Interest in the use of buprenorphine as an analgesic has increased in recent years. Its unique agonist-antagonist properties makes it a useful analgesic with a potential lower abuse liability in humans. Buprenorphine has been used as an analgesic in the postoperative period for the treatment of moderate-to-severe pain. Buprenorphine has also been found to have antihyperalgesic properties, which might make it an agent to consider for prevention and reduction of central sensitization. In addition, its high affinity for the mu receptor along with its slow dissociation from the receptors has led to new challenges when controlling postoperative pain in patients on buprenorphine maintenance therapy. This article highlights the challenges present in the postoperative period of using buprenorphine as an analgesic in patients with and without preoperative maintenance therapy.

PHARMACOLOGY AND PHARMACOKINETICS OF BUPRENORPHINE

Buprenorphine, a derivative of thebaine, is a semisynthetic opioid analgesic. It binds to mu, kappa, and delta opioid receptor subtypes and has a slow dissociation from these receptors. Its actions on both mu and kappa receptors make it useful as an analgesic and for the maintenance therapy in patients with a history of drug abuse. It is a centrally acting partial mu agonist and a kappa and delta antagonist.1 Buprenorphine can occupy the mu receptor almost maximally; therefore, it decreases the availability of the mu receptor making it useful in decreasing withdrawal symptoms.2 Buprenorphine binds to the mu receptor with high affinity but with a lower intrinsic binding capacity when compared with a full mu agonist.1

Buprenorphine has a rapid onset secondary to its high lipophilicity, which is greater than the lipophilicity of morphine. Buprenorphine penetrates the blood brain barrier more easily than morphine. The onset also depends on the route; for example, the onset of action of buprenorphine is 5 to 15 minutes for the intravenous or
intramuscular routes and 15 to 45 minutes for the sublingual route. The duration of action of buprenorphine is 6 to 8 hours.³ Jasinski and colleagues⁴ have suggested that the long duration of action of buprenorphine is due to its slow dissociation from mu receptors. Constipation rates in patients on buprenorphine are also low.⁵ Buprenorphine can be used in the presence of renal failure. Similar clearance of buprenorphine was found in patients with normal and impaired renal function.⁶

Buprenorphine is a potent analgesic. Sittl⁷ suggests that buprenorphine has an antinociceptive potency about 75 to 100 times greater than that of morphine. Buprenorphine has a dose-dependent effect on analgesia with no respiratory depression.⁸ Dahan and colleagues⁹ demonstrated that buprenorphine has a ceiling effect on respiratory depression, but not on analgesia. Dahan and colleagues,⁹ in a study on 20 volunteers, showed that there was a ceiling effect on respiratory depression by not on analgesia. This was demonstrated over a dose range of 0.05 to 0.6 mg buprenorphine in humans. Buprenorphine shows analgesic effects, but no respiratory depression, at doses up to 10 mg. Therefore, buprenorphine may have a differential effect on respiration and analgesia.

In 1994, Walsh and colleagues¹⁰ demonstrated that there is no ceiling for analgesia in patients receiving sublingual buprenorphine from 1 to 32 mg. Buprenorphine has been showed to have strong antihyperalgesic effects that can exceed its analgesic effects.¹¹

**METABOLISM OF BUPRENORPHINE**

Cytochrome P450 mediates the metabolism of buprenorphine in the liver.¹²,¹³ Buprenorphine is metabolized in the liver and the gut to norbuprenorphine. Buprenorphine and its metabolite, norbuprenorphine, undergo glucuronidation. Norbuprenorphine is an N-dealkylated metabolite that is reported to have one-fourth the potency of buprenorphine.¹⁴ Norbuprenorphine can produce respiratory depression 10 times greater than buprenorphine; however, the respiratory depression caused by norbuprenorphine can be reversed by naloxone.¹⁵ Buprenorphine appears to be excreted by the biliary route and gut and urine. It is thought that about 15 percent of the original dose of buprenorphine is excreted in the urine.¹⁶ Levels of buprenorphine metabolites appear to be increased in renal failure patients with similar buprenorphine levels as compared with controls.⁶ It must be remembered that buprenorphine cannot be dialyzed—most likely owing to its slow dissociation and high affinity to the mu receptor.¹⁵,¹⁷

**SIDE EFFECTS**

Buprenorphine is a lipophilic drug with a high affinity for mu receptors and slow dissociation rate, as well as decreased absorption into the cerebrospinal fluid. The high lipophilicity can affect the degree of side effects seen with buprenorphine as compared with morphine. Nausea, vomiting, euphoria, sedation, delayed gastric emptying, and pupillary constriction can all be seen with buprenorphine—but to a lesser degree than with morphine.¹⁰

