

Buprenorphine and Surgery: What's the Protocol?

Jeffrey J. Bettinger, PharmD
Jeffrey Fudin, PharmD, DAIPM, FCCP, FASHP
Charles Argoff, MD

Surgery presents a plethora of inherent risks for patients receiving long-term opioid therapy. Patients may require higher-than-usual postoperative opioid doses for acute pain due to an underlying physical tolerance, and may transition to another opioid shortly after a major surgical procedure requiring conscious sedation with sedative hypnotics and/or general anesthesia. Converting to or adding another opioid is generally manageable in the majority of cases. Many opioids are easily titratable, and conversion, although sometimes tedious, is achievable with careful monitoring.

Because of their pharmacological and pharmacokinetic characteristics, however, unique opioids such as tapentadol, tramadol, levorphanol, methadone, and buprenorphine require special consideration when preparing for either elective or same-day emergency surgery. This chapter introduces buprenorphine's unique characteristics and elucidates important considerations that are paramount to appropriately and safely managing pain in each of these surgical situations.

FDA-Approved Indications for Buprenorphine

Buprenorphine is US Food and Drug Administration (FDA) approved in various dosage formulations for treating opioid abuse disorder, acute pain (injectable), and chronic pain severe enough to require daily around-the-clock dosing (transdermal and buccal film). Formulations that are approved specifically for opioid abuse disorder but lack the FDA indication for analgesia are available as single entity buprenorphine (Subutex) and also co-formulated with naloxone; the combination products, available generically or as brand-name products, are summarized in Table 1, page 74.¹ Single entity buprenorphine products specifically indicated for pain appear in Table 2, page 74.

Table 1: Available Dosages of Buprenorphine/Naloxone Combination Products^a

Suboxone SL Tablet	Suboxone SL Film	Zubzolv SL Tablet	Bunavail Buccal Film
2 mg/0.5 mg	2 mg/0.5 mg	1.4 mg/0.36 mg	N/A
4 mg/1 mg	4 mg/1 mg	N/A	2.1 mg/0.3 mg
8 mg/2 mg	8 mg/2 mg	5.7 mg/1.4 mg	4.2 mg/0.7 mg
12 mg/3 mg	8 mg/2 mg + TWO 2 mg/0.5 mg films	N/A	6.3 mg/1 mg

^a buprenorphine dose/naloxone dose

Table 2: Available Dosages and Dosing Intervals For Buprenorphine Pain Control Products

Product	Buprenex Injectable	Belbuca Buccal Film, mcg	Butrans, mcg/h
Dose	0.3 mg/mL	75, 150, 300, 450, 600, 750, 900	5, 10, 15, 20 ^a
Dosing Interval	Every 6 to 8 hours	Every 12 hours	Change patch every 7 days

^a Available in European countries as Transtec Transdermal Patches in 35, 52.5, and 70 mcg/hour strengths. Unlike the US product, Transtec Transdermal Patches are intended to be changed at 96-hour intervals.

N/A, not applicable

Pharmacological and Pharmacokinetic Characteristics of Buprenorphine

Buprenorphine is a dehydroxylated phenanthrene and is chemically similar to other opioids such as hydrocodone, oxycodone, levorphanol, hydromorphone, oxymorphone, and others.² Unlike its chemical cousins, however, buprenorphine is a partial agonist at the μ -opioid receptor (MOR) and an antagonist at κ receptors.³ As a partial agonist, buprenorphine is able to activate MORs; at low to moderate doses, it can achieve the same or superior analgesia compared to a full μ opioid agonist.³ However, because it's a partial agonist, it exhibits a plateaued dose-response curve. As the dose of buprenorphine increases, the

response increases to a certain point before plateauing. This is also known as buprenorphine's ceiling effect, since doses beyond this ceiling will not yield increased analgesia or euphoria.³ A similar plateauing occurs in the retention of carbon dioxide (CO₂) concentrations. In the absence of concomitant sedative-hypnotics, CO₂ accumulation remains constant as the buprenorphine dose escalates, theoretically lowering the risk of overdose.^{4,5}

Although buprenorphine has a lower intrinsic activity than full opioid agonists at higher doses, it has the highest affinity of any opioid toward the MOR.⁶ Due to this incredibly strong binding of the MOR, buprenorphine can actually displace full opioid agonists, such as morphine and methadone, from the receptor. Buprenorphine, however, will not be easily displaced by those same opioids.^{3,7,8} Compared to many other opioids, it also has an extremely slow dissociation rate, which is a measure of disengagement from the target receptor.³ Buprenorphine's dissociation rate of about 166 minutes, along with its half-life of approximately 25 to 45 hours and high lipophilicity, causes it to be eliminated from the body relatively slowly over a 2- to 3-day period.³

