Perioperative Buprenorphine

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THE OPIOID USE DISORDER epidemic in the United States has increased the number of people in medication-assisted treatment programs. These programs, as defined by the Substance Abuse and Mental Health Services Administration, use medications in combination with counseling and behavioral therapies for the treatment of substance use disorders.[1] Currently, the Food and Drug Administration (FDA) has approved the following four formulations for the indication of opioid use disorder: buprenorphine, buprenorphine-naloxone, methadone, and naltrexone. Although naltrexone is an opioid-receptor antagonist, both the methadone and the buprenorphine formulations are long-acting opioids that are intended to decrease the physiological cravings that instigate drug seeking-behavior. Patients on buprenorphine or buprenorphine combined with naloxone currently present a significant perioperative challenge. This article aims to increase awareness of the challenges and controversies associated with buprenorphine therapy throughout the surgical continuum of care.

Buprenorphine is a schedule III opioid approved by the FDA for the treatment of acute pain in 1981, opioid use disorder in 2002, and chronic pain in 2010. Buprenorphine is available for administration in many different formulations, including a buccal film, sublingual tablet, transdermal patch, intravenous injection, deep intramuscular injection, subcutaneous injection, and subdermal implant. Many of the formulations come with unique and complex pharmacology. Monoproducts containing only buprenorphine are available in addition to forms combined with naloxone in a 4:1 ratio. The addition of naloxone aids in preventing misuse by inducing withdrawal symptoms when noninjectable formulations are abused and injected intravenously. Table 1 describes the different formulations of buprenorphine available in the United States along with the FDA-approved indication and elimination half-life.[2]

The pharmacokinetic and pharmacodynamic properties of buprenorphine differ from most common opioid analgesic agents. The rate of absorption and elimination half-life varies widely across formulations. Following an intravenous dose of buprenorphine hydrochloride 0.3 mg in postoperative adults, the mean elimination half-life was 2.2 hours, ranging from 1.2 to 7.2 hours.[2,3] This is much shorter than what has been observed for the buprenorphine buccal film (24 to 48 hours) and the subcutaneous injection (43 to 60 days).[2] This variability is attributed to the highly lipophilic nature of buprenorphine and its capacity to develop a drug depot when administered in the sublingual, buccal, or transdermal route.

Pharmacodynamic properties set buprenorphine apart from traditional opioid analgesics, such as morphine and fentanyl. Buprenorphine exerts its analgesic effect by binding with high affinity to the mu-opioid receptor in the central nervous system. Although it has a high affinity, it produces low intrinsic activity, or efficacy. Because of this, it is classified as a partial mu-opioid receptor agonist. Buprenorphine is not easily displaced from the receptor by either full mu-opioid receptor agonists, such as morphine, or by antagonists, such as naloxone. Competitive displacement of buprenorphine from the receptor is concentration and time-dependent, requiring very high concentration of the competing drug.[4] Contributing to the prolonged duration of action of buprenorphine is the rate at which it dissociates from the receptor. Buprenorphine dissociates slowly from the receptor (166 minutes), whereas fentanyl dissociates rapidly (6.8 minutes).[4] Buprenorphine is also an antagonists at the kappa opioid receptor, an agonist at the delta receptor, and a partial agonist

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Table 1. Buprenorphine Formulations Available in the Unites States[2]

Generic Name	Brand Name	Formulation	FDA-Approved Indication	Available Dosage Forms	Mean Buprenorphine Elimination Half-Life
Buprenorphine	Buprenex	Immediate release injection	Acute pain	0.3 mg/mL	2.2 h
Buprenorphine	Belbuca	Buccal film	Chronic pain	75 mcg 150 mcg 300 mcg 450 mcg 600 mcg 750 mcg 900 mcg	24-48 h
Buprenorphine	Butrans	Transdermal patch	Chronic pain	5 mcg/h 7.5 mcg/h 10 mcg/h 15 mcg/h 20 mcg/h	24-48 h
Buprenorphine	Subutex	Sublingual tablet	Opioid dependence	2 mg; 8 mg	31-35 h
Buprenorphine	Sublocade	Subcutaneous injectable	Opioid dependence	100 mg/0.5 mL 300 mg/1.5 mL	43-60 d
Buprenorphine	Probuphine	Subdermal implant	Opioid dependence	74.2 mg	24-48 h
Buprenorphine/ Naloxone	Bunavail	Buccal film	Opioid dependence	Buprenorphine/ Naloxone 2.1 mg/0.3 mg 4.2 mg/0.7 mg 6.3 mg/1 mg	16.4-27.5 h
Buprenorphine/ Naloxone	Suboxone	Sublingual film	Opioid dependence	Buprenorphine/ Naloxone 2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	24-42 h
Buprenorphine/ Naloxone	Zubsolv	Sublingual tablet	Opioid dependence	Buprenorphine/ Naloxone 0.7 mg/0.18 mg 1.4 mg/0.36 mg 2 mg/0.5 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg 8 mg/2 mg 8.6 mg/2.1 mg 11.4 mg/2.9 mg	24-42 h

FDA, US Food and Drug Administration.

