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## Enhanced Analgesia with Opioid Antagonist Administration

JANE E. LOITMAN, M.D., M.S.

### ABSTRACT

**Background:** Pain, not responsive to opioid analgesics, remains a problem for patients with chronic and cancer pain as well as their families, and clinicians. Opioid antagonists have various uses in pain and palliative care. Their use in the reversal of tolerance and hyperalgesia remains at the basic science level and has limited clinical exposure.

**Objective:** To improve symptom control and quality of life in patients with pain not responsive to opioid analgesics.

**Design:** Present three cases in which patients have undergone administration of opioid antagonists for the purpose of analgesia.

**Methods:** Patients on opioid analgesics received parenteral opioid antagonist, naloxone. Complete withdrawal under a sedative or conscious sedation was allowed and then the opioid at smaller doses was restarted and analgesia was observed.

**Results:** All patients had improved analgesia on a significantly lower dose of opioid analgesics.

**Conclusions:** Only three patients who have received this procedure were presented yet all have responded positively to this procedure. Further research is needed to elucidate the mechanism and clinical relevance in the acute use of opioid antagonists.

### INTRODUCTION

PAIN FROM CANCER OR CANCER TREATMENT needs aggressive, immediate attention. Using the World Health Organization (WHO) stepladder,<sup>1</sup> 90% of cancer pain is alleviated. A minority continue to have unmanageable pain. Patients with previous or concurrent substance abuse often present with pain intolerance and opioid tolerance. Three cases of refractory pain altered with naloxone are presented. The response is thought provoking and leads to many unanswered questions.

Opioid antagonists have various uses: detoxification, recidivism, and opioid toxicities from respiratory suppression to constipation.<sup>3-6</sup> In rapid detoxification, intravenous naloxone is ad-

ministered to an opioid-dependent patient to achieve opioid abstinence. Done under anesthesia, it prevents discomfort and improves long-term outcome in the dependent patient.<sup>7</sup>

In the setting of acute nociceptive postoperative pain, naloxone with patient-controlled analgesic (PCA) morphine failed to show decreases in opioid requirements or increases in analgesia.<sup>8-10</sup> The mechanism and responsiveness of acute nociceptive and chronic pain are different. Breitbart et al.<sup>11</sup> successfully used a drug holiday to help an opioid-dependent and -tolerant patient with cancer in pain. Drug holidays are used by pain specialists for outpatients with refractory chronic pain to reestablish analgesic responsiveness in an opioid dependent patient. A recent let-

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ter to the editor describes positive effects and discussion of an opioid antagonist concurrent with methadone.<sup>12</sup>

Three cases in which naloxone “reset the receptors” in an opioid-tolerant patient with pain and a case in which naloxone caused analgesia are presented.

Case 1 involves a 47-year-old married man with an acquired immunodeficiency syndrome (AIDS)-defining diagnoses since 1985 and a history of back pain after a fall in 1977. He also has a history of polysubstance abuse, antisocial behavior, a C3–5 fusion, and a L3–5 fusion. When first seen in 1999, he was taking 2200 mg/d of morphine along with an undetermined amount of heroin. His pain was felt to be neuropathic from AZT along with a secondary myofascial pain and arthritic bone pain. Over the next 2 years, he underwent trials of calcitonin, pamidronate, cyclobenzaprine, tizanidine, baclofen, amitriptyline, amantadine, mexilitine, selective serotonic reuptake inhibitors (SSRIs), and methadone. The methadone was started at 240 mg daily and titrated to 800 mg daily. He regularly rated his pain control at a 7.5–10 of 10. His urine toxicology screens were regularly negative for any substances other than methadone, yet on several occasions, he used greater than his prescribed amount of opioid analgesics.

After 4 months of discussion, he agreed to an opioid receptor reversal with naloxone. He was admitted to the hospital on 800 mg of methadone with 3600 mg of morphine and 24 mg of hydromorphone per day. He received a total of 1.2 mg of intravenous naloxone before any withdrawal symptoms appeared. He continued in withdrawal for approximately 20 minutes before opioids were readministered. He was discharged that day on 400 mg/d of methadone. On follow-up 3 days later, he reported 4 of 10 pain with more mobility in his back and a nonantaglic gait. Four years later, he continues to require opioid analgesics for persistent pain, although remembers the procedure as helpful.

Case 2 involves a sober 44-year-old father with a past history of intranasal heroin abuse presented with obstructive pneumonia. He was found to have a perihilar adenocarcinoma associated with pain. He completed radiation treatment to the mediastinum, lung mass, left temporal lobe brain metastases, and right ribs metastases. He also received carboplatin and paclitaxel with palliative radiation to his right sacroiliac joint and shoulder.

