2006

Enhanced analgesia with opioid antagonist administration

Jane E. Loitman
Washington University School of Medicine in St. Louis

JOURNAL OF PALLIATIVE MEDICINE
Volume 9, Number 6, 2006

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 linical 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 opioids 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,[1] 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.[3–6] In rapid detoxification, intravenous naloxone is administered to an opioid-dependent patient to achieve opioid abstinence. Done under anesthesia, it prevents discomfort and improves long-term outcome in the dependent patient.[7]

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.[8–10] The mechanism and responsiveness of acute nociceptive and chronic pain are different. Breitfeld et al.[11] 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-

Washington University School of Medicine, Barnes-Jewish Hospital, St. Louis, Missouri.

ter to the editor describes positive effects and discussion of an opioid antagonist concurrent with methadone.[12]

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 espophageal stricture, his medications included intrathecal fentanyl, 900 μg/d; 14 mg/d bupivicaine; and 472 μg/d clonidine as well as parenteral sufentanil 19 μg/hr with 29 μg 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 profolol, 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 μg/d, 21 mg/d bupivicaine, and 735 μg/d clonidine. Upon discharge, the fentanyl was changed to morphine and the bupivicaine 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[13–18] 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 mechanism remains unclear. Hypotheses in animals that best correlate with GM1 ganglioside effects, but those the discussions have remained at the basic science level.[19–23] 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.

REFERENCES

1. World Health Organization: *Cancer Pain Relief.* Albany, NY: WHO Publications Center, 1986.
2. Ventafridda V, Caraceni A, Gamba A: Field-testing of the WHO guidelines for cancer pain relief: Summary report of demonstration projects. In: Foley KM, Bonica JJ, Ventafridda V (eds): *Advances in Pain Research and Therapy, Volume 16. Proceedings of the Second International Congress on Pain.* New York: Raven Press Ltd., 1990, pp. 451–464.
3. Sykes N: An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. Palliat Med 1996;10:135–144.
4. Culpepper-Morgan JA, Intrurissi CE, Portenoy RK, Foley KM: Treatment of opioid-induced constipation with oral naloxone: a pilot study. Clin Pharmacol Ther 1992;52:90–95.
5. Liu M, Wittbrodt E: Low-dose oral naloxone reverses opioid-induced constipation and analgesia. J Pain Symptom Manage 2002;23:48–53.
6. Pappagallo M, Dickerson DE, Twycross R: Low doses of opioid antagonists enhance morphine analgesia and reduce adverse effects. Prog Palliat Care 2001;9:194–195.
7. Simon DL: Rapid opioid detoxification using opioid antagonists: History, theory and the state of the art. J Addict Dis 1997;16:103–122.
8. Mehlisch DR: The combination of low dose of naloxone and morphine in patient-controlled (PCA) analgesia does not decrease opioid requirements in the postoperative period. Pain 2003;101:209–211.
9. Sartain JB, Barry JJ, Richardson CA, Branagan HC: Effect of combining naloxone and morphine for intravenous patient-controlled analgesia. Anesthesiology 2003;99:148–151.
10. Cepeda MS, Africano JM, Manrique AM, Fragoso W, Carr DB: The combination of low dose of naloxone and morphine in PCA does not decrease opioid requirements in the post operative period. Pain 2002;96:73–79.
11. Breitfield C, Eikermann M, Kienbaum P, Jurgen P: Opioid "holiday" following antagonist supported detoxification during general anesthesia improves opioid agonist response in a cancer patient with opioid addiction. Anesthesiology 2003;98:571–573.
12. Cruciani RA, Lussier D, Miller-Saultz D: Ultra-low dose oral naltrexone decreases side effects and po-

tentiates the effect of methadone. J Pain Symptom Manage 2003:25:491–494.
13. Shen KF, Crain SM: Antagonists at excitatory opioid receptors on sensory neurons in culture increase potency and specificity of opiate analgesics and attenuate development of tolerance/dependence. Brain Res 1994;636:286–297.
14. Crain SM, Shen KF: Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. Pain 2000;84:121–131.
15. Alcaraz C, Vargas ML, Milanes MV: Chronic naloxone-induced supersensitivity affects neither tolerance to nor physical dependence on morphine at hypothalamus-pituitary-adrenocortical axis. Neuropeptides 1996;30:29–36.
16. Yoburn BC, Sierra V, Lutfy K: Simultaneous development of opioid tolerance and opioid antagonist-induced receptor upregulation. Brain Res 1990;529:143–148.
17. Crain SM, Shen KF: Modulatory effects of gs-coupled excitatory opioid receptor functions on opioid analgesia, tolerance, and dependence. Neurochem Res 1996;21:1347–1351.
18. Powell KJ, Abul-Husn NS, Jhamandas A, Olmstead MC, Beninger RJ, Jhamandas K: Paradoxical effects of the opioid antagonist naltrexone on morphine analgesia, tolerance, and reward in rats. J Pharmacol Exp Ther 2002;300:588–596.
19. Wu G, Lu ZH, Wei TJ, Howells RD, Christoffers K, Ledeen RW: The role of GM1 ganglioside in regulating excitatory opioid effects. Ann N Y Acad Sci 1998;19;845:126–138.
20. Crain SM, Shen KF: Neuraminidase inhibitor, oseltamivir blocks GM1 ganglioside-regulated excitatory opioid receptor-mediated hyperalgesia, enhances opioid analgesia and attenuates tolerance in mice. Brain Res 2004;995:260–266.
21. Shen KF, Crain SM: Cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence. Brain Res 2001;919:20–30.
22. Crain SM, Shen KF: Enhanced analgesic potency and reduced tolerance of morphine in 129/SvEv mice: Evidence for a deficiency in GM1 ganglioside-regulated excitatory opioid receptor functions. Brain Res 2000;856:227–235.
23. Crain SM, Shen KF: Modulation of opioid analgesia, tolerance and dependence by Gs-coupled, GM1 ganglioside-regulated opioid receptor functions. Trends Pharmacol Sci 1998;19:358–365.

Address reprint requests to:
Jane Loitman, M.D., M.S.
Barnes-Jewish Hospital
Palliative Care
1 BJH Plaza, Suite 16304
St. Louis, MO 63110

E-mail: jel7089@bjc.org