Itch, scratch, itch: the opioid-induced pruritus

Sorin Buga[1], Andrada Daniela Totoran[2]

1. MD, Clinical Professor, Department of Supportive Care Medicine, City of Hope National Medical Center, United States of America

2. Medical Student at the Faculty of Medicine and Pharmacy of Oradea, Romania

Abstract

Opioids are essential medications in relieving pain, particularly in cancer pain. According to the World Health Organization, 55% of patients with cancer undergoing active anticancer therapies and 66% of the patients with advanced, metastatic cancer do experience pain. Opioids are prescribed for relieving pain to a level that allows for an acceptable quality of life; however, the same opioids have many side effects that can potentially limit their use, with pruritus being one of them. Opioid-induced pruritus can be localized or generalized, and the literature shows that its spread and intensity are dependent on individual sensitivity, but mostly on the type, the dose and the route of administration of the used opioids. Various mechanisms of action and treatment options, described in this review article, were proposed for opioid-induced pruritus.

Keywords: *opioid-induced pruritus, neuraxial opioids, mu-opioid receptors antagonists, mixed opioid receptor agonist-antagonists, serotonin 5-HT$_3$ receptor antagonists, dopamine D$_2$ receptor antagonists*

Rezumat

Opioidele sunt medicamente esențiale în tratarea durerii din cancer. Organizația Mondială a Sănătății estimează că aproximativ 55% dintre pacienții cu cancer care urmează tratamente oncologice suferă de durere, iar în cazul pacienților cu cancer avansat sau metastatic, procentajul este de 66%. Opioidele sunt prescrise pentru ameliorarea durerii la un nivel care permite o calitate acceptabilă a vieții, dar în același timp acestea au numeroase efecte adverse care limitează utilizarea lor. Unul dintre aceste efecte secundare demne de menționat este pruritul indus de opioide. Pruritul indus de opioide este descris ca fiind localizat sau generalizat. Literatura de specialitate menționează faptul că intensitatea pruritului poate fi influențată de susceptibilitatea individuală, dar în mai mare măsură de tipul, doza și de calea de administrare a opioidelor utilizate. Acest articol descrie câteva mecanisme de acțiune și modalități de tratament pentru pruritul indus de opioide.

Cuvinte-cheie: *prurit indus de opioide, opioide cu administrare neuroaxială, antagoniști ai receptorilor opioizi miu, agoniști-antagoniști micști ai receptorilor opioizi, antagoniști ai receptorilor serotoninergici 5-HT$_3$, antagoniști ai receptorilor dopaminergici D$_2$*

Submission date: 25.09.2021
Acceptance date: 5.10.2021

Prurit, scărpinat, prurit – pruritul indus de opioide

Suggested citation for this article: Buga S, Totoran AD. Itch, scratch, itch: the opioid-induced pruritus. Oncolog-Hematolog.ro. 2021;56(3):27-30.

Introduction

Pruritus is an unpleasant sensation of the skin provoking a desire, even an urge, to scratch. The origin of the word "pruritus" comes from the Latin word *prurire*. It is also known as itching[2,3].

Opioid-induced pruritus (OIP) is not a life-threatening condition, but it may have a major impact on one's quality of life, by affecting sleep and causing anxiety or depression. These symptoms in turn may decrease the patient's satisfaction and compliance with the proposed opioid therapy and, as a result, in an increase of the healthcare costs[4,5].

Incidence of opioid-induced pruritus

Various factors, such as the type, the dose and the route of administration of the opioid drug, along with individual sensitivity could affect the incidence of OIP. Some articles mentioned pregnancy as a potential favoring factor for opioid-induced pruritus, most likely resulting from an interaction between estrogens and the opioid receptors[6-8]. The literature mentions an incidence of OIP anywhere between 2% to 20% after oral administration, 10% to 50% after intravenous administration, and 30% to 100% after neuraxial administration[4,7].