**CLINICAL APPLICATION OF BUPRENORPHINE AS ANALGESIA**

Buprenorphine for the control of postoperative pain has been used in several routes, leading to new treatment options worldwide. Johnson and colleagues³ showed that effective management of postoperative pain can be achieved in patients who are not dependent on uploads. Buprenorphine was introduced in the United States in 1981 as an analgesic via the parenteral route with the trade name of Buprenex.
Use of buprenorphine as an analgesic in Europe, however, had started much earlier—in the parenteral form at the dose of 0.3 mg/mL and in the sublingual form at the dose of 0.2 to 0.4 mg. Studies have shown parenteral buprenorphine to be a potent analgesic with a dose of 0.3 mg of buprenorphine to be equivalent to 10 mg of morphine sulfate in patients who are not dependent on opioids. Buprenorphine has since been used for pain control via the intrathecal, sublingual, intramuscular, epidural, and transdermal routes as evidenced by several clinical trials.

**EPIDURAL BUPRENORPHINE**

Buprenorphine has been used successfully via the epidural route without significant respiratory depression and with good analgesia. Epidural buprenorphine is most likely absorbed rapidly from the epidural space into the systemic circulation and acts centrally in the supraspinal regions to produce analgesia similar to intravenous buprenorphine. Adequate epidural analgesia with buprenorphine for postoperative pain relief has been achieved for coronary artery bypass surgery, gynecologic surgery, genitourinary surgery in children, upper and lower abdominal surgeries, and for the treatment of rib fractures. The epidural dose of buprenorphine ranges from 4 to 8 μg per hour, which is as effective as epidural morphine at a dose of 80 μg per hour for most surgeries. Lower abdominal surgeries might require a higher dose of 15 μg per hour of epidural buprenorphine.

Buprenorphine is a semisynthetic lipophilic opioid that is less water-soluble than morphine; thus, the effectiveness of the epidural can depend on the site of injection of the drug. Takata and colleagues found that heptectomy patients had good pain relief with long duration when buprenorphine was injected into the thoracic epidural space, but not when injected into the lumbar epidural space. This was in contrast to epidural morphine, which produced excellent and long lasting pain relief when injected at the lumbar or the thoracic levels.

**INTRATHECAL BUPRENORPHINE**

Buprenorphine has been shown to provide more prolonged pain control in cesarean-section–delivery patients compared with controls who did not take buprenorphine. Celleno and Capogna compared the effects of intrathecal hyperbaric bupivacaine with two groups taking 0.03 and 0.045 mg of intrathecal buprenorphine in addition to the hyperbaric bupivacaine and found that there was a longer pain-free interval in patients receiving buprenorphine. They also found that, within the patient groups receiving buprenorphine, a longer effect was seen in patients receiving the higher dose of buprenorphine.

**INTRAVENOUS BUPRENORPHINE FOR ANALGESIA**

Intravenous buprenorphine has been shown to provide analgesia as adequate as intravenous morphine. Abrahamsson and colleagues showed that buprenorphine provides analgesia for up to 13 hours in dose ranges from 5 to 15 μg/kg.

**SUBLINGUAL BUPRENORPHINE FOR ANALGESIA**

Sublingual buprenorphine is a well-known agent for maintenance therapy for patients with opioid abuse. However, there have been studies demonstrating the effectiveness of sublingual buprenorphine for providing pain relief in the postoperative period. Witjes and colleagues showed that sublingual buprenorphine provided adequate pain relief...
as the sole agent in about 80% of patients in the postoperative period after cholecystectomy.

**SUBCUTANEOUS BUPRENORPHINE**

Buprenorphine can be given subcutaneously for pain relief in the early postoperative period at a dose of 30 μg per hour. This route is especially useful for patients with poor intravenous access.

Intramuscular buprenorphine is also especially useful in the presence of poor intravenous access. The duration of pain relief is approximately 6 hours, with a peak effect at about 1 hour, and onset at about 15 minutes. It can be used for patients requiring round-the-clock opioid therapy in the presence of acute or chronic pain.

**INTRAARTICULAR ROUTE OF BUPRENORPHINE**

Buprenorphine has shown to significantly reduce the amount of analgesia required after knee arthroscopy when injected intraarticularly. A study by Varrassi and colleagues showed that intraarticular bupivacaine and intraarticular buprenorphine produced comparable pain control after knee arthroscopy.

**BUPRENORPHINE IN REGIONAL ANESTHESIA**

Buprenorphine could have peripherally mediated opioid analgesia and be a useful adjunct in regional anesthesia. Candido and colleagues showed that addition of buprenorphine to local anesthetic in axillary brachial plexus blocks prolonged postoperative analgesia.