Dilemmas for the Surgical Patient Receiving Buprenorphine

These pharmacological and pharmacokinetic characteristics could be problematic for surgical patients who are chronically using buprenorphine. A new full opioid agonist given postoperatively to control a patient's acute pain will not displace buprenorphine from the MOR, leaving the patient susceptible to increased pain and agitation. Starting an opioid agonist while the patient still has buprenorphine in his or her systemic circulation can create other problems as well. As soon as the patient's body eliminates all of the buprenorphine, the new opioid will be able to occupy all available MORs. This abrupt transition could greatly increase the frequency of side effects and risk of opioid-induced respiratory depression. Consequently, providers should have proper procedures in place for surgical patients currently receiving buprenorphine.

Procedure for Elective Surgery

The primary difference between elective surgery and same-day emergency surgery is that elective surgery allows ample time prior to the surgery for preparation and appropriately planning for patient management. Hence, elective surgery provides a clear advantage to patients on chronic buprenorphine therapy, since it generally allows sufficient time for a team of clinicians to ensure

that a plan, such as completely tapering a patient off of buprenorphine, can be successfully completed. However, this is still a difficult process with specific dilemmas that must be addressed.

Due to buprenorphine's relatively long half-life and slow dissociation rate from the MOR, the Substance Abuse and Mental Health Services Administration (SAMHSA) recommends that patients should be tapered off from buprenorphine gradually over 2 to 4 weeks (depending on the dose) prior to surgery.⁹ This period allows buprenorphine to be fully cleared from the body well before the need to initiate full opioid agonists for postsurgical pain management. Buprenorphine would otherwise block the MORs and prevent the opioid agonists from eliciting analgesia.

If the patient has been using buprenorphine to treat a pain disorder, short-acting opioid agonists, such as hydrocodone, oxycodone, or morphine, should be prescribed on an as-needed basis so the patient has adequate pain relief prior to the surgery. Once the patient is admitted for surgery, the hospital or clinic would then be able to begin its pre-, intra-, and postoperative patient pain management plan according to its institutional policies. After the surgery, when the patient no longer requires the use of additional opioids for postsurgical pain management, buprenorphine may be reintroduced and titrated until an adequate dose is achieved.

This scenario assumes that the patient had not been illegally obtaining buprenorphine from non-medical sources to self-treat an opioid abuse disorder prior to surgery. A patient who had done so but not disclosed it to his or her providers would most likely require incredibly high doses of opioid agonists during and after the surgery to overcome buprenorphine's low intrinsic activity and high binding affinity. When the buprenorphine cleared out of the patient's body after 2 to 3 days, the patient would then be at significant risk for respiratory depression. Given this possibility, providers may want to universally screen patients for buprenorphine use prior to surgery.

In addition, patients taking buprenorphine for substance abuse disorders are susceptible to relapse during the "washout period" prior to surgery. To overcome these potential hurdles, we suggest that a multidisciplinary team including pain specialists should be keenly aware of the issues involved in the pre- and postsurgical care of these patients and be prepared to appropriately taper them off of buprenorphine therapy. If providers suspect that a patient is illegally using buprenorphine or abusing other opioids during this washout period, they should begin urine drug monitoring and/or take serum samples to

ensure that the patient receives optimum care throughout the surgical process.

Procedure for Same-Day Surgery

Same-day emergency surgery in patients receiving buprenorphine regularly for any reason is more difficult than elective surgery for the reasons described above. Emergency surgery leaves no time to sufficiently and completely taper the patient off of buprenorphine; even if stopped abruptly, about 2 to 3 days would still be needed to entirely clear the drug from the patient's body.

In this case, providers have three main options, depending on the anticipated level of pain:

- If they deem that the surgery will only cause mild to moderate acute pain, they may continue buprenorphine, while adding and optimizing non-opioid pain modalities.
- If the providers anticipate that surgery will cause moderate pain, they can treat the patient with intravenous buprenorphine.
- If they anticipate severe pain, providers can discontinue buprenorphine in lieu of high-dose and carefully titrated short-acting opioids until the buprenorphine is cleared from the patient's body.¹⁰⁻¹⁴

From our experience, we have found that hydromorphone or fentanyl is the best option for managing severe postsurgical pain under these circumstances; we have a preference toward the latter due to its similar lipophilicity. Some of our experienced colleagues prefer to prescribe a full opioid agonist with similar lipophilicity to buprenorphine, such as fentanyl; this will more successfully compete for those MORs compared to other full agonists such as morphine. However, there is no standard conversion or dosage recommendations that have been studied or that can be considered a standard of care.¹⁴ Optimizing nonopioid analgesics, including nerve blocks, also plays an important role in all of these scenarios.