An article stated that the incidence of opioid-induced pruritus related to morphine could be at about 65% to 70% after the epidural administration and at about 62% to 85% after the intrathecal route. The percentages tend to run high as well for sufentanyl (around 55% with epidural and 80% with intrathecal delivery) or for fentanyl (67% after epidural use and 67% to 100% after intrathecal administration)[9]. However, another article mentioned that the highest prevalence (up to 100%) was associated with intrathecal morphine[10].

The frequency of opioid-induced pruritus rises with increasing opioid dosages[8,10].

There are data showing that the risk for OIP in parturient patents could be anywhere between 60% and 100% after neuraxial delivery, and that it is related to the dose of the opioid used. The postulated mechanism is, as previously mentioned, a possible interaction of estrogens with the opioid receptors[9].

Mechanisms of opioid-induced pruritus

The mechanism of OIP is not yet fully understood, but most likely more than one pathway may be involved in producing this disturbing opioid side effect[4,7].

Multiple hypotheses aiming to explain the mechanisms of OIP have been proposed in literature:

1. Centrally mediated process *via* μ-opioid receptors with a possible presence of an "itch center" or of an activation of the medullary dorsal horn or of an antagonism of inhibitory transmitters[8-11].

2. Mast cells activation with subsequent histamine release that could be triggered by systemic or neuraxial administration of some opioids such as morphine, hydromorphone, codeine or meperidine[1,9]. One article recommended using oxycodone, oxymorphone or fentanyl, drugs that could cause less histamine release[12].

3. 5-HT_3 receptors activation after neuraxial administration of opioids, based on the presence of a dense concentration of serotonin receptors in the dorsal part of spinal cord and the nucleus of the trigeminal nerve in the medulla[9].

4. Release of prostaglandins (PGE_1 and PGE_2), known to untie histamine from the mast cells and to potentiate pruritus induced by histamine. The same prostaglandins enhance C fiber transmission to the central nervous system. This theory may explain the antipruritic effects of nonsteroidal anti-inflammatories (NSAIDs)[9].

5. Opioid antagonism of the neurotransmitters gamma-aminobutyric acid and glycine in the central nervous system[7,9].

6. Stimulation of dopamine D2 receptors that could explain the use of droperidol[10].

An article indicated that the pruritus associated with opioids is most likely an adverse effect rather than an allergic reaction[13].

Intensity of opioid-induced pruritus

The severity of OIP varies from mild to severe, with one article mentioning that about 50% to 60% of the patients may require treatment or hospitalization after the administration of morphine epidurally[7].

Topography of opioid-induced pruritus

Usually, the pruritus related to spinal or epidural administration of opioids tends to spread cephalad from the site of injection, at the face and upper thorax, whereas pruritus after the intravenous administration could be also localized in the facial area but it could as well be of a generalized type. This topographic distribution of the OIP could be explained by the fact that the dorsal part of spinal cord and the trigeminal nerve nucleus are areas with a high density of both mu-opioid and serotonin 5-HT3 receptors[7].

Transmission of OIP sensation

The pruritic sensation received from the free nerve endings in the skin is transmitted by the unmyelinated C fibers and myelinated A delta fibers to the central spinothalamic tract[1].

Treatment of opioid-induced pruritus

Several treatment options have been proposed based on the aforementioned mechanisms for opioid-induced pruritus.

1. μ opioid receptor antagonists

Opioid antagonists are the recommended treatment option for OIP, according to multiple articles; however, their usage is limited due to reports of decreased analgesia[10].

A) Naloxone

Naloxone is a synthetic derivative of oxymorphone that antagonizes all the μ, κ and δ opioid-receptor sites and, as a result, it was approved for the reversal of opioid overdose and for the reversal of respiratory depression resulting from the therapeutic opioid use in children and adults. Its onset of action occurs within 2 minutes after the intravenous administration and after 2 to 5 minutes after the subcutaneous, intramuscular and other parenteral routes of administration. It has a short duration of action, 30 to 60 minutes, depending on the dose and the route of administration[4,7,8].

The recommended dose of naloxone hydrochloride for adults for a total reversal of opioid overdose is 0.4-2 mg, repeated every 2 to 3 minutes, to a maximum dosage of 10 mg intravenously, whereas the dose for the reversal of an opioid-induced respiratory depression is 0.1-0.2 mg repeated every 2 to 3 minutes, as needed in an intravenous bolus[8].

