Chapter 14
Buprenorphine: Side Effects and Tolerability

Tabitha Washington and Gilbert J. Fanciullo

Introduction

Buprenorphine is a potent partial opioid agonist and is available in parenteral, sublingual, and transdermal applications. Concern regarding its side effect and tolerability profile, as well as incomplete understanding surrounding its pharmacokinetic and pharmacodynamic profile has limited its use. Its association with addiction treatment has reduced the acceptance of prescribing for its analgesic properties by both patients and practitioners. Patients negatively associate the drug with its use in addiction and may feel stigmatized when the drug is recommended by their provider for treatment of pain [1, 2].

As discussed in previous chapters, buprenorphine is a partial mu opioid agonist with a high affinity for the mu opioid receptor; in addition, it is a nociceptin receptor (ORL1) agonist and a kappa receptor antagonist. Its binding at different receptors is responsible for its analgesic activity as well as its side effect profile. An understanding of these receptors and their actions can help practitioners understand and treat side effects from buprenorphine.

Buprenorphine has partial mu agonistic activity, as compared to the full agonistic activity of other opioids such as morphine, oxycodone, and methadone. This means that its maximal analgesic effects are less than that of full agonists, and reach a ceiling where higher doses do not result in increasing effect. Because it is a partial agonist, higher doses of buprenorphine can be given with fewer adverse effects such as respiratory depression, than are seen with higher doses of full agonist opioids. At lower doses, buprenorphine is much more potent than morphine. Individuals who are not dependent on opioids have a strong analgesic and positive opioid effect when they receive an acute dose of buprenorphine.

T. Washington, MD, MS (✉) • G.J. Fanciullo, MD, MS
Department of Anesthesiology, Dartmouth Hitchcock Medical Center, Dartmouth Medical School, One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: Tabitha.A.Washington@kp.org

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Buprenorphine has a higher affinity for the mu receptor than other opioids; therefore, if a patient is already taking other opioids, buprenorphine introduction may displace the existing drug and may precipitate acute opioid withdrawal. However, if a patient is already on buprenorphine, it is bound tightly to the mu receptor, and therefore does not readily dissociate upon injection of other mu agonists. Therefore, adding another opioid can help control pain and does not produce opioid withdrawal symptoms.

Buprenorphine's equivalent analgesic potency as compared to morphine is about 30 times greater. There is a ceiling for the analgesic effects secondary to the low intrinsic activity of buprenorphine at the mu receptor. In the United States, parenteral and transdermal forms are FDA approved for analgesia with usual doses of 0.3–0.6 mg every 6–8 h. For analgesia, dosing is usually 3–4 times a day as the duration of analgesia is 4–8 vs. 24–48 h for opioid withdrawal.

If a practitioner understands buprenorphines properties, and unique pharmacokinetic and pharmacodynamic aspects, and is comfortable with its use, it will be an extremely useful agent for the treatment of patients with chronic pain. This understanding will allow for proper patient selection, outcome measurement, and monitoring in the treatment of pain.

Side Effects

Buprenorphine has a side effect profile similar to full opioid agonist and can include nausea, vomiting, dizziness, constipation, headache, and others [3], but the intensity or severity of side effects may be less than produced by full agonists.

Risk of Abuse, Addiction, Misuse, Overdose, and Tolerance

Abuse has been reported in epidemiological and human clinical studies with patients taking buprenorphine [4, 5]. Psychological dependence or addiction to buprenorphine can occur in patients following chronic administration. Psychological dependence is a syndrome characterized by maladaptive behaviors employed to obtain the opioid and the continued need for and use of the drug despite its harmful effects. Physical dependence is a state in which withdrawal symptoms may occur with decreased opioid levels caused by a multitude of scenarios; cessation, dose reduction, antagonists, or others. This may also occur with buprenorphine; however, since buprenorphine dissociates slowly from the mu opioid receptor, withdrawal symptoms are usually mild [6]. Withdrawal symptoms are similar in characteristic to other opioid discontinuation and can persist for up to 2 weeks. As compared with full opioid agonists, patients to whom buprenorphine is administered who are already dependent on full mu receptor agonists (such as fentanyl, morphine, oxycodone, etc.) may develop withdrawal symptoms. This is the result of buprenorphines

high affinity for the mu receptor displacing the full agonist; however, having less intrinsic activity at this receptor, it precipitates withdrawal.

Although there is reported abuse with patients on buprenorphine [4, 5], there may be a lower incidence of physical dependence and limited development of tolerance secondary to its partial agonist activity. Buprenorphine activates the opioid receptor at lower levels, is relatively less reinforcing, and is a less abused opioid. It is an option for patients with chronic pain and can be closely monitored by providers, as with other opioids. Buprenorphine can be identified in urine toxicology by gas chromatography mass spectroscopy (GCMS), however it is costly.

Although buprenorphine has a better safety profile than methadone, buprenorphine-related overdose deaths have been reported [7–9]. Most of these deaths, similarly to full opioid agonists, have occurred with a combination of benzodiazepines or alcohol. In addition, most involved intravenous use of buprenorphine.

Buprenorphine is a partial agonist; however, its analgesic dose response curve is linear over the therapeutic dose range, suggesting it acts as a full agonist in respect to analgesia through this range. In patients with chronic opioid use, tolerance can develop to the analgesic effects of the opioid requiring higher doses to be administered to produce similar effects. The development of tolerance may be secondary to desensitization or down regulation of the mu opioid receptors [10]. In a study looking at opioids and their receptors, both fentanyl and morphine were shown to down regulate their opioid receptors, while buprenorphine had an increase [11]. In a study of patients maintained on buprenorphine as compared with fentanyl for the treatment of cancer and noncancer pain, there was a more substantial increase in daily dose of fentanyl as compared with buprenorphine [12].

