

Effectiveness of Full Agonist Opioids in Patients Stabilized on Buprenorphine Undergoing Major Surgery: A Case Series

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A review of the medical literature failed to reveal clear, agreed-upon guidelines for practitioners on the postoperative provision of full agonist opioids for patients maintained on buprenorphine. Some controversy appears to exist about whether to maintain patients on their buprenorphine regimen up to the time of surgery. We describe the surgical outcomes and pain assessments for a series of five patients who underwent seven major surgical procedures. The patients were maintained on stable doses of sublingual buprenorphine. Postoperative pain was adequately controlled using full agonist opioids according to self-report and physician assessment. The observations from this case series lend support to the practice of maintaining stable buprenorphine dosing for patients who require major surgery.

Keywords: buprenorphine, perioperative, full agonist opioids, pain management, perioperative, surgery

INTRODUCTION

The use of buprenorphine, a partial mu opioid agonist, is increasing in the United States since the Food and Drug Administration approval of two new high-dose sublingual formulations in October 2002. These Schedule III medications are marketed as Suboxone (buprenorphine and naloxone combined in a 4:1 ratio) and Subutex (buprenorphine), manufactured by Reckitt Benckiser Pharmaceuticals, Inc., Richmond, VA. Both forms, containing either 2 mg or 8 mg of buprenorphine, are approved for the treatment of opioid addiction.

Buprenorphine has a much longer history of use as an analgesic in Europe (since 1979) in a parenteral (0.3 mg/mL) and lower-dose sublingual form (0.2–0.4 mg). It was also introduced in 1981 for parenteral use in the

United States as an analgesic only as Buprenex (Reckitt Benckiser Pharmaceuticals, Inc., Richmond, VA). In the parenteral form, it is a highly potent analgesic, and in the nonopioid-dependent patient, a dose of 0.3 mg of buprenorphine is equivalent to 10 mg of morphine sulfate. Buprenorphine became available in a transdermal form in 2001 in Europe and is increasingly used for all types of chronic pain, including cancer and neuropathic pain.^{1,2} The use of buprenorphine for both the treatment of chronic pain and the treatment of substance use disorder has been thoroughly reviewed.^{3–7} Prescribing buprenorphine for the indication of pain in the United States requires the usual licenses and precautions for controlled substances but no special certification, as is the case for prescribing buprenorphine for the treatment of opioid dependence.⁵

Buprenorphine has been used as an effective analgesic for postoperative pain in patients not dependent on full agonist opioids.^{8–10} A literature review revealed no evidence-based guidance on optimal methods for managing patients maintained on daily doses of buprenorphine should they need nonemergent major surgery.^{11–14} These publications focus on two

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specific concerns: (1) that the use of full agonist opioids for patients stabilized on buprenorphine may be problematic because of the tight binding at the mu receptor, leading to partial opioid blockade and reduced analgesia^{12,15} and (2) that postoperative care in the opioid-dependent patient has special risks, requiring careful monitoring for respiratory depression as well as adequate pain control.^{12,14}

This article will discuss the literature and present our clinical experience with five buprenorphine-maintained patients who underwent seven planned major surgical procedures. The primary aims of this article are to describe the course for each surgery and the outcome in providing analgesia (by physician or patient self-report). All of the information presented here was extracted from hospital and clinic charts with patient consent.

LITERATURE REVIEW

There are conflicting recommendations for managing surgical patients maintained on buprenorphine. A review by Roberts and Meyer-Whitting¹⁴ outlines the options for perioperative management of these patients. The authors emphasize the feasibility of using full agonist opioid pain control while continuing buprenorphine throughout the perioperative period. There is additional discussion on the need for careful monitoring given the risk of respiratory depression when high doses of full opioid agonist analgesics (such as morphine) are used to overcome the partial blockade of the mu receptor by buprenorphine. They also discuss, but do not necessarily favor, the option to cease buprenorphine up to 72 hours before surgery with conversion to a full agonist opioid, typically methadone, so that no partial blockade persists postoperatively.

Another review article in the anesthesia literature discusses perioperative management of opioid-dependent patients maintained on buprenorphine or methadone, recommending that the patient take their morning dose on the day of surgery.¹¹ The authors discuss the benefits of the prolonged activity of either analgesic intra-operatively by minimizing the risk of opioid withdrawal during surgery and, in agreement with Roberts and Meyer-Whitting, do not appear deterred by the partial opioid blockade when buprenorphine is used.