We recommend that any patient who is receiving high-dose, full agonist opioids to overcome buprenorphine's blockade of MOR should remain hospitalized for 3 days after the discontinuation of buprenorphine. Sending the patient home on megadoses of a full agonist while the MOR is still blocked is quite dangerous.¹² When the full agonist is carefully administered in the hospital setting, a diminished daily dosage should occur prior to patient discharge so that the patient goes home with a reasonably average opioid dose rather than a megadose.

In addition, nonopioid adjuvant analgesics and/or nerve blocks can be extremely important for most efficiently and effectively managing postoperative pain. Once a patient's pain is controlled, he or she may be converted back to buprenorphine therapy, especially if it's being given as a treatment for a substance abuse disorder.

Conclusion

Buprenorphine is a unique medication. Because of its pharmacological and pharmacokinetic properties, it can create a multitude of challenges when managing acute pain perioperatively. Postoperative pain management for patients chronically receiving buprenorphine is a complex task requiring skilled clinicians to overcome these challenges. To address these issues, we strongly suggest that hospitals establish a clear and comprehensive policy and an interdisciplinary team of clinicians with expertise in medicine, behavioral health, and pharmacy. With close monitoring, appropriate use of nonopioid adjuvant analgesics, and a team-based care approach, it is possible to provide adequate postoperative pain relief while ensuring that patients requiring long-term buprenorphine therapy are adequately cared for in the postoperative setting.

COPY: In Kean N, 2nd ed., Opioid Prescribing and Monitoring in Behavioral Health. U.S. September 2017.

References

1. Fudin J, Cleary JP, Gottwald J. A brief review of buprenorphine products. *Pharmacy Times*, March 22, 2016. Available at: <http://www.pharmacytimes.com/contributor/jeffrey-fudin/2016/03/a-brief-review-of-buprenorphine-products>. Accessed July 21, 2017.
2. Cleary J, Brennan MJ, Fudin J. Opioid rotation from Opana ER following FDA recall for removal. *Pract Pain Manag*. July 21, 2017. Available at: <https://www.practicalpainmanagement.com/resources/opioid-rotation-opana-er-following-fda-call-removal?page=0,2>. Accessed July 21, 2017.
3. Center for Substance Abuse Treatment. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004. (Treatment Improvement Protocol (TIP) Series, No. 40.) Available at: <https://www.ncbi.nlm.nih.gov/books/NBK64245/>. Accessed July 24, 2017.
4. Dahan A, Yassen A, Bijl H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth*. 2005;94(6):825-834.
5. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth*. 2006;96(5):627-632.
6. Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. *Regul Toxicol Pharmacol*. 2011;59(3):385-390.
7. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DB, Johnson RE. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther*. 1988;247(1):47-53.
8. Strain EC, Walsh SL, Bigelow GE. Blockade of hydromorphone effects by buprenorphine/naloxone and buprenorphine. *Psychopharmacology (Berl)*. 2002;159(2):161-166.
9. Center for Substance Abuse Treatment. *Key Application Program (KAP) Keys for Physicians: Based on TIP 40, Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005. Available at: <https://store.samhsa.gov/shin/content/KAPT40/KAPT40.pdf>. Accessed July 25, 2017.
10. Roberts DM, Meyer-Witting M. High-dose buprenorphine: perioperative precautions and management strategies. *Anaesth Intensive Care*. 2005;33(1):17-25.
11. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med*. 2006;144(2):127-134.
12. Marcucci C, Fudin J, Thomas P, Sandson NB, Welsh C. A new pattern of buprenorphine misuse may complicate perioperative pain control. *Anesth Analg*. 2009;108(6):1996-1997.
13. Kornfeld H, Manfredi L. Effectiveness of full agonist opioids in patients stabilized on buprenorphine undergoing major surgery: a case series. *Am J Ther*. 2010;17(5):523-528.
14. Macintyre PE, Russell RA, Usher KA, Gaughwin M, Huxtable CA. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. *Anaesth Intensive Care*. 2013;41(2):222-230.

COPY: In Kean N, 2nd ed., Opioid Prescribing and Monitoring Pub. Vertical Health, LLC. September 2017.