He was seen for poorly controlled cancer-related neuropathic pain. His oral morphine was switched to methadone, 50 mg four times daily, with pamidronate, amitriptyline, tizanidine, and dexamethasone. He failed outpatient follow-up. A month later, his oncologist restarted him on a regimen of oral morphine 180 mg/d with gabapentin 600 mg three times daily, which produced somnolence and myoclonus. After reconsultation for constant 10 of 10 pain, a methadone PCA, titrated to 2.1 mg/hr produced 4 of 10 pain. He found the pump cumbersome and chose to continue on oral methadone. After admission to hospice, his medication compliance and use of adjuvants (dexamethasone, compounded ketamine gel, mirtazepine, topiramate, and modafinil) improved. Inpatient admission resulted in temporary and modest relief on a hydromorphone PCA of 4.4 mg/hr with 2 mg rescues. He again rejected the PCA and was discharged to home with “adequate” 8 of 10 pain on oxycontin 180 mg three times per day with methadone 20 mg for breakthrough pain. His pain returned to an “intolerable” 10 of 10. After 6 weeks of discussion, he agreed to an opioid receptor reversal with naloxone. At home, 0.8 mg of intravenous naloxone resulted in yawning, goosebumps, nausea, a bowel movement, and a pain score of 0 of 10. He required oxycodone for dyspnea and was stabilized on 40 mg of oxycontin daily. Four months later, still on 40 mg oxycontin, he died without physical pain.

Case 3 involves an 18-year-old with a history of longer than 2 years of leiomyosarcoma that presented on his adrenal gland. His sister had died from leiomyosarcoma prior to his diagnosis, so he and his family’s emotional response to this diagnosis produced significant anxiety. He had previously been seen by a pediatric anesthesiologist for his pain and presented to me after he turned 18. NPO secondary to an esophageal stricture, his medications included intrathecal fentanyl, 900  $\mu\text{g}/\text{d}$ ; 14 mg/d bupivacaine; and 472  $\mu\text{g}/\text{d}$  clonidine as well as parenteral sufentanil 19  $\mu\text{g}/\text{hr}$  with 29  $\mu\text{g}$  every 6 minutes as needed and methadone, 30 mg twice daily. He was also on 15 mg/hr midazolam with 15 mg every hour as needed. His pain was secondary to hyperalgesia and anxiety. He was started on ultra-low-dose naltrexone twice daily and mirtazepine and had a brief period of improved symptoms. His pain and nausea became worse when he was switched from benzodiazepine to lorazepam at 3 mg/hr with 0.5 mg every hour as needed. After

2 weeks, he agreed to come in for an opioid receptor reversal with naloxone. He was admitted with a 9–10 of 10 pain but he expressed such fear of this procedure that he requested sedation. Sedated per his request with propofol, intravenous naloxone 0.6 mg resulted in a change in pupil size, yawning, and involuntary defecation, then a pain score of 0–2 of 10 pain with intrathecal fentanyl at 1400  $\mu\text{g}/\text{d}$ , 21 mg/d bupivacaine, and 735  $\mu\text{g}/\text{d}$  clonidine. Upon discharge, the fentanyl was changed to morphine and the bupivacaine was reduced, although because of disease and anxiety, he required extensive supportive care.

## DISCUSSION

The reversal of opioid tolerance has been attempted in a variety of ways. The simultaneous administrations of opioids and N-methyl-D-aspartate (NMDA) antagonists have had disappointing results. Either the effect or side effects have limited their success clinically. Crain and Shen have looked at mu antagonism in other settings. The animal studies on tolerance and dependence<sup>13–18</sup> and the failure to improve analgesia with NMDA antagonists led to my first naloxone experience in the 1990s. The results were profound. I have used this technique on a series of patients for refractory pain after serial trials of opioids, adjuvants, procedures, and complementary techniques. These patients have tolerated the acute discomfort of withdrawal to obtain improved analgesia in less than 1 hour on approximately one third of the original opioid dose. Their sensitivity to titration was renewed. The opioid receptors appear to have “reset.” Case 1 had a lasting effect, case 2 resulted in complete analgesia, and case 3 had tremendous analgesic dose reduction.

There is no literature on naloxone in patients with chronic pain. Ultra-low-dose naltrexone is described but the effect is limited and without end point. The positive response with naloxone demonstrates an incomplete understanding of tolerance, analgesia, and hyperalgesia. Both patients had physiologic reasons for physical pain, histories of substance abuse, and tolerance. Similarly, tolerance and/or hyperalgesia do not adequately explain the reversal of symptoms in case 2. The combination of mechanisms may explain symptom improvement and/or opioid dose reduction but not pain elimination. The exact mech-

anism remains unclear. Hypotheses in animals that best correlate with GM1 ganglioside effects, but those the discussions have remained at the basic science level.<sup>19–23</sup> Exploration in a controlled clinical setting is warranted to further understand the mechanism and possible clinical role of opioid antagonists in the treatment of refractory chronic and cancer pain.

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