In contrast with these recommendations from the anesthesia literature, an article authored by Alford et al,¹² clinicians in the substance abuse field, and cited by several subsequent review articles,^{9,16} appears to recommend that preoperative patients maintained on

buprenorphine be switched to a full agonist opioid before surgery. These authors address the issue of acute pain management in patients receiving either methadone or buprenorphine and recommend that hospitalized patients in acute pain be rotated off buprenorphine. Ballantyne and LaForge,¹⁶ in their review of the intersection between addiction and pain, cite Alford et al¹² to justify the recommendation to discontinue buprenorphine a week in advance of a major surgery. Vadivelu and Hines,⁹ in another review of buprenorphine pharmacology, again citing Alford et al,¹² reiterate that hospitalized patients experiencing acute pain should be rotated off of buprenorphine. These recommendations are also reflected by the caution noted by the Center for Substance Abuse Treatment of the U.S. Department of Health and Human Services in their published Treatment Improvement Protocol (TIP) that "it may be difficult to achieve analgesia with short acting opiates in patients who have been maintained on buprenorphine."¹⁵

The effectiveness of full agonist opioids in buprenorphine-treated patients has been discussed in other recent publications. Budd and Collett¹⁷ conclude that persistent blockade of the mu opioid receptor does not occur, and the effectiveness of full agonist opioids is not precluded in either acute or chronic situations. Sittl¹⁸ concludes that morphine is effective as a medication for breakthrough pain in patients treated with transdermal buprenorphine. Mercadante et al,¹⁹ in an open-label study of 29 cancer patients receiving transdermal buprenorphine, describe the safety and effectiveness of intravenous (IV) morphine for episodic breakthrough pain. Another review article on the treatment of acute pain in opioid-dependent patients outlines the recommended use of full agonist, short-acting opioids postoperatively for analgesia for patients maintained on transdermal buprenorphine.²⁰ There have also been reports on the use of full agonist opioids in buprenorphine-maintained obstetric patients.^{21,22} Furthermore, a prospective study of patients receiving transdermal buprenorphine for chronic pain versus no opioid for open-heart surgery revealed no problems with analgesia or respiratory depression in the buprenorphine group.²³

Finally, a case report describes postoperative analgesia treatment in a buprenorphine-maintained patient; however, it is not directly applicable to the cases of postoperative pain we present.¹³ The case was a nonopioid-dependent patient who appears to have self-medicated cocaine withdrawal with street-procured Suboxone (of unknown dose) and who then underwent hip arthroplasty with inadequate postoperative analgesia after standard doses of hydromorphone. The patient eventually left the hospital against medical advice. The cocaine withdrawal and

preoperative self-medication with Suboxone are quite specific to this case and do not allow generalizability of this case report to surgical patients who are stabilized on buprenorphine.

Book et al¹⁰ describe the postoperative course of a patient who underwent breast implant removal. This buprenorphine-maintained patient self-medicated after discharge with up to 72 mg/day of sublingual buprenorphine to achieve effective analgesia. The case is notable for challenging the generally agreed upon understanding that buprenorphine analgesia has a ceiling effect at lower doses but does not provide a reassuring guideline for treating postoperative buprenorphine-stabilized patients.

CASE REPORTS

In our clinical practice, we have found that full agonist opioids are effective for breakthrough pain in buprenorphine-maintained chronic pain patients. When this was extrapolated to patients undergoing major surgical procedures, we found that patients did well with oral or IV full agonist opioids postoperatively. We report on five patients and seven major surgeries with successful analgesia and no significant adverse events (Table 1). The intra-operative and postoperative medications reported for all patients include only opioids, bupivacaine, and ketamine. Other analgesic medications, such as ketorolac, other nonsteroidal anti-inflammatory drugs, and acetaminophen, are not reported here.

All patients in this report were seen in the private practice of one of the authors (HK), and all had been stabilized on sublingual buprenorphine for chronic musculoskeletal pain for at least 1 year before major surgical procedures. One patient also had frequent recurrent pain from nephrolithiasis. Several had remote histories of opioid dependence. The buprenorphine provided was in the form of Suboxone in all cases except the patient who underwent surgery 4, whose

buprenorphine was in the form of a compounded gelatin troche.

