

treatment session, and she demonstrated a response to stimulation, nonetheless. Finally, the results demonstrated here are consistent with results from other groups.<sup>2</sup>

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## ***Intravenous Naloxone Plus Transdermal Buprenorphine in Cancer Pain Associated with Intractable Cholestatic Pruritus***

To the Editor:

The complex and unpredictable series of symptoms that comes with the terminal stage of neoplastic disease significantly compromises patients' quality of life, and poses harsh therapeutic challenges for clinicians. Good control of severe cancer-related cholestatic pruritus seems to be hard to achieve and pruritus still undermines the remaining physical and relational capabilities of seriously ill cancer patients. Its pathogenesis remains substantially unknown and its treatment mostly empirical.

An increased central opioidergic tone seems to be an important component of cholestatic pruritus, with hyperactivity of the serotonergic system playing a primary role. These elements were the basis for the therapeutic choice successfully applied in the following clinical case.

### ***Case***

A 65-year-old woman, about 40 kg in weight, had advanced stage colon carcinoma with liver metastases, and was receiving both chemotherapy (systemic and locoregional) and (palliative) radiotherapy. She had severe nociceptive

pain (pain score of 9 on a 0–10 scale) in the lumbosacral region, which radiated to the lower limbs and was worsened by movements (pain score 10). As a result of the pain, she had to lay on her right side, in a genupectoral position. On physical examination, she was in poor physical conditions (Karnosky Status score 30–40), had a normal sensorium, a permanent external colostomy, and a nodular liver on palpation. She appeared dehydrated and was mildly icteric.

The patient reported mild-moderate, continuous pruritus, evidenced from widespread wounds due to scratching activity on the upper limbs and trunk. She was asked to report and quantify the pruritus daily, using a numerical rating scale, where 0 = no pruritus and 10 = worst imaginable pruritus. The score she reported during the first visit was 8. She reported a change in sleep-waking cycle, particularly due to the continuous desire to scratch herself.

Prior treatments for itch included oral beta-methasone 2 mg/day, and chlorphenamine (an antihistamine) intramuscularly per day for episodic pruritus fits. There was no substantial efficacy other than transient slight relief after the injected antihistamine.

The first pain treatment, with paracetamol (acetaminophen) 500 mg plus codeine 30 mg, given orally three times a day, was not successful, and indeed, worsened the scratching activity. For this reason, it was replaced by oxycodone 5 mg twice daily, an agent with lower pruritic potential action.<sup>1</sup> However, this new effort did not produce positive results either on pruritus or on pain. At the second visit, two days later, she reported an unchanged pain score and a further worsening of the pruritus, with presence of many crusts and wounds all over her body. The main purpose of our clinical strategy was then to decrease the concentration of prior agents inducing pruritus, so cholestyramine,<sup>2</sup> a resin bile acids sequestrant, was prescribed orally twice a day (8 g/day) for five days, to then be increased if necessary to three times a day, for a total dosage of 12 g/day. This was to reduce the peripheral irritative action of bile salts. Buprenorphine, a semisynthetic partial agonist opioid, was chosen to at least partially decrease opioidergic activation (and thus pruritus), while also addressing the need for pain

relief.<sup>3</sup> The patient was advised to apply a half patch of buprenorphine 35 µg/hour; at the same time, an elastomeric pump (total volume 275 mL, infusion speed 2 mL/hour), containing betamethasone 20 mg, metoclopramide 50 mg, and ranitidine 500 mg, was positioned and combined with adequate fluid therapy. Sublingual buprenorphine (0.2 mg) was prescribed for breakthrough pain, at a maximum of four tablets per day. After seven days, this new pharmacological plan was moderately effective. The pain score fell to 3 and the pruritus score to 6, with itching still present and stressful. During the week, the patient had taken an average (SD) of  $2.42 \pm 0.97$  buprenorphine tablets per day (range, 1–4). No therapeutic change was made.

After a further four days, the jaundice became increasingly severe. The pruritus again became very severe and refractory to treatment (pruritus score = 10). Blood tests evidenced a bilirubin value of 19.8 mg/dL. Paroxysms became more frequent and unbearable, and the patient's face also was marked with signs of scratching. At the same time, the pain score increased to 6 at rest and to 8 during movement. Based on clinical experience, ondansetron, a serotonin 5-HT<sub>3</sub> receptor antagonist that may inhibit opioid-induced analgesia and pruritus perception,<sup>4,5</sup> was tried. Transdermal buprenorphine 35 µg was applied, and a daily sublingual buprenorphine 0.2 mg tablet and slow intravenous ondansetron 8 mg were administered. The same dose of ondansetron was prescribed every 12 hours. After one hour, the pain score was 3, but the pruritus score was unchanged. It remained the same after 48 hours, whereas the pain was found to be well controlled.

Seeking to further modulate central opioidergic transmission,<sup>6</sup> naloxone was administered intravenously, in a continuous infusion using an elastomeric pump. The dose was 0.02 µg/kg/minute. Careful monitoring of the patient's vital signs, neurological status, level of consciousness, and symptoms over the following 24 hours was scheduled. The objective was to detect the onset of any withdrawal symptoms and/or excruciating pain.

