between drug administration and onset of pruritus.

Receptors that mediate the pruritus associated with morphine administration are likely to be the μ-opioid receptor. Intrathecal morphine-induced scratching in monkeys is mainly mediated by this receptor. In cholestatic rats with scratchy behavior, the density of μ-opioid receptors in the brain is significantly decreased, further implicating the μ-opioid receptor.

In contrast with morphine, fentanyl penetrates the spinal cord rapidly because of its highly lipophilic nature, leaving little drug to ascend cephalad in cerebrospinal fluid. In a study of 65 parturients undergoing elective cesarean section, parturients were randomly assigned to receive intrathecal 1) fentanyl (25 μg) only, 2) bupivacaine (2.5 mg) only, or 3) fentanyl (25 μg) plus bupivacaine (2.5 mg). Pruritus occurred within 5 minutes following either intrathecal fentanyl or fentanyl plus bupivacaine administration.

Facial areas innervated by the trigeminal nerve are predominantly affected. The distribution of itching in such a fashion is likely to be due to cephalad spread of opioids in the cerebrospinal fluid and subsequent interaction with the trigeminal nucleus and nerve roots. Scott and Fischer suggest a central encephalergic mechanism for this localization of pruritus. 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. Furthermore, the ophthalmic division of the spinal sensory nucleus of the trigeminal nerve is most inferior, thus supporting the observation that the pruritus following intrathecal opioid administration is typically in the nose and upper part of face regions.

Koenigstein has described the presence of an itch center in the lower medulla that includes the trigeminal nucleus. Injection of high doses of morphine (0.2 to 1.0 mg/Kg) into the cisterna cerebellomedullaris of cats induces itch behavior. Intracisternal injection of alizarin blue produces itch and stains in depth only the lower part of the medulla oblongata. When these observations are considered together, they provide convincing evidence of an itch center in the medulla oblongata. Opioid administration into the cerebral ventricles also induces behavioral excitation that is not reversible with naloxone. It is thus postulated that CNS excitation may be a result of mechanisms other than opioid receptor activation. This property of opioids may also participate in the pathophysiology of itch.

Opioid antagonism of inhibitory neurotransmitters gamma-aminobutyric acid and glycine in the CNS may be a possible mechanism of opioid-induced pruritus. Intrathecal administration of the glycine antagonist strychnine in cats produces similar itch and scratch behavior as large doses of intrathecal morphine. It could be that antagonism of the inhibitory neurotransmitter glycine is responsible in both cases.

The current therapeutic strategies for spinal opioid-induced pruritus are unsatisfactory. Several agents from numerous drug families have been employed, although none has proved to be totally effective. Recent insights into pathophysiological mechanisms may offer promising developments in the prevention of neuraxial opioid-induced pruritus.

Although nonpharmacological therapy can be used, this review discusses currently used pharmacologic agents in the prevention and treatment of neuraxial opioid-induced pruritus.

### Prevention

#### Antihistamine Drugs

Antihistamines are useful in the treatment of urticarial pruritus and those diseases in which histamine release plays a role. In neuraxial opioid-induced itch, histamine is not released and does not appear to be causative. Antihistamines are thus unlikely to have any role in the

---

**Table 1. The Treatment and Prevention of Neuraxial-Induced Pruritus, Mechanisms and Sites of Action**

<table>
<thead>
<tr>
<th>Pharmacologic Agents</th>
<th>Mechanism</th>
<th>Site of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid antagonists</td>
<td>μ-Receptor inhibition</td>
<td>Medullary dorsal horn, nucleus trigeminalis</td>
</tr>
<tr>
<td>Propofol</td>
<td>Depression of nerve transmission</td>
<td>Medullary dorsal horn</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Cyclooxygenase enzyme inhibition</td>
<td>Endoplasmic reticulum of macrophages</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Depression of nerve transmission</td>
<td>Medullary dorsal, horn nucleus trigeminalis</td>
</tr>
<tr>
<td>5-Hydroxytryptamine type 3 (5-HT₃) antagonist</td>
<td>5-HT₃ receptor inhibition</td>
<td>Medullary dorsal horn, nucleus trigeminalis</td>
</tr>
</tbody>
</table>