Patients underwent major surgical procedures with high levels of predicted postoperative pain. Patients were well known to the practice and were in generally good health, with the exception of the first patient described (surgery 1), who was diabetic and obese. Assessment of the effectiveness of pain control postoperatively was based on written notations in the hospital chart as assessed and recorded by one or more of the following services: anesthesia, surgery, hospitalist, pain medicine, physical therapy, and nursing. All patients underwent surgical procedures with no preoperative interruption of their daily standard dose of buprenorphine.

Surgery 1

A 60-year-old male who was diagnosed with a hepatic flexure carcinoma underwent a right colectomy and cholecystectomy. Pain control and overall clinical outcome were positive, except for prolonged intubation through postoperative day (POD) 1 because of obesity. Postoperative analgesia included an epidural containing morphine and an IV patient-controlled analgesia (PCA), also containing morphine, with doses at the high end of 27 mg/day gradually reduced to 6 mg/day before discharge. The patient's dose of sublingual buprenorphine was increased to 32 mg/day during the hospitalization. Because of intubation, no verbal pain reports were available for POD 1. After being extubated, the patient reported that pain was well controlled throughout the remainder of the hospitalization. The hospital stay, although longer than the others in this series, was uneventful, and the patient was discharged on the increased dose of buprenorphine. He was also given oral hydrocodone 10 mg for breakthrough pain at discharge.

Surgery 2

A 43-year-old male underwent a right total knee replacement. Postoperative analgesia was provided by

Table 1.

	Surgical Procedure	Length of stay (days)	Pain assessment at discharge	Preoperative buprenorphine (mg)
1	Right-side colectomy	9	"Pain free"	24
2	Knee replacement (R)	4	"Excellent pain management"	12
3	Knee replacement (L)	3	"Excellent analgesia"	12
4	Small bowel resection	5	"Good analgesia"	2
5	Bilateral mastectomy w/ reconstruction	4	"Pain fluctuates . . . responds to hydromorphone"	8
6	Breast reconstruction	2	"Good pain control"	6
7	X-STOP removal	3	"Excellent pain control"	16

epidural morphine and bupivacaine, IV and oral hydromorphone, ketamine, sustained release and immediate release oxycodone, and sublingual buprenorphine. The epidural morphine was limited to a single dose of 0.2 mg, given in the recovery room, and epidural bupivacaine was maintained for 48 hours. IV hydromorphone was provided on POD 1 to 3 at an average dose of less than 1 mg/hour. Oral hydromorphone and oxycodone were introduced on POD 2 and 3, sublingual buprenorphine was continued during the hospital stay, and the patient was discharged on 16 mg of buprenorphine and on oral hydromorphone for breakthrough pain. Throughout the hospital stay, the pain and orthopedic services reported excellent analgesia.

Surgery 3

The same patient, 2 years later, underwent a left total knee replacement. His postoperative pain management included epidural opioids and bupivacaine, IV and oral opioids, and IV and oral ketamine. Epidural hydromorphone averaged 7 mg per day for the first 2 days, after which the epidural was discontinued. Epidural bupivacaine was also given during this timeframe, and additional epidural fentanyl was given as a PCA averaging 70 µg/day. On the day of surgery, the patient received 5 mg IV morphine. After the epidural was discontinued, oral opioids, both short and long acting, were provided at low dosages. Ketamine was given IV both intra-operatively and later on the day of surgery and was continued orally during POD 1 to 3 before discharge. Pain was well managed with this regimen. In this case, sublingual buprenorphine was not given during this brief hospitalization but was restarted without difficulty at discharge at the preoperative dose.

Surgery 4

A 60-year-old male was admitted for surgery with a small bowel stricture with peritoneal mass. A malignancy was removed. The surgery was uneventful. The pain was easily managed in the recovery room and throughout the postoperative period with uniformly favorable pain ratings on POD 1 to 4. Full agonist opioids were used without difficulty at conventional doses. For example, fentanyl 150 µg was given intra-operatively, and hydromorphone 1 mg was used in the recovery room. An epidural catheter delivered bupivacaine and hydromorphone until POD 3, and an average of 0.2 mg per hour of epidural hydromorphone was infused. PCA IV hydromorphone was also used through POD 4 and averaged between 5 and 10 mg per day. Parenteral buprenorphine was restarted on POD 3 without difficulty, and the patient was discharged on sublingual buprenorphine at his preoperative dose.

