Case Series of Successful Postoperative Pain Management in Buprenorphine Maintenance Therapy Patients

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Buprenorphine maintenance therapy patients frequently have severe postoperative pain due to buprenorphine-induced hyperalgesia and provider use of opioids with limited efficacy in the presence of buprenorphine. The authors report good-to-excellent pain management in 4 obstetric patients using nonopioid analgesics, regional anesthesia, continuation of buprenorphine, and use of opioids with high μ receptor affinity. (Anesth Analg 2017;125:1779–83)

The population of patients receiving chronic buprenorphine maintenance therapy (BMT) is large and includes many pregnant women. Most BMT patients are maintained on 1 of 2 sublingual preparations: Suboxone (Indivior Inc, Richmond, VA), a combination of buprenorphine and naloxone, or Subutex, which is solely buprenorphine. Pregnant illicit opioid users with poor access to BMT clinics may also use illicit buprenorphine to manage their own opiate withdrawal. Buprenorphine, an opioid with a long serum half-life and active metabolites, binds tightly to the μ-opioid receptor, and there is a ceiling to the analgesia buprenorphine can provide.1–7 Consequently, parturients who present for cesarean delivery or tubal ligation while receiving BMT may have severe postoperative pain.6,7

Multimodal, rather than opioid-only, analgesia is generally preferable. There are 4 options for preoperative buprenorphine management: (1) continue buprenorphine and add additional postoperative buprenorphine,6 (2) continue baseline buprenorphine and add traditional opioids with high μ receptor affinity,9 (3) reduce the baseline buprenorphine preoperatively,10 or (4) discontinue buprenorphine and start a traditional opioid preoperatively.11–13 This last approach is not practical for many obstetric BMT surgical patients. First, buprenorphine has a half-life of 24–60 hours, so patients presenting for urgent or obstetric BMT surgical patients. First, buprenorphine has a half-life of 24–60 hours, so patients presenting for urgent or emergent surgery do not have time preoperatively to achieve complete washout. Second, patients fearing a relapse of their opiate addiction may refuse to abstain from buprenorphine. Third, many obstetricians refuse to ask their pregnant patients to abstain from buprenorphine because they fear unmonitored and untreated fetal withdrawal symptoms. A multimodal approach to BMT patients was recently described by Anderson et al.14 We utilized a similar multimodal approach in the 4 obstetric cases described.

Each patient gave written permission for the authors to publish this case series.

CASE DESCRIPTIONS

1. A 22-year-old Gravida 2, Para 1 healthy parturient presented for an elective repeat cesarean delivery. Her only medication was buprenorphine/naloxone (Suboxone) 8 mg/2 mg twice daily. The patient was placed in a seated position, and we inserted a paramedian epidural catheter at T10–11, then inserted a 25-gauge Whitacre spinal needle at L2–3, and injected hyperbaric bupivacaine 15 mg and epinephrine 0.1 mg. The anesthetic level was T4 bilaterally, and the patient was comfortable during the cesarean delivery. Postoperatively, we continued Suboxone 8 mg/2 mg twice daily. We initiated a patient-controlled epidural infusion of bupivacaine 0.0625% at 4 mL/h with a bolus dose of 2 mL and a lockout interval of 30 minutes. The patient also received scheduled ketorolac 30 mg intravenously (IV) every 6 hours for 4 doses, then scheduled ibuprofen 800 mg per os every 8 hours. The patient was able to maintain 5-second leg lifts 5 hours postoperatively and was able to move to a chair with assistance 8 hours postoperatively. One day after surgery, the patient could ambulate without assistance. She received an average of bupivacaine 5 mL/h during the first 24 hours and an average of 4 mL/h during the second 24 hours after the cesarean delivery. Her maximum pain scores were 1/10 during the first 24 hours and 0/10 during the second 24 hours after cesarean delivery. At 48 hours, we stopped the epidural infusion and observed the patient for 2 hours. Her pain score remained 0/10, so we removed the epidural catheter and discontinued the buprenorphine/naloxone (Suboxone).