---

**Notes:**

1. Scott et al., 11
2. Fischer, 6
3. Antihistamines are thus unlikely to have any role in the treatment of neuraxial opioid-induced pruritus.
prevention of neuraxial opioid-induced pruritus. Sedative properties of antihistamines may be helpful because they temporarily allow much needed sleep. They interrupt the itch-scratch cycle, but without relieving itch sensation.11

**Opioid Antagonists**

Opioid antagonists may have a role in the prevention of neuraxial opioid-induced pruritus. In a quantitative systematic review, Kjellberg and Tramer32 analyzed clinical trials including those in which opiate antagonists were used in the prevention of intrathecal and epidural opioid-induced pruritus. Trials with intravenous (IV) naloxone, oral naltrexone, and IV nalbuphine were compared. Combined data suggested that naloxone infusions were efficacious, but at infusions greater than 2 \( \mu \text{g.Kg}^{-1}.\text{hr}^{-1} \), the number of patients requiring rescue analgesia was significantly increased.40 Oral naltrexone (6 to 9 mg) was more efficacious than control although analgesia was also decreased at higher doses.41 Nalbuphine as a 40-mg bolus IV injection has a reported efficacy and is not associated with decreased pain scores, although it is associated with increased drowsiness compared with control.32 In this systematic review, the authors were unable to find a dose-dependent decrease in the incidence of pruritus with opioid antagonists, possibly because of the high doses used in these trials. More studies are needed to assess dose responsiveness and optimal dosages required.32 Furthermore, whether peripheral opioid antagonists such as methylnaltrexone would decrease the incidence of pruritus is unknown. The study of these agents may allow further insight into peripheral versus central mechanisms of neuraxial opioid-induced pruritus.

**Propofol**

Propofol has been shown to produce marked depression of posterior horn transmission in the spinal cord and probably exerts its antipruritic action through this inhibition.15 Torn and colleagues15 examined the efficacy of propofol (10-mg bolus followed by 30 mg/24 hr infusion) in preventing intrathecal opioid-induced pruritus. Propofol infusion decreased the incidence of pruritus compared with control (20% vs. 60%).15

**Nonsteroidal Antiinflammatory Drugs**

Nonsteroidal antiinflammatory drugs have a well-recognized role in the relief of postoperative pain. NSAIDs inhibit cyclooxygenase and decrease formation of PGE1 and PGE2 and this effect may modulate the perception of pruritus. Colbert and colleagues13,14 investigated the anti-pruritogen effects of NSAIDs (diclofenac and tenoxicam) in patients who received intrathecal13 and epidural14 opiates, respectively. Tenoxicam significantly decreased pruritus scores associated with epidural morphine compared with the control.13 The efficacy of diclofenac in decreasing intrathecal opioid-induced pruritus scores was also significant.14

**Droperidol**

Among the neuroleptic drugs, droperidol has been studied. It has been postulated that droperidol can decrease the excitatory side effects, such as pruritus, of neuraxial opioids.42 Furthermore, droperidol is a weak 5-HT3-receptor antagonist, an action that may be beneficial. There is conflicting evidence regarding the effectiveness of droperidol in the treatment or prevention of pruritus.43–46 Horta and colleagues6 studied 140 parturients undergoing cesarean section following epidural anesthesia including 2 mg of morphine. Patients were randomly allocated to four groups: 1) morphine only, 2) 1.25 mg, 3) 2.5 mg, and 5) 5 mg, respectively, of droperidol was administered with epidural morphine. Although efficacy increased with the dose of epidural droperidol so also did sedation, the decreased incidence of pruritus remained when patients with somnolence were excluded. In this study, however, there was no statistically significant difference in outcome between control and droperidol-treated groups.

**5-HT3 Receptor Antagonists**

There is a relatively high density of 5-HT3 receptors in the nucleus of the spinal tract of the trigeminal nerve in the medulla oblongata.45 Injection of morphine in this anatomical region produces a dose-dependent, naloxone-reversible pruritus on the face of the monkey.46 These observations suggest that the 5-HT3 receptor is implicated in the development of pruritus associated with the application of neuraxial opioids. Yeh and colleagues4 studied 60 parturients who were scheduled for elective cesarean section. After intrathecal morphine (0.15 mg) administration, patients in the ondansetron group received 0.1 mg/Kg4 ondansetron IV. The incidence of pruritus was significantly lower in the ondansetron (25%) compared with placebo group (85%).4

**Treatment**

There are a limited number of studies concerning the treatment of established pruritus.19 Agents that have been studied include opioid antagonists, propofol, and 5-HT3 receptor antagonists.