**TRANSDERMAL BUPRENORPHINE**

The high lipid solubility of buprenorphine makes it a suitable agent to be used via the transdermal route. This route uses hydrogels for the delivery of buprenorphine with the application of iontophoresis. Transdermal buprenorphine has been used for the treatment of chronic pain. Transdermal buprenorphine is being used in Europe for the treatment of acute pain, cancer pain, and neuropathic pain. The patch is available at 35, 52.5, and 70 μg per hour for 3 days. The onset of action of transdermal buprenorphine is 12 to 24 hours and the duration of action of each patch transdermal buprenorphine is 3 days.

**PAIN CONTROL OF PATIENTS ON PREOPERATIVE BUPRENORPHINE**

Opioid-dependent patients are often treated with buprenorphine. Worldwide, opioid dependence has been on the increase in the last decade and many of these patients present for surgery and for postoperative pain control. In 1996, buprenorphine was available in France as a substitution treatment for heroin addicts. In the United States, the Food and Drug Administration approved buprenorphine to be marketed only in the form of sublingual tablets (Subutex) or with naloxone (Subuxone) to treat opioid dependence. The rescheduling of buprenorphine from a schedule V to a schedule III narcotic was published in the Federal Register in October, 2002. Methadone, also used for the treatment of opioid abuse, is a schedule II drug. Schedule II drugs have more abuse potential than schedule III drugs.

Postoperative pain control of patients on preoperative buprenorphine can be a challenge and can complicate postoperative pain management. The possibility that the tight binding with the μ receptor could lead to partial opioid blockade with resultant
reduction in postoperative analgesia when treated with opioids has been raised as a point of concern. There is also concern for relapse in patients taking buprenorphine for opioid dependence, which may also complicate pain management in the postoperative period. This should be taken into consideration while caring for opioid-dependent patients on buprenorphine in the postoperative period. The National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study, presented at the American Psychiatric Association annual meeting in 2010,42 showed that tapering with buprenorphine over 9 months led to almost universal relapse in persons dependent on prescription opioids.

Reviews of literature include several studies on and management strategies for preoperative pain in patients who are on buprenorphine as maintenance therapy for drug abuse.41–44

Alford and colleagues44 have recommended that patients be converted to full opioid agonist preoperatively. Roberts and Meyer-Witting43 suggest that buprenorphine be continued throughout the perioperative period and full agonist opioid be used for pain control when monitoring for respiratory depression and pain control. They also suggest that buprenorphine be discontinued up to 72 hours before the surgery and converted to a full agonist such as methadone to eliminate the existence of any partial blockade.

Ballantyne and La Forge45 recommend that buprenorphine be discontinued for about a week before surgery.

Several studies in contrast to this concept suggest that full opioid agonists are effective in buprenorphine-treated patients. Budd and Collett16 concluded that full opioid agonists are effective in acute and chronic pain syndromes in the presence of buprenorphine use and that buprenorphine does not produce persistent blockade of the mu receptor. There are other reports that demonstrate the effective use of full opioid agonists such as morphine in patients treated with buprenorphine and that buprenorphine use can be continued into the postoperative period. Mitra and Sinatra46 recommend that patients on maintenance therapy take their morning dose of buprenorphine or methadone on the day of surgery to decrease the risk of opioid withdrawal during surgery.

Mehta and Langford47 recommend the use of short-acting full opioid agonists for postoperative pain control in patients using transdermal buprenorphine. Morphine has shown to be an effective breakthrough medication in patients on transdermal buprenorphine. A study by Mercadante and colleagues48 of 29 cancer patients demonstrated the effectiveness of morphine for pain control as a breakthrough medication in patients receiving transdermal buprenorphine.

A study by Jones and colleagues49 done on obstetric patients also demonstrated the successful use of opioid agonists in the presence of buprenorphine maintenance.49

Finally, buprenorphine has been used effectively to control postoperative pain in buprenorphine-maintained patients.40 Budd and Collett16 suggest that sublingual buprenorphine could be used effectively as a breakthrough agent to control pain in patients on buprenorphine in the postoperative period.

ADVANTAGES

Buprenorphine can be safely used in the presence of renal failure.50 The long duration of action9 and safety of buprenorphine via the transdermal route makes it a useful agent for use in elderly patients.51 Buprenorphine appears to have antihyperalgesic effects that can be useful for chronic-pain patients undergoing surgery in the postoperative period. Koppert and colleagues52 studied the antihyperalgesic and analgesic effects of buprenorphine in humans via sublingual and the intravenous route with
the magnitude of pain and secondary hyperalgesia assessed by transcutaneous stim-
ulation. They found that the antihyperalgesic effects were stronger than the analgesic
effects of buprenorphine using both the intravenous and the sublingual route. They
also found that the antihyperalgesic effects were stronger and of longer duration as
compared with the pure mu receptor agonist studied in the same model. Buprenor-
phine may have potential in the prevention and reduction of central sensitization in
difficult chronic pain states during the postoperative period.

