Are we still scratching the surface? A case of intractable pruritus following systemic opioid analgesia

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ABSTRACT

This article describes a case of severe opioid-induced pruritus following systemic morphine administration. Symptoms did not resolve after administration of antihistamines or rotation to fentanyl or hydromorphone, but oral oxycodone and small-dose intravenous naloxone did alleviate the patient's itching. The pathogenesis of opioid-induced pruritus and the rationale for opioid rotation are briefly discussed. Current and possible future therapeutic options are mentioned.

Key words: pruritus, systemic opioids, opioid rotation

INTRODUCTION

Generalized itch (pruritus) is an uncommon side effect of systemic opioid use, but it occurs frequently in conjunction with preoperative epidural or intrathecal opioid administration.[1] Occurrence and severity depend on the type of opioid used and individual tolerance.[2,3] The mechanism underlying the pruritogenic effect of systemic opioids is still not completely understood. The high incidence of pruritus seen with intraspinal administration of opioids suggests that spinal opioid receptors may be involved.[4] Recently, opioids have been shown to induce itching via specific binding to opioid receptors in the central and peripheral nervous system, mimicking the physiological effects of endorphins and enkephalins.[5] The relationship between itching and pain is bidirectional. Itching can be reduced by painful stimuli, and, vice versa, analgesia may reduce this inhibition and thus enhance the itch. This phenomenon is particularly relevant to spinally administered μ opioid receptor agonists, which induce segmental analgesia and segmental pruritus.[5,6] Because the perception of itching is modified by endogenous opioids via central receptors, it seems logical that opioid antagonists such as naloxone would demonstrate a high capacity to suppress pruritus induced by systemic opioid use.[7] In this case study we report the occurrence of severe itching after intravenous morphine administration in an opioid-tolerant patient. Pruritus was resolved by changing the opioid and route of administration and by adding a small dose of intravenous naloxone.

CASE REPORT

A 15-year-old nonatopic male with desmoplastic small round cell tumor of the pelvis (postresection), who was undergoing chemotherapy (vincristine) and radiation therapy and had developed secondary acute myelogenous leukemia and neutropenic fever, was seen in consultation for mucositis pain. The reported "burning" pain involved the entire oral cavity, radiating down to the epigastric area. At that time, he was experiencing significant side effects from prior opioid use (nausea, vomiting, itching). Physical exam was remarkable for grade II mucositis. The patient was flushed in the face and scalp but had no urticaria lesions.

Upon admission, the patient was started on hydromorphone (Dilaudid) 0.4 mg every four hours; this dose was titrated rapidly up to 0.8 mg intravenously every four hours as needed. Because of resultant nausea, vomiting, and suboptimal analgesia, hydromorphone was changed to morphine sulfate 5 mg intravenously every three hours. With the first dose of morphine, the patient displayed onset of severe pruritus accompanied by urinary retention. Although his pain was better controlled after several subsequent doses, the itching was severe enough that it made him unwilling to continue taking morphine. Diphenhydramine 50 mg every six hours and hydroxyzine 50 mg every four hours were used as needed, without any noticeable improvement. Skin exam remained unremarkable, with some flushing without erythema, rash, dermatitis, or urticaria. Routine laboratory studies were also unremarkable; no eosinophilia was noted. Morphine was changed empirically to a continuous intravenous

infusion of fentanyl, administered as patient-controlled analgesia (PCA) at a basal rate of 50 µg/h. Titration of the dose up to 70 µg/h resulted in good pain control but made no difference with regard to the patient's itching. Over the next 12 hours, fentanyl was discontinued, and hydromorphone was restarted at 0.8 mg/h basal rate and 0.8 mg demand dose every 10 minutes. An average of 5 mg/h of additional hydromorphone was delivered via demand doses. The patient reported significant worsening of pruritus with every self-administered demand dose. After the pain management team was consulted, the patient was started on oxycodone oral elixir 45 mg every three hours as needed, and a continuous intravenous infusion of naloxone at 0.25 µg/kg/h was added. The hydromorphone PCA remained available to be used for demand doses of 1 mg every hour if the patient lost the capacity to swallow. During the next 24 hours, the patient used an average of 0.4 mg/h of hydromorphone as demand doses, with optimal pain control and no recurrence of itching. Until the patient's white blood cell count recovered and subsequent resolution of mucositis was seen, pain management continued, with oxycodone oral solution titrated up to 60 mg every three hours and hydromorphone intravenously as needed. Naloxone infusion was tapered and discontinued after seven days. After naloxone was discontinued, there was no further itching, and no other opioid-related side effects were observed.

DISCUSSION

Opioid medications effectively treat pain, but they are associated with unwanted adverse effects, including nausea, vomiting, and pruritus. Pruritus can be severely distressing and as disabling as severe pain, and it may limit the acceptance of opioid therapy by both patients and caregivers.

Neurophysiologically, pruritogenic substances stimulate a subset of specialized skin C-fibers and initiate an itch sensation. These fibers are distinct from the polymodal C-type neurons, which transmit nociceptive (i.e., painful) stimuli to the central nervous system.[8] Many endogenous substances are regarded as "mediators of itch," such as amines (e.g., histamine), proteases, opioids, lipid peroxidation metabolites (e.g., leukotrienes, prostaglandins), neuropeptides (e.g., substance P), cytokines, growth factors (e.g., nerve growth factor), and many others. These agents may either directly sensitize the itch-mediating sensory nerve endings to various neuropeptides (such as substance P) or act on mast cells in the skin, leading to subsequent release of itch mediators, among which histamine functions as a key player.[9,10] Therefore, the bidirectional sensory neuron–mast cell interaction seems to be at the core of those processes that give rise to the onset of pruritus.