However, when trying to address the opioid-induced pruritus, the clinician should employ a low enough dose of naloxone to reverse only the pruritus and not the analgesic effect of the opioid. For this purpose, the research recommended a continuous infusion of naloxone, because it produces less fluctuation of naloxone concentrations compared to the bolus injections and also compensates for the relatively short half-life of the naloxone[4,8].

The dose of naloxone in a continuous intravenous infusion, by which the incidence of OIP could be decreased by approximately 25%, should be 0.25-2 mcg/kg body weight/hour. The naloxone dose should not exceed 2 mcg/kg body weight/hour to prevent the reversal of analgesia[4]. A "piggyback" continuous infusion of naloxone at a dose of 0.25 to 1 mcg/kg/hour was also recommended by the National Comprehensive Cancer Network (NCCN) in its guidelines for adult cancer pain[8].

B) Naltrexone

Naltrexone is an oral opioid receptor antagonist and an analogue of naloxone, approved in 1984 by the US Food and Drug Administration (FDA) for the treatment of alcohol, heroin and opioid addiction. It has a longer half-life (4 hours versus less than 60 minutes) and twice the potency of naloxone. The recommended initial dose is 25 mg orally followed by a maintenance dose of 50 mg daily[8,14].

C) Methylnaltrexone

Methylnaltrexone is a derivative of naltrexone developed for the treatment of opioid-induced constipation in patients with advanced illness. It has a decreased ability to cross the blood-brain barrier and, like other peripherally acting mu opioid receptor antagonists (POMARAs), it targets the peripheral opioid-binding sites in the gastrointestinal tract. As a result of its limited activity on

the central μ-opioid receptors, it may have a limited or no effect on the centrally mediated pruritus[8].

D) Nalmefene

Nalmefene is an opioid antagonist used primarily in Europe for the management of alcohol dependence and investigated for the treatment of other addictions, such as pathological gambling. At doses of 15-25 mcg, nalmefene was found to decrease the need for antiemetic and antipruritic medications[4].

2. Mixed agonist-antagonist opioid receptors

A) Nalbuphine

Nalbuphine is a synthetic, mixed agonist-antagonist opioid analgesic developed for the control of moderate to severe pain. It has an activating effect on the kappa opioid receptors which are known to antagonize the effects of the mu-receptors at central and peripheral levels and, as a result, nalbuphine was indicated off-label for the prevention and treatment of opioid-induced pruritus[4,6,11].

Nalbuphine at doses of 10 mg intravenously induces analgesia with less respiratory depression compared to the mu-receptor agonists, and at lower doses, of 3 or 5 mg intravenously, it has been shown to address the opioid-induced pruritus more effectively than naloxone or propofol[6,7].

Other studies revealed nalbuphine being superior to propofol in the prevention of OIP. A prospective double-blind study compared propofol 20 mg with nalbuphine 3 mg after intrathecal morphine following caesarean delivery. The treatment was significantly more successful in the nalbuphine group than in the propofol group (83% versus 61%, respectively; $p<0.001$)[4].

Nalbuphine – either as an intermittent injection, or as a low-dose admixture to mu-opioid agonist infusions – emerges as a potential first-line treatment of opioid-induced pruritus when comparing the relief of pruritus with effects on analgesia and sedation[6].

B) Butorphanol

Butorphanol is a mixed kappa-opioid receptor agonist and a mu-opioid receptor antagonist that was approved by the FDA for the management of pain severe enough to require an opioid analgesic and for which the alternative treatments are inadequate. Several studies have shown that butorphanol could decrease opioid-related pruritus when administered epidurally with morphine or in combination with bupivacaine and morphine. Other studies, however, mentioned the fact that butorphanol itself can induce pruritus. It is recommended to monitor the patients receiving butorphanol in combination with any CYP3A4 inhibitors or inducers and it is to be avoided in patients younger than 18 years of age[4,15].