Charuluxananan and colleagues50 studied nalbuphine and propofol treatment of intrathecal morphine-induced pruritus in 181 parturients undergoing elective cesarean section. The treatment success rate was higher in the nalbuphine (3 mg IV) group compared with the propofol (20 mg IV) group (83% vs. 61%). Decreased analgesia associated with treatment was not significantly different between the groups.50 Nalbuphine also has been shown to be more effective in the treatment of neuraxial opioid-induced pruritus than either naloxone50 or diphenhydramine.51

Borgeat and colleagues57 evaluated the efficacy of IV propofol (10 mg) versus placebo following intrathecal morphine administration. In their study, in the absence of a positive treatment response, a second drug treatment was given 5 minutes later. The persistence of pruritus 5
minutes after the second dose was considered a treatment failure and these patients received a supplementary dose of propofol (10 mg) and were reevaluated 5 minutes later. Treatment success rate was significantly greater in the propofol group (84%) than in the placebo group (16%). In addition they found that 90% of the treatment failures in the placebo group were successfully treated by a supplementary dose of propofol. At the dose administered (10 mg), side effects were rare and minor. The use of propofol infusions, however, requires constant supervision.

Other studies in which propofol (10 mg) versus placebo was examined in the treatment of intrathecal morphine-induced pruritus, did not demonstrate a beneficial effect. The incidence of neuraxial opioid-induced pruritus is higher in the obstetric population, which may be due to interaction between the higher plasma estrogen levels with opioid receptors. This may explain difference in efficacy of propofol between the nonobstetrical and obstetrical population. Significant treatment success with ondansetron in epidural (2 mg) and intrathecal (0.2 mg) morphine-induced pruritus has been found in patients undergoing major orthopedic surgery. Other studies have demonstrated the effectiveness of ondansetron in the treatment of neuraxial opioid-induced pruritus in various patient populations, such as orthopedic, general, and pediatric patients.

**Conclusion**

Although pruritus after neuraxial administration of opioids is a common side effect, to date few studies have elucidated the mechanisms, mediators, neural pathways, and pathophysiology of this symptom. We agree with Kjellberg and colleagues, who analyzed 22 trials of drugs used in the treatment and prevention of opioid-induced pruritus, that the quality and the amount of data from these trials is not satisfactory. The fact that pruritus is an entirely subjective sensation and that simply the discussion of skin itching will make some individuals scratch, can make study design of the effectiveness of an antipruritic agents difficult. A better understanding of the pathophysiology would lead to improved preventative and treatment strategies.

In the management of neuraxial opioid-induced pruritus we recommend that minimal analgesic doses of opioids should be used to provide pain relief during and after surgical operations. NSAIDs may be a possible prophylactic therapy for opioid-induced pruritus. The efficacy of subhypnotic dose (10 mg), propofol as an antipruritic agent, is conflicting. Propofol administered as a bolus (10 mg) alone or as a bolus (10 mg) followed by 30-mg/24-hour infusion, has been reported to be an efficient drug treatment for spinal morphine-induced pruritus after gynecologic and orthopedic surgery. However, in two studies that included parturients undergoing elective cesarean section including spinal morphine, propofol (10 mg) in two divided doses 5 minutes apart was not efficacious. Additional clinical studies are thus necessary to determine the optimal effective dose of propofol that is not associated with excess sedation.

5-HT3 receptor antagonists should be the drugs of first choice. Ondansetron and propofol as prophylactic agents have been associated with minimal side effects, furthermore ondansetron has no effect on the quality of analgesia. An added benefit of ondansetron is its ability to prevent and treat postoperative nausea and vomiting. With multiple pathways involved in the pathophysiology of pruritus, combination therapy should be examined. Ondansetron and propofol seem to be the most promising agents whose antipruritic properties need to be investigated further.

**References**