In less than two hours, the pruritus had disappeared almost completely, in both persistent and paroxysmal episodes, with a score 2 on the 0–10 scale. To attempt to improve the result,

the naloxone dosage was increased to 0.04 µg/kg/minute the next day. After five hours, the patient complained again of lumbosacral pain, although the pruritus had further decreased. The naloxone dosage was then reduced to 0.02 µg/kg/minute. With this dosage, optimal results were indeed obtained for both pain (verbal rating scale = 2 at rest, with no movement due to the patient's general condition) and pruritus (numerical rating scale = 1). She stopped scratching herself. The following days, there were no side effects and the infusion was continued for 17 days, after which the patient died. The treatment was considered miraculous by relatives.

### Comment

The many causal or palliative therapeutic attempts to control pruritus in this case were inadequate. The *criterium ex adiuvantibus* seems to support the hypothesis that the pathophysiology of pruritus is related to increased central opioidergic tone.<sup>7</sup> Considering the increase in serotonergic neurotransmission, anecdotal experience suggests that the serotonin 5-HT<sub>3</sub> receptor antagonist, ondansetron, could act effectively in cholestatic pruritus treatment. However, in a controlled randomized trial, which assessed the results obtained after administration of ondansetron vs. placebo, only a transient improvement in pruritus in cholestatic patients was demonstrated, as in this case.<sup>8</sup>

Currently, some studies suppose that the onset of cholestatic pruritus is due to hyperactivity of central opioidergic neurotransmission, because of three scientific findings: (1) the association of increased opioidergic neurotransmission or opioid agonist neuromodulation with the presence of pruritus of central origin, which seems to be reversible with the use of receptor-specific antagonists, such as naloxone; (2) clinical and experimental results that suggest that cholestasis is associated with an increased opioidergic tone; and (3) preliminary results report a widespread improvement in cholestatic pruritus perception after the administration of opioid antagonists.<sup>9</sup>

The efficacy of naloxone on ongoing cholestatic pruritus previously has been reported in many other clinical areas.<sup>10</sup> Naloxone, a drug

that has long been present in the arsenal of clinical anesthetic practice, has the properties of a pure antagonist of opioidergic transmission, which can control the side effects of common opioids. Since the mid-1970s, naloxone has been used to prevent and treat pruritus, and this became standard practice, thanks to several studies of epidural analgesia with opioids, but also because of the observations of uremic or cholestatic patients affected by this intolerable symptomatology.<sup>11,12</sup> As emphasized by other authors, the use of buprenorphine as a partial agonist of both mu and kappa receptors, with partial antinociceptive activity at spinal and supra-spinal levels,<sup>13</sup> could attenuate opioidergic tone, allowing both analgesia and control of adverse events due to the hyperactivity of the same neural pathways.<sup>14</sup> Following the fine thread that connects studies and pilot experiences<sup>15</sup> on the use of naloxone in cholestatic pruritus, the risk of causing the patient to have acute opioid withdrawal symptoms was clear, and so buprenorphine was administered to block the opioid receptors. Buprenorphine has previously been used in opioid addiction conditions, and was antagonized with difficulty by naloxone compared with pure agonists.<sup>16</sup> The therapeutic success achieved was probably due to this two-way activation/inactivation of the opioid-correlated descending pain modulating pathways, and this mechanism increases the overall well-being of the patient, in terms of both pain and pruritus, and in the absence of further adverse events. The overall relief observed during the patient's last days of life is evidence of the constant monitoring of the clinical situation, mediated by the methods of administering the drugs—the transdermal delivery of the buprenorphine and the infusion by elastomer pump, and the lower dose. This choice produced optimal control of the complex condition presented by this terminally ill patient, and guaranteed constant effective drug concentrations without dangerous fluctuations in plasma levels and symptoms. This present case, which shows the potential efficacy of naloxone in cancer cholestatic pruritus, confirms the results of several studies in the literature,<sup>17,18</sup> and suggests the safety and efficacy of buprenorphine plus naloxone as a treatment for severe cholestatic jaundice.

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### Nocturnal Hypoxemia in Patients with Cancer

To the Editor:

In a survey of 100 palliative care inpatients with a variety of cancers, we found that 35 experienced nocturnal hypoxemia, as defined by an oxygen saturation (SaO<sub>2</sub>) <90% for ≥2% of the monitored nighttime, together with higher levels of mental fatigue.<sup>1</sup> When considering possible etiologic factors, we had excluded patients with a daytime SaO<sub>2</sub> <90% or known obstructive sleep apnea. Those with nocturnal hypoxemia were more likely to have pulmonary disease and lower values of percent predicted forced expiratory volume in 1 second and day SaO<sub>2</sub>. There was no difference in performance status, body mass index, sniff nasal inspiratory pressure, and opioid or other sedative drug use between those with and without nocturnal hypoxemia.<sup>1</sup> However, sleep per se can reduce ventilation.<sup>2</sup> This does not normally lead to a significant change in the oxygen content of blood because of the horizontal portion of the oxygen dissociation curve. Nonetheless, patients with a lower day SaO<sub>2</sub> will lie closer to the steep part of the oxygen dissociation curve and a reduction in