3. General anesthetics

Propofol

Propofol is known to cause a marked depression of posterior horn transmission in the spinal cord and, as a result, a decrease in the severity of opioid-induced pruritus[10].

Several studies using subhypnotic doses of propofol administered prophylactically have shown a decrease in the incidence of pruritus following intrathecal or epidural administration of morphine. The doses used in two such studies were 10 mg bolus followed by a continuous infusion of 30 mg/24 h in one study versus a single dose of propofol 20 mg in another one[4].

A prospective, randomized, double-blind, placebo-controlled study looked at OIP after the administration of 10 mg of propofol in patients who have received morphine intrathecally during gynecological, orthopedic, thoracic or gastrointestinal surgeries. The propofol group had a significantly higher success rate compared with placebo (84% versus 16%, respectively; $p<0.05$)[4].

However, two studies showed that subhypnotic doses of propofol did not relieve the pruritus in women who underwent caesarean section and received intrathecal morphine sulfate for postoperative pain relief[10].

In addition, propofol may transiently cause hypnosis in postoperative patients[4,9,10].

4. Serotonin 5-HT_3 receptor antagonists

Ondansetron

Several studies investigated the efficacy of ondansetron in relieving opioid-induced pruritus, based on the known fact that dense concentrations of serotonin receptors are present in the dorsal part of spinal cord and in the nucleus of the spinal tract of the trigeminal nerve in the medulla[3,9]. The results were controversial, with some studies showing good response from ondansetron and others showing no benefit[10].

There was a randomized placebo-controlled study investigating ondansetron 4 mg intravenously or 8 mg sublingually versus placebo in male patients receiving intrathecal morphine that showed a decreased incidence of OIP with ondansetron, regardless of the way of administration, compared with placebo[4].

Another placebo-controlled randomized study looked at ondansetron 4 mg intravenously in patients who received intrathecal morphine for post-caesarean section analgesia. The study showed that ondansetron relieved OIP (80% versus 36% success rate, $p<0.001$), particularly in patients with nausea and vomiting in addition to pruritus[4,7].

5. Dopamine D_2 receptor antagonists

Droperidol

Droperidol is a potent antagonist of the dopamine D_2 receptors which has also a weak anti-5-HT_3 activity[3,10].

A randomized study by Horta et al. explored the effectiveness of the prophylactic administration of intravenous droperidol 1.25 mg compared to placebo and also of alizapride 100 mg, propofol 20 mg and promethazine 50 mg in reducing the incidence and severity of OIP after neuraxial opioid administration in 300 women undergoing caesarean section. The study showed the opioid-induced pruritus having the lowest prevalence in the droperidol subgroup compared to placebo or to the propofol or alizapride subgroups[4,10,16].

Another study looked into a group of 40 patients who underwent hip replacement and noticed that OIP was significantly diminished in the subjects who received epidural droperidol[10].

6. Histamine H_1 receptor antagonists

H1 receptor blockers may alleviate the peripherally generated OIP, but they have little or no effect on the centrally induced one. It is suspected that the antihistamines – particularly the first-generation group – may be effective in reducing pruritus mostly due to their sedative effects since sleep interrupts the itch-scratch cycle[3,7,10].

A placebo-controlled trial by Juneja et al. concluded that hydroxyzine 50 mg administered intramuscularly was effective in attenuating the incidence of severe opioid-induced pruritus in 40 patients requiring epidural morphine for postoperative pain relief[17].

However, another study found that promethazine 50 mg was ineffective in preventing OIP[4].

7. Nonsteroidal anti-inflammatories

The NSAIDs may help with opioid-induced pruritus by blocking the release of prostaglandins (PGE_1 and PGE_2), a fact demonstrated by several studies. It was proven in a study that 20 mg of intravenous tenoxicam was effective in reducing pruritus after epidural fentanyl, and 100 mg of diclofenac intrarectally decreased morphine-induced pruritus in another study. The results have not been promising with celecoxib, a cyclooxygenase 2 isoenzyme inhibitor[3,10].