American Journal of Therapeutics (2010) 17(5)

Surgery 5

A 42-year-old female diagnosed with ductal carcinoma in situ of the breast underwent bilateral subcutaneous mastectomy with reconstruction and implantation of tissue expanders. The patient was maintained on 2 mg of sublingual buprenorphine throughout the hospitalization. This patient was treated with an Accufuser local anesthetic pump containing bupivacaine, with a push button operated by the patient, as a PCA. Because of the anticipated need for high doses of full agonist opioids, cardiac monitoring and pulse oximetry were maintained throughout the hospitalization. Postoperatively, she also had an IV PCA containing hydromorphone averaging 26 mg/day, discontinued on POD 2. She required both substantial doses of oral hydromorphone (up to 96 mg on POD 2) and additional IV hydromorphone (up to 16 mg on POD 2). Pain scores were higher in this case but responded well to the hydromorphone. She was discharged on sublingual buprenorphine at the preoperative dose and on oral hydromorphone for breakthrough pain.

Surgery 6

The same patient, 8 months later, underwent removal of bilateral tissue expanders with subsequent placement of implants. She received 350 µg fentanyl intra-operatively. On the day of surgery, she received 4 mg of sublingual buprenorphine, 5.4 mg of IV hydromorphone, and 16 mg of oral hydromorphone. Pain was well controlled. Before discharge midday on POD 1, she received 6 mg of hydromorphone orally and 2 mg buprenorphine sublingually. She was discharged on the day after surgery. A bupivacaine Accufuser, as provided in the previous surgery, was used during the hospitalization and was left in place for home use at discharge. She was discharged on sublingual buprenorphine at the preoperative dose and on oral hydromorphone for breakthrough pain.

Surgery 7

The patient, a 58-year-old male with significant history of back pain and chronic pain syndrome, underwent surgical removal of two X-Stop spacer devices from his lumbar spine, inserted 2 years previously. The current procedure also involved lumbar decompression at two levels. Intra-operatively, the patient received 600 µg of fentanyl, and in the recovery room he received an additional 200 µg of fentanyl IV along with 4 mg of IV hydromorphone. After transfer to the floor on the day of surgery and on POD 1, the patient received an average of 20 mg/day of IV hydromorphone, by way of PCA, and 3 mg/day of sublingual buprenorphine.

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On POD 1, he received 28 mg of oral hydromorphone and was discharged on the morning of POD 2 with a reduced need for hydromorphone for breakthrough pain on his preoperative dose of sublingual buprenorphine. Reported pain control was excellent, and he progressed to physical therapy.

DISCUSSION

Clinical management of acute pain in patients maintained on buprenorphine is an emerging and important issue in pain medicine.²⁴ Because increasing numbers of patients are being stabilized on buprenorphine for opioid dependence or chronic pain, the recommendations for perioperative management of buprenorphine dosing will have increasing importance. Our experience, as illustrated by the above cases, does not support the recommendation that patients must be converted from buprenorphine to methadone before elective major surgery.¹²

Potential complications arise when buprenorphine is discontinued for more than a few days and patients are placed on full agonist opioids before surgery, making it difficult to reconvert to buprenorphine. This is caused by the necessary induction protocol, which can require 24 hours or more for the patient to be off full agonist opioids to avoid unpleasant precipitated withdrawal symptoms when buprenorphine is reintroduced. Many patients find re-induction difficult to tolerate because of the emergence of opioid withdrawal, with its attendant anxiety, and an acute exacerbation of chronic pain symptoms. Underlying medical illness, including cardiac, pulmonary, neurologic, and gastrointestinal disorders, may also destabilize during even early opioid withdrawal. The sedative given to reduce the severity of symptoms, usually benzodiazepines, can risk increased complications.

In the described seven surgeries, effectiveness of full agonist opioids was central to the postoperative analgesia. This was the case even in the three surgeries in which nonopioids made important contributions (epidural bupivacaine in 3 surgeries, subcutaneous bupivacaine by way of PCA in 2 surgeries, and ketamine in 2 surgeries). Our experience of the robust effectiveness of full agonist opioids in patients stabilized on buprenorphine undergoing major surgery supports the strategy of uninterrupted buprenorphine treatment in these patients.

It is our hope that this case series and literature review highlights the need for a more collective dialogue on the optimal perioperative treatment of buprenorphine-maintained patients and the subsequent development of definitive treatment guidelines.

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American Journal of Therapeutics (2010) 17(5)

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