

## Dexmedetomidine as a novel therapeutic for postoperative pain in a patient treated with buprenorphine

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### ABSTRACT

*Buprenorphine is a partial agonist/antagonist used for the outpatient management of pain and addiction. It avidly binds to the opioid receptors and has a long and varied half-life. Its effects can impair the efficacy of opioids used for postoperative pain. The authors present a case of a patient managed with buprenorphine as an outpatient who presented for revision spine surgery and had significant postoperative pain that was successfully treated with hydromorphone and dexmedetomidine. This is the first reported use of dexmedetomidine for postoperative pain in a patient treated with buprenorphine.*

*Key words: opioid, Precedex, Suboxone, Subutex*

### INTRODUCTION

Buprenorphine (trade name Suboxone [buprenorphine/naloxone sublingual tablet] and Subutex [buprenorphine sublingual tablet]; Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA) has been available worldwide as both a parenteral and sublingual analgesic since 1970s and is available in a transdermal form in Europe. The passage of the Drug Addiction Treatment Act of 2000 allowed for individual practitioners to prescribe buprenorphine for detoxification or office-based opioid therapy. It is a synthetic derivative of the morphine alkaloid thebaine and acts primarily at the mu-opioid receptor as a partial agonist, producing supraspinal analgesia, respiratory depression, and miosis.<sup>1-4</sup> Approximately 30 times as potent as morphine, it produces effective analgesia at low receptor occupancy (5-10 percent).<sup>3-6</sup> As a partial mu-receptor agonist, it has a

wide safety profile and demonstrates a ceiling effect for respiratory depression and other toxicities.<sup>7</sup> Sublingual doses greater than 24-32 mg do not produce any greater opioid agonist effects (positive mood, sedation, respiratory depression, and miosis)<sup>7</sup>; however, some studies indicate analgesic effects beyond that exceed the opioid-induced side effects.<sup>8,9</sup> The half-life is long (24-60 hours) and varies depending on the patient and dose.<sup>4</sup> The duration of clinical effects can be 24-48 hours due to its high affinity for and slow dissociation from mu receptors; however, dosing three times daily is often necessary for analgesia.<sup>10</sup>

Buprenorphine has proven to be useful for the dual treatment of pain and opioid dependence or addiction.<sup>4,11,12</sup> Its high receptor affinity can produce blockade of the effect of full mu-opioid agonists, such as heroin, and can actually precipitate withdrawal in patients actively taking opioids.<sup>3,4,10,13</sup> Similarly, buprenorphine can interfere with full agonist treatment for pain. The potentially long half-life of buprenorphine and its ability to antagonize the effects of opioids create the possibility of markedly increasing opioid requirements in the perioperative period in those patients who are taking the drug. This may complicate perioperative pain management and, of greater concern, can result in serious adverse events. We present a case of the treatment of severe postoperative pain in a patient taking buprenorphine as a portion of the preoperative, outpatient pain management, which was not discontinued before the redo spinal fusion. We offer our experience using dexmedetomidine as a novel therapeutic in this clinically challenging situation.

## CLINICAL REPORT

A 41-year-old male, American Society of Anesthesiologists physical status 2, underwent a posterior spinal fusion with instrumentation at L<sub>3</sub>-L<sub>5</sub> and bilateral posterior fusion with the left posterior iliac crest as the donor site. He had a history of chronic low back pain and was taking sublingual buprenorphine 16 mg daily in divided doses for pain, which was not discontinued before the operation. His last dose of buprenorphine was immediately before going to the operating room. He was maintained intraoperatively with a remifentanyl infusion as a portion of his general anesthetic and given morphine 10 mg and fentanyl 50 µg before surgery ended. The patient's time in the postanesthesia care unit was prolonged and complicated by pain scores of 9-10/10 (Pain scale 0-10: 0, no pain; 10, worst pain imaginable) despite high doses of opioids. Before being discharged to the postsurgical inpatient unit, the patient received fentanyl 500 µg, morphine 50 mg, clonidine 100 µg, ketorolac 30 mg, and lorazepam 1 mg intravenously, in addition to oxycodone 20 mg by mouth. His pain score was reduced to 4/10 before being discharged to the postsurgical unit. Throughout the first night, the patient controlled analgesia (PCA) was increased due to uncontrolled pain and his total morphine PCA dose in the first 13 hours after discharge from the recovery unit was 167 mg with innumerable denied doses.