DISADVANTAGES

Drugs such as opioids, sedatives, hypnotics, anesthetic agents, antidepressants, and
psychostimulants, which can induce or inhibit cytochrome P450 and can potentiate
the central effects of buprenorphine. Buprenorphine should be used with extreme
caution when used with benzodiazepines. Lai and Teo53,54 showed that 19 of the 21
buprenorphine-related deaths in Singapore occurred with concurrent use with bupre-
norphine. Benzodiazepines with buprenorphine can exert a synergistic effect on the
central nervous system and cause sedation and respiratory depression.55

SUMMARY

Several decades ago, the analgesic properties of buprenorphine were discovered.
Buprenorphine has been administered via different routes—including epidural,
intrathecal, intramuscular, sublingual, transdermal, and intraarticular—for the
control of pain in the postoperative period. Newer routes, such as sublingual
and transdermal, have increased the possibility of its developing into a useful anal-
gesic for the treatment of postoperative pain. In addition, it could be an useful
adjunct to local anesthetic for pain control in peripheral nerve blocks for the
control of postoperative pain.33

Its approval for the use as an agent for the treatment of opioid abuse has led to
increasing numbers of patients presenting for surgery on buprenorphine. Pain control
in the postoperative period with patients on preoperative buprenorphine can be
complicated and is a challenge. Concern for decreased analgesia in the postoperative
period exists. Different management strategies have been put forward with an attempt
to tackle this issue. Alford and colleagues44 recommend the discontinuation of bupre-
norphine and conversion to pure opioid agonist before surgery while several others
have shown effective pain control with pure opioid agonists such as morphine in the
presence of buprenorphine in the postoperative period. Budd and Collett16 suggest
that, in addition to being controlled with opioid agonist, postoperative pain control
in patients with preoperative buprenorphine may be controlled with sublingual bupre-
norphine. More research and outcome studies are necessary to confirm its usefulness
for the control of postoperative pain in patients with acute pain or a preoperative
history of chronic pain, in the treatment of patients with preoperative buprenorphine,
and in the prevention and reduction of central sensitization postoperatively.

REFERENCES

1. Negus SS, Mello NK, Linsenmayer DC, et al. Kappa opioid antagonist effects of
the novel kappa antagonist 5’-guanidinonaltrindole (GNTI) in an assay of
schedule-controlled behavior in rhesus monkeys. Psychopharmacology (Berl)
nance dose on mu-opioid receptor availability, plasma concentrations, and
24. Kaetsu H, Takeshi M, Chigusa S, et al. [Analgesic effects of epidurally adminis-
tered fentanyl for postoperative pain relief—comparison with buprenorphine].
management of pain in multiple rib fractures. Acta Anaesthesiol Scand
for postoperative pain relief in patients after lower abdominal surgery]. Masui
27. Takata T, Yukioka H, Fujimori M. [Epidural morphine and buprenorphine for post-
28. Celleno D, Capogna G. Spinal buprenorphine for postoperative analgesia after
29. Abrahamsson J, Niemand D, Olsson A, et al. [Buprenorphine (Temgesic) as a pero-
combination with naproxen or paracetamol for post-operative pain relief in chole-
31. Matsumoto S, Mitsuhashi H, Akiyama H, et al. [The effect of subcutaneous admin-
istration of buprenorphine with patient controlled analgesia system for post-oper-
knee arthroscopy. A randomised, prospective, double-blind study. Acta Anaes-
33. Candido K, Winnie A, Ghaleb A, et al. Buprenorphine added to the local anes-
thetic for axillary brachial plexus block prolongs postoperative analgesia. Reg
34. Fang J, Hwang T, Huang Y, et al. Transdermal iontophoresis of sodium noniva-
mide acetate. V. Combined effect of physical enhancement methods. Int J Pharm
35. Budd K. Buprenorphine and the transdermal system: the ideal match in pain
36. Simpson K. Individual choice of opioids and formulations: strategies to achieve
317–22 [in German].
38. Kress H. Clinical update on the pharmacology, efficacy and safety of transdermal
39. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain:
results of a phase III, multicenter, randomized, double-blind, placebo-controlled
following general surgery in a buprenorphine-maintained patient. Am J Psychi-
atriy 2007;164(6):979.
42. The national drug abuse treatment clinical trials network prescription opioid
addiction treatment study presented at the American Psychiatric Association
annual meeting 2010.