at the nociceptin opioid receptor.[5] Although further studies are required, these unique properties may be beneficial in the management of depression, anxiety, neuropathic pain, and opioid-induced hyperalgesia in patients with opioid use disorders or chronic pain.[5-7]

In the perioperative setting, there is current debate on whether buprenorphine should be continued or discontinued throughout the surgical continuum of care. The concern is derived from the pharmacodynamic properties of buprenorphine, which suggest that in the presence of

buprenorphine, full mu-opioid receptor agonists will be unable to bind to the already occupied receptor. A study evaluating the effect of buprenorphine maintenance dose on mu-opioid receptor occupancy reported a dose-dependent receptor occupancy. The mean whole-brain mu-opioid receptor occupancy was 41%, 80%, and 84% at 2 mg, 16 mg, and 32 mg doses, respectively.[8] Clinically, this causes the concern that administration of traditional opioids may not effectively provide analgesia, leading to inadequate postoperative pain control.

Buprenorphine, in and of itself, is an effective analgesic agent at low-to-moderate doses.[9] Available formulations of buprenorphine range drastically, providing doses from 5 mcg/h (transdermal patch) to 12 mg (sublingual film). This reflects the potency of low-dose formulations for pain compared with higher doses used for patients with opioid use disorders. Partial activation of the mu-opioid receptor results in analgesia, but has been publicized to have a ceiling effect on respiratory depression.[10,11] Recently published systematic reviews and meta-analyses of randomized controlled trials comparing buprenorphine with morphine for acute pain management found no difference in analgesic efficacy.[12,13] Of equal importance is that buprenorphine displayed a similar clinical adverse effect profile to morphine with respect to respiratory depression, sedation, nausea, vomiting, and hypotension. This finding indicates that despite data showing a ceiling effect on respiratory depression in healthy volunteers and animal models, the clinical setting may be quite different.[10] Patients continuing buprenorphine in the perioperative setting should be monitored closely, especially when used in combination with other medications with sedative properties. Other at-risk populations include the young, frail, and elderly.[10] If respiratory depression occurs, larger than usual doses of naloxone may be required to reverse the effects. Some experts recommend a 2-mg bolus followed by a 4 mg per hour continuous infusion under close observation.[10]

Various strategies have been suggested to guide the perioperative management of patients on buprenorphine therapy.[14] These strategies include preoperative discontinuation, preoperative dose reduction, and continuation throughout the perioperative phases of care. Many existing recommendations for the perioperative management of buprenorphine recommend discontinuing buprenorphine before surgery despite insufficient evidence to support these recommendations.[15] Concerns with discontinuing therapy include potential experience of withdrawal symptoms, inadequate analgesia secondary to inadequate conversion to a full agonist opioid, and for patients with opioid use disorder, the risk of relapse and overdose. This risk should not be underestimated. More recent evidence, while not robust, suggests that discontinuing or reducing the dose of buprenorphine preoperatively may not be the most effective management strategy and that continuing buprenorphine with supplemental doses may offer the most effective analgesia.[15-18]

For patients who continue buprenorphine throughout the surgical continuum of care, it becomes critically important to optimize multimodal analgesic management strategies. These include modalities such as regional anesthesia, acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentenoids, ketamine, lidocaine infusion, magnesium, and dexmedetomidine. Cases reporting difficult to control postoperative analgesia commonly fail to implement multimodal strategies.[17] For breakthrough pain management, some experts advocate for increasing the buprenorphine as the primary opioid analgesic. Alternatively, opioids with a high affinity for the mu-opioid receptor, such as hydromorphone, fentanyl, or sufentanil, may be more effective than those with lower affinity.[19,20] Higher opioid dose requirements than traditionally administered may be required.

Discontinuing buprenorphine in a patient stabilized on therapy for opioid use disorder or chronic pain can be a logistical challenge for the patient, the prescribing clinicians, the nurses, and the health care system. Patients will need to be transitioned to another opioid before surgery, risking over-dosing or under-dosing. In addition, reinduction to therapy postoperatively necessitates arrangement for appropriate discharge plans to safely reinitiate maintenance buprenorphine therapy. It is also important to be aware that initiation of high-dose buprenorphine in the presence of full opioid agonist may precipitate withdrawal symptoms in patients dependent on opioids.

Optimal use of buprenorphine in the perioperative setting, either for the treatment of opioid use disorder or chronic pain, has not been established. Current evidence is challenging the original recommendation to discontinue buprenorphine before and during the perioperative period, proposing that the risks of opioid use disorder relapse and poor acute postoperative pain control outweigh any benefits. With the increasing use of buprenorphine in the United States, it is important for perioperative staff members to understand the clinical challenges. During the preoperative assessment, attention should be paid to the buprenorphine dose, route of administration, indication, timing of last dose, and the patient's risk for relapse. Postoperatively, clinicians should be aware of the pharmacodynamic properties of buprenorphine, which may impact the patient's response to postoperative opioid analgesic strategies. Multimodal analgesic therapy must be optimized in these patients, regardless of the continuation or discontinuation of buprenorphine.

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