The next morning, the acute pain service was called to evaluate the patient for the first time because of uncontrolled pain despite escalating opioid dosing. He was found curled up in the fetal position in the bed, crying, frustrated, and refusing to open his eyes due to severe pain. After learning that the patient had continued his high-dose buprenorphine until the immediate preoperative period, the decision was made to transfer him to an intensive care unit (ICU) for high-dose PCA therapy and a dexmedetomidine (trade name Precedex®; Hospira, Inc., Lake Forest, IL) infusion. During the 8 hours before transfer to the ICU, the high-dose hydromorphone PCA provided little relief (PCA settings 0.5 mg bolus every 6 minutes with a 0.5 mg/hour continuous infusion; 25.8 mg hydromorphone intravenously in 8 hours). On his arrival to the ICU, a dexmedetomidine bolus of 0.5 µg/kg was administered, followed by an infusion at 0.5 µg/kg/hour. Soon after the dexmedetomidine bolus, he noted a significant improvement in his pain. In the 8 hours

following the initiation of the dexmedetomidine infusion, his pain scores improved to a 4-5/10 and his PCA usage decreased by more than 75 percent (7 mg hydromorphone over 10 hours). He became calm and cooperative.

The morning of postoperative day (POD) #2, the patient was up in a chair watching television. He continued to report high pain scores when getting out of bed but was vastly improved from the prior day with resting pain scores of 5-6/10. Although still on the dexmedetomidine infusion of 0.5 µg/kg/hour along with the hydromorphone PCA, he was alert, cooperative, and did not show any physical signs of extreme pain. His sedation scores ranged from 0 (alert and calm) to -1 (drowsy, not fully alert but has sustained awakening) on the Richmond Agitation Sedation Scale (+4 = combative; -5 = unarousable).<sup>14</sup> His heart rate, blood pressure, respiratory rate, and oxygen saturation remained within normal limits throughout. Overall, he described his pain as significantly improved and "acceptable" when on the dexmedetomidine infusion over 3 days. The total PCA usage decreased significantly on POD #5 and he was discharged from the ICU to the postsurgical unit. On POD #7, he was transitioned to oral sustained-release morphine 60 mg three times daily and oxycodone 10 mg as needed before being discharged to home on POD #9.

## DISCUSSION

The management of patients with chronic pain in the acute perioperative setting is a difficult challenge and guidelines are generally based on anecdote and opinions. The pharmacokinetic and pharmacodynamic properties of buprenorphine make it particularly appealing for the outpatient treatment of pain and addiction, and its use will likely continue to grow.<sup>4</sup> In the United States, the two branded buprenorphine prescriptions increased from 48,000 in 2003 to 1.9 million in 2007.<sup>15</sup> Although its properties are ideal for outpatient maintenance therapy, it poses unique challenges in the setting of acute pain. As the use of buprenorphine for pain and addiction continues to grow, anesthesiologists will be presented with more challenging situations that pose risk to patients.

This is the first described case of the use of dexmedetomidine as a postoperative analgesic in a patient treated with chronic buprenorphine therapy and offers a novel therapy to physicians placed in

this clinically challenging situation. The combination of buprenorphine and dexmedetomidine has been described for surgical anesthesia in the veterinary literature.<sup>16</sup> Previous review articles on the perioperative management of buprenorphine encourage the anesthesiologist to maximize alternatives to opioids, including local anesthetics, regional anesthesia, acetaminophen, and nonsteroidals.<sup>17,18</sup> Because of the type of surgery, postoperative regional anesthesia was not an option. Although there are studies showing impaired bone growth<sup>19-25</sup> and others indicating no difference<sup>26,27</sup> with nonsteroidal anti-inflammatory drugs, the surgeons refused nonsteroidals because of the concerns that it may undermine the stability of the bony fusion. Some physicians recommend the use of low-dose ketamine for difficulty in managing postoperative pain<sup>28-30</sup>; however, the dysphoric effects associated with ketamine infusions, even in very low doses,<sup>31,32</sup> would not have been ideal in this patient. In addition, ketamine infusions are normally administered with benzodiazepines, which in combination with high-dose opioid PCAs, can predispose a patient to respiratory depression. Lidocaine infusions have also been used with success in postoperative pain but can be associated with mild side effects.<sup>33,34</sup>

Although this patient continued to complain of high postoperative pain scores, clinically, he greatly improved immediately following the initiation of dexmedetomidine therapy. It is unlikely that the switch to hydromorphone alone could account for the significant improvement in the patient's pain following the initiation of the dexmedetomidine infusion, as his pain remained relatively unchanged in the 2 hours following the change to hydromorphone and before the dexmedetomidine, while awaiting an ICU bed. In addition, he had a significant reduction in his opioid usage after the initiation of dexmedetomidine with improved pain scores and subjective improvement noted by the nurse.