Respiratory Depression

Buprenorphine is a partial mu opioid agonist and therefore does not activate the mu receptor fully, resulting in a ceiling effect that prevents larger doses of the opioid from producing greater effects [13]. This can result in a greater margin of safety from death by respiratory depression with increased doses as compared to full agonist [14, 15].

Buprenorphine has been reported to cause less respiratory depression as compared with full agonists [16, 17]. There are, however, reports of carbon dioxide retention in critically ill patients [18] and is a relative contraindication in severe respiratory compromise (hypoxia, hypercapnia, elderly, obstructive disease, central nervous system [CNS] depression), as with all opioids. The metabolite of buprenorphine, norbuprenorphine is a potent respiratory suppressant. Dahan et al. [19] showed a nonlinear effect on $PaCO_2$, with a ceiling effect at doses greater than 1.4 μg/kg. In a comparative study of intramuscular buprenorphine 0.3 mg and IM morphine 10 mg, there was no difference seen in peak analgesic effect, while buprenorphine resulted in little significant change in respiration rate, pulse, or blood pressure [20]. A study showed increasing dose of buprenorphine for analgesia

increased pain relief with limited respiratory depression, in contrast to fentanyl, which caused a dose-related increase in respiratory depression [14].

In general, buprenorphine alone is the cause of death in a minority of patients on maintenance therapy for addiction. Most deaths were attributed to polysubstance abuse with benzodiazepines present. The respiratory depressant effects of buprenorphine may be increased when used in combination with other depressants (alcohol, benzodiazepines, and opioids); therefore careful monitoring of patient's is recommended. In addition, due to buprenorphine's tight binding at the opioid receptor, buprenorphine-induced respiratory depression may not be fully reversed by the administration of a single dose of naloxone and therefore higher and repeated doses may be necessary, but can be effective [21].

Gastrointestinal

The most common side effects of buprenorphine are its gastrointestinal side effects. Nausea and vomiting can occur in up to 25 % of patients [22–24]. In a few studies, buprenorphine was reported to cause more nausea and vomiting as compared to morphine [20, 25]. As with other opioids, these symptoms seem to be secondary to the direct stimulation of chemoreceptor trigger zones and/or the vestibular system, and gastric stasis. If patients develop these symptoms, they may respond to medications, including promethazine and serotonin antagonist such as ondasetron. Campora et al. surveyed 260 cancer patients for opioid-induced vomiting. The incidence was similar to other opioids, 8 % had moderate to severe nausea, and 23 % had nausea and vomiting [22].

Constipation is a commonly encountered side effect of opioid use that can significantly affect a patient's quality of life. Constipation is due to direct action on opioid receptors in the gut wall, decreased intestinal motility, and dehydration of stool. The incidence of constipation with buprenorphine has been shown to be lower than with morphine use [26–28]. Previous studies have shown that long-term use of buprenorphine is associated with a low incidence of constipation [29]. This may be in part due to its preparation; as parenteral or transdermal preparations bypass the mu opioid receptors in the intestines. Treatment is similar with all opioids, with a focus on prevention by means of stool softeners and a motility agent, and in severe cases using a peripheral opiate antagonist (e.g., Alvimopan or methylnaltrexone).

Hepatitis has been reported in patients taking high doses. Increased liver enzymes have been found in patients who are receiving buprenorphine and who have hepatitis C [30]. In addition, 53 cases of buprenorphine-associated hepatitis were reported in France since 1996 [27, 31, 32]. One report suggested an association between buprenorphine injection and liver toxicity, possibly from buprenorphines increased bioavailability when administered parenterally [33]. In summary, patients with a history of hepatitis C are at increased risk for elevations of liver function tests while on buprenorphine; however, these increases appear to be mild and clinically insignificant. Acute intravenous use of buprenorphine can result in high elevations of

liver function tests in patient with a history of hepatitis. Baseline periodic liver function tests are recommended in patients receiving buprenorphine and are at increased risk of hepatotoxicity (e.g., history of alcoholism, intravenous drug use, or preexisting liver disease).

Patients may also experience abdominal pain, anorexia, diarrhea, or dyspepsia with use [34].

Central Nervous System

As with other opioids, CNS depression can result in impaired cognition, somnolence, and alterations in consciousness. When given in combination with other CNS depressants, these attacks can worsen. However, the slightly lower incidence of CNS effects with buprenorphine may be a result of its kappa antagonist properties [29]. While buprenorphine can cause headaches, studies have shown a decreased incidence of dizziness and headaches in patients on buprenorphine [26, 27].

In general, opioids including buprenorphine can result in increased intracranial pressure. Therefore, use these medications cautiously in patients with head injuries, intracranial lesions or other circumstances when CSF pressure may be increased.

Cardiac

QT interval prolongation has been associated with buprenorphine use. In clinical trials in patients receiving buprenorphine or methadone for treatment of opioid dependence, buprenorphine use was associated with less effect on QT interval than methadone [34]. A study of buprenorphine transdermal patch demonstrated QT prolongation at a dose of 40 μg/h. In contrast 10 μg/h did not demonstrate meaningful effect on the QT interval [34].

Buprenorphine can precipitate hypotension in some patients, similar to other opioids [20].

Skin

Allergic reactions from buprenorphine have occurred, although uncommon, anaphylactic shock is possible. Patients using the transdermal system have reported skin reactions including pruritus, rash, erythema, and skin irritation around the patch site [24, 35–37]. For patients with pruritus, 1/3 will have resolution of symptoms without patch discontinuation [38], although patients also usually respond to diphenhydramine or hydroxyzine.

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