2. A 23-year-old Gravida 2, Para 1 healthy parturient presented in active labor for urgent repeat cesarean delivery. The patient was on a waiting list for a BMT clinic. While waiting, she illicitly purchased and consumed buprenorphine 4 mg 3 times daily. In the seated position, we performed a combined spinal–epidural anesthetic at L2–3. We injected bupivacaine 15 mg intrathecally and placed a lumbar epidural catheter...
3. A 34-year-old Gravida 6, Para 5 parturient presented for postoperative pain relief. The anesthetic level was T3 bilaterally, and the patient was comfortable during the cesarean delivery. We initiated a patient-controlled epidural infusion of bupivacaine 0.0625% at 10 mL/h with a bolus dose of 2 mL and a lockout interval of 15 minutes. We initiated buprenorphine 4 mg every 8 hours. The patient also received scheduled ketorolac 30 mg IV every 6 hours for 4 doses, and then scheduled ibuprofen 800 mg per os every 8 hours. The patient was comfortable with pain scores of 3 to 4/10 for the first 24 hours. Then a mechanical pump problem stopped the infusion and the patient’s pain score increased to 10/10. Comfort and a pain score of 2/10 returned with an epidural bolus of 10 mL bupivacaine 0.25%. We continued the epidural infusion for a second day. We then discontinued the epidural infusion. The patient’s pain remained mild 2 hours later, when we removed the epidural catheter. The main adverse effect with this lumbar epidural analgesia (PCA) infusion with a dose of 0.1 mg, lockout of 10 minutes, and maximum hourly dose of 0.6 mg. She received 1.9 mg of hydromorphone over the first 24 hours. The patient also received scheduled ketorolac 30 mg IV every 6 hours for 4 doses, and then scheduled ibuprofen 800 mg per os every 8 hours. After the start of the PCA hydromorphone, the patient’s highest pain score was 5/10. The hydromorphone PCA was discontinued on the second postoperative day, with no increase in pain scores. The patient was discharged on ibuprofen.

4. A healthy 25-year-old Gravida 2, Para 2 parturient presented 14 hours postpartum for bilateral tubal ligation. Her only medication was buprenorphine 4 mg/day, which she purchased illicitly while waiting for an appointment at a BMT clinic. The patient was seated during intrathecal injection of bupivacaine 15 mg and sufentanil 10 µg. We obtained a T8 sensory level, and the patient was comfortable during the operation. Three hours postoperatively, the patient rated her pain as 4 to 5/10. She received ketorolac 30 mg IV, and her pain decreased to 1 to 2/10. We continued the scheduled ketorolac 30 mg IV every 6 hours and administered buprenorphine 4 mg/day while the patient was in the hospital. The patient’s pain score was 2/10 or lower for the next 24 hours, when she was discharged on acetaminophen and diclofenac.

**DISCUSSION**

Patients receiving buprenorphine generally have higher opioid use and worse pain control after cesarean delivery than opioid-naive patients. Published surgical case reports document high postoperative opioid requirements and poor pain control whether or not buprenorphine is held preoperatively (Table 1). Our cesarean delivery patients have had the best analgesia with the least leg weakness when we utilized postoperative thoracic epidural analgesia, as illustrated in case 1.

Buprenorphine is an agonist at both the μ-opioid (Ki = 0.2157 nM) and the nociceptin (opioid receptor-like 1) (Ki = 285 nM) receptors, and an antagonist at the κ-opioid and δ-opioid receptors. Buprenorphine binds more tightly to the μ-opioid receptor (ie, has a lower Ki or equilibrium inhibition constant) than most commonly used μ-opioid agonists (Table 2). Opioids with low Ki values have greater binding affinity at the μ receptor but not necessarily greater potency than other opioids. We believe that better analgesia in BMT patients can be achieved by using opioids with Ki values close to the Ki of buprenorphine (such as sufentanil or hydromorphone) rather than opioids that bind more weakly to the μ-opioid receptor (Table 2). High-dose hydromorphone was used successfully in several published case reports. However, other authors have reported pain control ranging from poor-to-excellent with the use of hydromorphone, fentanyl, or morphine (Table 1). Some authors report poor pain control until discontinuation of the buprenorphine. Factors other than opioid-binding properties, such as the preoperative buprenorphine dose, the nature of the surgery, and the use of regional anesthesia and nonopioid pain control adjuvants, are also important to consider during postoperative pain management.

Activation of the nociceptin receptor antagonizes the analgesia provided by activation of the μ-opioid receptor. Because of this, the pain relief provided by increasing doses of buprenorphine creates a bell-shaped curve in mice, with the greatest analgesia at moderate buprenorphine doses and less pain relief at higher doses. Morphine does not have this ceiling effect. The buprenorphine dose associated with maximum postoperative analgesia has not been determined in BMT patients. However, a nonoperative study in opioid-addicted volunteers reported maximum buprenorphine analgesia at a daily dose of 4 to 8 mg.

Heroin addicts and patients maintained on either methadone or buprenorphine exhibit hyperalgesia, as measured by withdrawal latency in the cold pressor test, when compared to opioid-naive controls. This hyperalgesia dissipates very slowly with opioid abstinence; chronic pain patients still demonstrated hyperalgesia 121 ± 23 weeks after discontinuation of methadone or buprenorphine.