Dexmedetomidine is a selective  $\alpha$ -2 adrenoceptor agonist approved by the Food and Drug Administration for continuous intravenous sedation of mechanically ventilated patients in the ICU for 24 hours and nonintubated patients for procedural sedation.<sup>35</sup> The use of dexmedetomidine by anesthesiologists in the perioperative setting for sedation and pain control has greatly increased in recent years.<sup>35-37</sup> The opioid-sparing effects without respiratory depression make it a particularly attractive alternative in a formidable situation such as the

present case.<sup>35,36,38</sup> The potential hypotension and bradycardia seen with dexmedetomidine, especially during the loading phase, can be attenuated by ensuring that the patient is euvolemic and either administering a lower loading dose than that which is recommended by the company or increasing the time in which it is given. The combination of high-dose PCA therapy and dexmedetomidine warranted a transfer to the ICU. Until more data on the use of dexmedetomidine in patients outside of the ICU are available, it should be administered in a monitored setting. Dexmedetomidine is only approved for 24 hours of therapy; however, recent studies have shown decreased delirium in ICU patients treated with dexmedetomidine versus those sedated with lorazepam<sup>39</sup> and midazolam<sup>40</sup> in infusions for up to 72 hours without ill effect from the prolonged infusions. Although we cannot ascribe a strict causal relationship to the use of dexmedetomidine and the control of this patient's severe pain, the pharmacologic properties and side-effect profile of dexmedetomidine make it an appealing choice for patients receiving buprenorphine in the perioperative period. The ability to draw significant conclusions from this clinical scenario is limited, as with all case reports. Future study is warranted.

The need for hemodynamic monitoring during the dexmedetomidine infusion was not the only reason for which the ICU admission was necessary. Buprenorphine has a long but variable half-life (24-60 hours) that depends on the patient and the dose.<sup>4</sup> Sidebotham et al.<sup>41</sup> showed that there is a dose-dependent increase in adverse events associated with PCA opioids, and the doses consistent with higher complications were less than that used in the present case. As the time during which buprenorphine would inhibit the full agonist properties of the hydromorphone could not be predicted, the potential for a serious complications, such as apnea with subsequent cardiovascular arrest, required close nursing care.

The difficulties presented in this case have led to the creation of an institutional flowchart protocol for the perioperative management of patients taking buprenorphine as outpatients. Based on the available data and clinical experience of the members of our group, it has been determined that patients having surgeries in which moderate to severe postoperative pain is expected will be electively transitioned to traditional mu opioids for 5 days before their operation. Therefore, the above case would now be

cancelled to allow for transitioning. Although we acknowledge that it would be ideal to conduct a randomized trial to determine the best management, the available buprenorphine literature along with cases such as the one presented indicate that those patients not weaned off of buprenorphine preoperatively will not receive adequate analgesia from traditional mu opioids postoperatively and would have painful courses with high potential for adverse events. As such, this type of study would be unethical. Despite best efforts to appropriately manage patients preoperatively, patients will still present for urgent and emergent surgeries. In this event, the  $\alpha$ -2 mediated analgesia provided by dexmedetomidine may be an ideal adjunct to traditional postoperative therapy.

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## ACKNOWLEDGMENTS

The authors thank Kevin K. Tremper, MD, PhD (Robert B. Sweet, Professor of Anesthesiology and Chairman, Department of Anesthesiology, University of Michigan, Ann Arbor, MI) and George Mashour, MD, PhD (Assistant Professor, Department of Anesthesiology, University of Michigan, Ann Arbor, MI) for guidance and support. Chad M. Brummett, MD, is supported by the Department of Anesthesiology, University of Michigan. The authors do not have any disclosures. Abstract was presented at the American Society of Regional Anesthesia and Pain Medicine Meeting, November 20-23, 2008, Huntington Beach, CA.

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