During the past 20 years, three opioid receptors—µ, δ, and κ—have been identified, and the genes coding for these receptors have been cloned.[11] The opioid receptors are transmembrane domain receptors linked to G proteins. The binding of opioids to these receptors initiates a cascade of events, culminating with protein phosphorylation and diverse physiological responses. Opioids are thought to produce their analgesic effect via agonist binding to Gi/Go-receptor-coupled complexes. These receptors inhibit the electrical firing of neurons and therefore block the perception of pain or the relay of pain signals from pain receptors. Opioids may also bind—at very small doses (pico- or nanomolar concentrations)—to Gs-coupled receptors. This connection activates an excitatory pathway that might explain the hyperalgesia occasionally reported with opioid administration, as well as some opioid-induced side effects such as pruritus, nausea, and vomiting.[12]

Recent animal studies have shown that histamine does not seem to be a player in mechanisms of opioid-induced itching and add further support to the idea that antihistamines are not effective in treating opioid-induced pruritus.[13,14] Most clinically used opioid analgesics are selective for the µ receptor, and this is the target receptor for morphine and other commonly used opioids, including oxycodone, hydromorphone, methadone, and fentanyl.[15] In addition, oxycodone, methadone, and buprenorphine may have clinically important activity at other opioid receptors.[16] In opioid-induced itching, µ opioid endogenic peptides (β endorphin, endomorphin-1, and endomorphin-2) are overly secreted, and the µ opioid receptors are proposed to be overexpressed as compared to κ opioid endogenic peptides (dynorphin A, dynorphin B, and dynorphin-associated peptides) and κ opioid receptors.[7]

Systemic administration of naloxone is a very potent and effective means of preventing or reversing itching invoked by agonists. Opioid receptor antagonists can be expected to effectively combat itch when it is invoked by µ opioid receptor analgesics or mediated by endogenous opioid peptides. The dose-response curve for opioid-induced itching appears to be bell shaped, similar to the progression of nausea and vomiting caused by the same medications.[17] It is also worth noting that opioid receptor antagonists produce parallel rightward shifts in the dose-response curves of morphine-induced scratching.[18] These observations indicate that the antipruritic effects of naltrexone and nalmefene are derived at opiate receptors through a competitive and reversible antagonist action. In contrast, in animal studies, κ agonists such as U-50488H produce downward shifts in the dose-response curve of morphine-induced scratching, and a selective antagonist can reverse their antipruritic actions.[19] The new synthetic κ receptor agonist TRK-820 was used to reduce itching and scratching in a mouse model, and its results seemed promising for possible translation into a

therapy for humans.[20] These observations indicate that κ agonists do not produce μ antagonism but rather inhibit μ-receptor-mediated itch through κ activation.

In our case, the use of intravenous morphine sulfate, a commonly used full μ receptor agonist, initiated the itching, which did not improve when morphine was changed to hydromorphone or fentanyl, μ1 and μ2 receptor agonists. When oral oxycodone was started in conjunction with intravenous naloxone, the itching improved significantly and resolved over the next 24 hours. Even after naloxone was discontinued, itching did not recur. Oxycodone is a semisynthetic opioid, derived from thebaine; it is classified as a pure opioid with a great affinity for μ receptors, greater than to κ receptors.[21] Despite a 10- to 40-fold lower affinity for the μ opioid receptor, oral oxycodone has nevertheless been found to produce pain relief that is generally comparable to that afforded by oral morphine. It has great bioavailability (60 percent), with roughly double the potency of and fewer adverse effects than morphine.[22] It has recently been proven, in both animal and human studies, that oxycodone analgesia is governed by the parent drug, with a negligible contribution from its circulating oxidative and reductive metabolites.[23]

CONCLUSIONS

A patient's response to a medication depends on multiple considerations: pharmacokinetics, pharmacodynamics, and environmental and genetic factors. Opioid rotation helps some patients achieve better pain control with fewer associated adverse effects.[24] The pharmacological mechanisms underlying this phenomenon involve the diverse and combined effects of agonist binding to opioid receptors (μ, δ, κ); incomplete cross-tolerance; the diverse genetic background of patients, including allelic variations in the opioid receptors themselves; and differences in drug-clearance mechanisms.[25,26]

In the case described above, the resolution of the patient's pruritus seemed to be the result of two different, combined interventions. Oxycodone might have reestablished a balance between μ and κ opioid receptors, most likely through a predominantly κ1 agonistic effect, while naloxone provided an additional antipruritic effect through its action as a μ antagonist, with no reversal of analgesia at the small dose used. We are inclined to believe that even though the two interventions coincided, naloxone did not play a singular role, since itching did not recur after its discontinuation.

Data from prospective studies indicate that chronic itch is observed in 2 to 10 percent of patients receiving oral morphine for chronic cancer pain.[27] To date, the neurobiological mechanisms of the interaction between μ and κ opioid receptors in itch-selective neurons remain unclear. Recent studies in monkeys reinforce the idea that the μ opioid receptor—not histamine or the κ or δ receptor—mediates itching invoked by opioid analgesics. It is possible that activation of κ receptors in specific sensory neurons produces the antipruritic effect.[28] Current recommendations for the treatment of opioid-induced pruritus are empiric and anecdotal, as there are no prospective studies to support them. In general, treatment is based on the postulated mechanisms of action. Discontinuation of the offending drug, rotation to another opioid, and prevention/treatment with an opioid antagonist are all proposed management strategies. Therefore, it is pivotal to verify whether κ agonists have a broader application as antipruritics in humans. Future studies are required to establish different pruritus models and to investigate the types of κ agonists that are effective against itching invoked by pruritogenic agents other than opioids. These studies will make a substantial contribution to the in vivo pharmacology of pruritus and offer functional evidence of κ agonists' potential as a new generation of antipruritics.

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