In the described cases, patients reached a point 48–72 hours after surgery beyond which they needed only buprenorphine and nonsteroidal anti-inflammatory agents for pain control. Thus, outpatient full agonist opioids may not be needed for many BMT patients after cesarean delivery or postpartum tubal ligation. Outpatient Suboxone can only be prescribed by physicians specifically licensed to do so. Therefore, we did not provide outpatient prescriptions for Suboxone. Ketamine and dexmedetomidine have
| Reference                  | Surgery or Hospitalization | Preoperative Opioid Regimen                                      | Initial Pain Control Regimen | Subsequent Pain Control Regimen | Adjuncts and Regional Anesthesia | Pain Control/Home Regimen | Summary                                                                 |
|---------------------------|---------------------------|-------------------------------------------------------------------|------------------------------|---------------------------------|---------------------------------|---------------------------|------------------------------------------------------------------------|
| McCormick et al 16        | Emergent; 50-y-old M with bilateral fasciotomies                  | Buprenorphine/naloxone for chronic pain and opioid dependence; unknown dose and duration of use | PCA hydromorphone 0.5 mg/15 min | Buprenorphine/naloxone stopped on admission; hydromorphone PCA 0.8 mg/15 min basal rate 0.5 mg/h | Adjuvants: none; | Pain control with high-dose IV hydromorphone. Transitioned to per os oxycodone, home on hydrocodone/acetaminophen | opioid tolerant; pain relief ~48 h after last dose of buprenorphine/naloxone and increased hydromorphone |
| Harrington and Zaydfudim 13 | Emergent; 30-y-old M in MVC: TBI, hepatic and splenic lacerations, multiple rib fractures, and right olecranon fracture | Initially unknown, found to be buprenorphine/naloxone (2 mg/0.5 mg); unknown duration | Analgesics were weaned on postinjury day (PID) 3 and then abruptly stopped on PID 4 when buprenorphine/naloxone was restarted. PID 6: 50 mg morphine/d plus adjuvants for delirium | Buprenorphine/naloxone restarted on PID4 and subsequently stopped on PID 6 | Adjuvants: haloperidol, lorazepam, midazolam for delirium and agitation PID6 Regional: none | Pain and delirium difficult to control throughout hospitalization. Home on 120 mg oxycodone ER/d | Home dose of oxycodone higher than reported dose of morphine on PID 6. Delirium improved after buprenorphine/naloxone dc. Clinical picture complicated by significant TBI |
| Brummett et al 18         | Scheduled; 41-y-old M with posterior spinal fusion with instrumentation L3-5 | 16- mg buprenorphine daily (8 mg BID); unknown duration | Morphine and then hydromorphone 0.5 mg q 6 min, 0.5 mg/h basal rate (25.8 mg/8 h) | Buprenorphine stopped POD 1; dexmedetomidine infusion | Adjuvants: dexmedetomidine infusion; NSAIDs contraindicated Regional: none | Dexmedetomidine infusion, d/c buprenorphine allowed weaning of total hydromorphone PCA use. Home on morphine ER 60 mg TID and PRN oxycodone | Pain difficult to control until buprenorphine dc and dexmedetomidine infusion started |
| Huang et al 17            | Scheduled; 47-y-old F with Clagett window closure                  | Buprenorphine/naloxone 32 mg/8 g daily (16 mg/4 mg BID)           | Thoracic epidural; hydromorphone PCA 0.6–0.8 mg/5 min (max 4 mg/h) | Buprenorphine/naloxone weaning POD 16; hydromorphone IV 50–70 mg/24 h, MSContin (Purdue Pharma LP, Stamford, CT) 24 mg BID | Adjuvants: multiple Regional: thoracic epidural until POD 7 | Not controlled until buprenorphine/naloxone weaned to 16 mg/d with IV PCA. Complicated postoperative course; home POD41 on hydromorphone per os 9 mg TID and multiple adjuvants | Opioid tolerant; pain difficult to manage until buprenorphine/naloxone weaned and eventually discontinued on POD 35 |
| Kornfeld and Manfredi 9   | Scheduled; 7 cases with expected moderate to high pain expected postoperatively | Buprenorphine range from 2 to 24 mg/d, not held before surgery | Continued home buprenorphine 5 of 7 patients | High-dose opioids (epidural and IV) | Adjuvants: none reported Regional: 6/7 cases | Good-to-excellent pain control in 7/7 patients; buprenorphine continued or increased in 5/7. Restarted buprenorphine on POD 3 in 2/7, 5/7 home on per os hydromorphone, 1/7 per os hydrocodone, 1/7 not specified home regimen | Opioid tolerant, use of regional anesthesia, and buprenorphine not held preoperatively |