Conclusions

In conclusion, opioid-induced pruritus is a common side effect of the opioids, especially after the neuraxial administration, with unclear mechanisms of action and with still conflicting data regarding the efficacy of various treatments. ■

Conflict of interests: The authors declare no conflict of interests.

References

1. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Geneva: World Health Organization; 2018. Available at: https://www.who.int/publications-detail-redirect/9789241550390
2. Taylor JS, Zirwas MJ, Sood A. Pruritus – Cleveland Clinic Center for Continuing Education. Available at: https://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/dermatology/
3. Siemens W, Xander C, Meerpohl JJ, Buroh S, Antes G, Schwarzer G, Becker G. Pharmacological interventions for pruritus in adult palliative care patients. *Cochrane Database Syst Rev*. 2016 Nov 16;11(11):CD008320. doi: 10.1002/14651858.CD008320.pub3.
4. Ganesh A, Maxwell LG. Pathophysiology and management of opioid-induced pruritus. *Drugs*. 2007;67(16):2323-33. doi: 10.2165/00003495-200767160-00003.
5. Benson JL, Campbell HE, Phillips CN. Opioid-induced pruritus. *Consult Pharm*. 2015 Apr;30(4):221-7. doi: 10.4140/TCP.n.2015.221.
6. Jannuzzi RG. Nalbuphine for Treatment of Opioid-induced Pruritus: A Systematic Review of Literature. *Clin J Pain*. 2016 Jan;32(1):87-93. doi: 10.1097/AJP.0000000000000211.
7. Golembiewski J. Opioid-induced pruritus. *J Perianesth Nurs*. 2013 Aug;28(4):247-9. doi: 10.1016/j.jopan.2013.05.008.
8. Miller JL, Hagemann TM. Use of pure opioid antagonists for management of opioid-induced pruritus. *Am J Health Syst Pharm*. 2011 Aug 1;68(15):1419-25. doi: 10.2146/ajhp100475.
9. Szarvas S, Harmon D, Murphy D. Neuraxial opioid-induced pruritus: a review. *J Clin Anesth*. 2003 May;15(3):234-9. doi: 10.1016/s0952-8180(02)00501-9.
10. Reich A, Szepietowski JC. Opioid-induced pruritus: an update. *Clin Exp Dermatol*. 2010 Jan;35(1):2-6. doi: 10.1111/j.1365-2230.2009.03463.x.
11. Tey HL, Yosipovitch G. Targeted treatment of pruritus: a look into the future. *Br J Dermatol*. 2011 Jul;165(1):5-17. doi: 10.1111/j.1365-2133.2011.10217.x.
12. Katcher J, Walsh D. Opioid-induced itching: morphine sulfate and hydromorphone hydrochloride. *J Pain Symptom Manage*. 1999 Jan;17(1):70-2. doi: 10.1016/s0885-3924(98)00115-8.
13. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. *Am Fam Physician*. 2006 Oct 15;74(8):1347-54.
14. Ekelem C, Juhasz M, Khera P, Mesinkovska NA. Utility of Naltrexone Treatment for Chronic Inflammatory Dermatologic Conditions: A Systematic Review. *JAMA Dermatol*. 2019 Feb 1;155(2):229-236. doi: 10.1001/jamadermatol.2018.4093.
15. Phan NQ, Lotts T, Antal A, Bernhard JD, Ständer S. Systemic kappa opioid receptor agonists in the treatment of chronic pruritus: a literature review. *Acta Derm Venereol*. 2012 Sep;92(5):555-60. doi: 10.2340/00015555-1353.
16. Horta ML, Morejon LC, da Cruz AW, Dos Santos GR, Welling LC, Terhorst L, Costa RC, Alam RU. Study of the prophylactic effect of droperidol, alizapride, propofol and promethazine on spinal morphine-induced pruritus. *Br J Anaesth*. 2006 Jun;96(6):796-800. doi: 10.1093/bja/ael072.
17. Juneja MM, Ackerman WE 3rd, Bellinger K. Epidural morphine pruritus reduction with hydroxyzine in parturients. *J Ky Med Assoc*. 1991 Jul;89(7):319-21.