Palliative Care Rounds

Severe Pruritus of Cholestasis in Disseminated Cancer: Developing a Rational Treatment Strategy. A Case Report

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Abstract
Severe pruritus is a frequent complication of cholestasis. Both serotonin and opioids play an important role in the development of this symptom. Guidelines to provide rational management of pruritus of cholestasis do not exist. We describe a patient with complex and malignant course of pruritus. She responded to several measures proposed (among other naltrexone), but rapily became tolerant to them. Buprenorphine with an ultra low dose of naloxone was able to control her symptoms without development of tolerance until her death. J Pain Symptom Manage 2005;29:100–103. © *2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Pruritus, itch, cholestasis, naltrexone, buprenorphine

Introduction

Severe pruritus is a frequent complication of cholestasis. However, not all patients with cholestasis develop pruritus. The reason for this is unknown. The pathogenesis of the pruritus is thought to be related to increased opioidergic tone, but there are indications that the serotoninergic system is also involved. Based on this knowledge, several strategies to control the pruritus of cholestasis have been introduced over the last decade. In this paper, we present a patient with cancer and pruritus associated with intrahepatic cholestasis, for whom complex treatment was necessary. Rational choices and treatment strategy will be discussed using current evidence.

Case Report

The patient was a female, 78 years of age. She had a long history of hypothyroidism, hypertension, cardiac decompensation and Type II diabetes mellitus. She now had colon carcinoma with progressive liver metastases despite chemotherapy. She was jaundiced and complained of pruritus. The patient denied experiencing nausea and vomiting. She had only a vague pain in her lower back and right hip. Pre-admission promethazine up to 50 mg at bedtime was not successful. Upon admission,

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her medications included: glimepiride, nifedipine, furosemide, digoxin, metoprolol, losartan, lactitol, L-thyroxine, acetaminophen-codeine, diazepam and acenocoumarol. On examination, she was clearly wasted and jaundiced. Her liver was enlarged and tumorous. She was continuously scratching. Her legs were covered with excoriations and crusts. She scored her pruritus as 9–10 on a scale of 10.

Despite discontinuation of several drugs, her pruritus remained severe. Pruritus was treated with paroxetine 20 mg daily, but without improvement. Mirtazapine 30 mg at bedtime appeared unsuccessful. Tropisetron 1–2 mg subcutaneous injections were given as needed. This drug had a rapid but short antipruritic effect, lasting for 1–2 hours. A continuous subcutaneous infusion of tropisetron10 mg every 24 hours was effective but was discontinued after several days because of skin irritation. Naltrexone 12.5 mg orally first evoked severe opioid abstinence symptoms including nausea, vomiting, frequent bowel movements and sweating. The next day, she tolerated the naltrexone 12.5 mg three times daily, and her pruritus score dropped for the first time from 9–10/10 to 4/10. To maintain this effect, the dose of naltrexone needed to be increased to 400 mg daily over four weeks. The pruritus scores increased again to 7–8/10 and she started to experience more intensive pain in her right upper abdomen. Breakthrough episodes of pruritus during this period were successfully controlled with subcutaneous injections of tropisetron 5 mg. Because of increasing pain, naltrexone was tapered off over 2 days and sublingual buprenorphine 0.2 mg three times daily was started. The pruritus scores dropped rapidly to 4–5/10. Later on, it was again necessary to increase the frequency of administration of buprenorphine to 3–4 hourly to provide round-the-clock relief. With this regimen, however, she started to be confused within several days and became anxious and restless, especially at night. A continuous subcutaneous infusion of ultra-low dose naloxone 0.2 mg/24 hours was started. This dramatically improved the patient's mental condition, and the pruritus scores dropped to 0–2/10. This therapy was continued for two weeks, until the patient deteriorated and was no longer able to swallow tablets. She was then sedated with a subcutaneous infusion of haloperidol, morphine and midazolam. She died peacefully three days later, 6 weeks after admission to the hospice. Throughout her time in the hospice, the skin was treated regularly with emollients and she was taking regular baths with natrium bicarbonate (0.5kg/bath), with considerable but short-lived effect.

Discussion

H_1-antihistamines, like promethazine, are ineffective in the treatment of severe pruritus due to cholestasis and should not be used for this indication. If there is benefit from these drugs, it relates to the improvement in sleep, similar to the effect of benzodiazepines. Recently, several methods of treatment of pruritus accompanying cholestasis have been proposed.[1–3] Most of these methods were developed in relation to pruritus associated with chronic, nonmalignant cholestasis. Several of these therapies were extrapolated with some success to more progressive conditions such as pruritus due to malignant intra- or extra-hepatic cholestasis, but formal clinical trials have not been performed. There is no consensus about the optimal treatment of pruritus. Also, nothing is known about treatment combinations.

Generally, in cancer patients, opioid antagonists have not been used to treat pruritus so as to avoid a reversal of opioid analgesia. It is, therefore, our practice to start treatment with paroxetine.[4] In a mixed population of 26 mainly cancer patients with intractable, severe pruritus, including only three patients with pruritus due to cholestasis, paroxetine 20 mg daily led to a 50% or more reduction of pruritus scores in 37% of patients.[4] Initial and temporary nausea was a prerequisite for good antipruritic effect. Paroxetine did not reverse analgesia. Mirtazapine has been reported to have antipruritic activity similar to that of paroxetine without inducing nausea and vomiting.[3] In our patient, mirtazapine was unsuccessful. No controlled studies with this drug are available.

Ondansetron, a 5-HT_3 receptor antagonist, has been reported to be an effective antipruritic in cholestasis in several case reports. But this effect has been found to be small and probably irrelevant in two clinical trials.[5,6] In our patient, injections of tropisetron abolished the breakthrough episodes of pruritus. This effect was