(Continued)
### Table 1. Continued

| Reference | Surgery or Hospitalization | Preoperative Opioid Regimen | Initial Pain Control Regimen | Subsequent Pain Control Regimen | Adjuvants and Regional Anesthesia | Pain Control/Home Regimen | Summary |
|-----------|----------------------------|----------------------------|------------------------------|----------------------------------|----------------------------------|---------------------------|---------|
| Macintyre et al¹⁹ | Retrospective analysis, 51 patients on opioid substitution therapy; buprenorphine (average 13.7 mg); methadone (average 78.9 mg); neither intentionally held preoperatively | Higher PCA morphine equivalent dosage | | | Adjuvants: ketamine, paracetamol, some patients given NSAIDs; Regional: none | No difference in morphine equivalents used in methadone versus buprenorphine groups. Home regimen not specified | If buprenorphine withheld on day of surgery, days of PCA use increased. Morphine equivalents used did not include methadone or buprenorphine |
| Jones et al⁷ | Retrospective report of 18 opioid-dependent patients; buprenorphine (4–24 mg/d; average 18.8 mg at delivery, n = 8); methadone (40–100 mg/d; average 79 mg at delivery, n = 10) | Oxycodone/acetaminophen 5 mg/500 mg q 4–6 h PRN | | | Adjuvants: ibuprofen; Regional: 6/8 in buprenorphine group and 6/10 in methadone group | Good pain control with PRN NSAIDs and PRN oxycodone/acetaminophen 5/500 mg. Home regimen not specified | No difference in oxycodone use postdelivery between buprenorphine and methadone group |
| Chern et al¹¹ | Scheduled; 37-y-old F with vaginal mesh trimming | Buprenorphine 24 mg SL/d (8 mg SL q 8 h) | Unknown | Buprenorphine continued | Adjuvants: none reported; Regional: none reported | Poor pain control, unknown home regimen | Buprenorphine continued with unknown pain regimen |
| Chern et al¹¹ | Scheduled; removal of vaginal mesh and cystoscopy (same patient as above) | Buprenorphine 24 mg/d (8 mg SL q 8 h) stopped 5 d before surgery and started per os hydromorphone 4 mg every 4–6 h (max 20 mg/d) | Preoperative/ intraoperative: 1100 µg fentanyl PACU: 1100 µg fentanyl, 8.5 mg hydromorphone | Hydromorphone PCA basal 2 mg/h and 0.6 mg q 10 min | Adjuvants: ketorolac 30 mg every 6 h; Regional: none | Home on hydromorphone 4 mg per os every 3 h | Opioid-tolerant patient; pain improved with high-dose hydromorphone |
| Israel and Poor¹² | Scheduled; 37-y-old F with bilateral mastectomies | Discontinued buprenorphine and started fentanyl patch (doses unknown) 72 h before surgery | Fentanyl patch and fentanyl PCA (dose unknown) | Fentanyl patch, per os oxycodone (10–30 mg every 3 h) | Scheduled acetaminophen | Home on oxycodone (10–30 mg every 3 h) and acetaminophen | Opioid tolerant, pain improved with high-dose oxycodone and fentanyl patch |

**Abbreviations:** BID, twice a day; dcd, discontinued; d/c, discontinuing; ER, emergency room; F, female; M, male; MVC, motor vehicle collision; NSAIDs, nonsteroidal anti-inflammatory drugs; PACU, postanesthesia care unit; PCA, patient-controlled analgesia; POD, postoperative day; PRN, as needed; SL, sublingual; TBI, traumatic brain injury; TID, 3 times a day.
been successfully added to multimodal analgesia in BMT patients. 18,19 We did not use either drug but encourage other clinicians to consider doing so.

The American Academy of Pediatrics supports breastfeeding in BMT patients. 24 The concentrations of buprenorphine and its metabolites are low in human milk and are low or undetectable in the plasma of 14-day-old breastfed infants of BMT patients. 25 The incidence of neonatal abstinence syndrome is lower in infants of mothers receiving methadone or buprenorphine who are breastfed than in those who are fed formula. 26

In summary, because of the high affinity of buprenorphine for the μ receptor, activation of the nociceptin receptor, and buprenorphine-induced hyperalgesia, BMT patients have severe postoperative pain more frequently than opioid-naive patients. However, good-to-excellent postoperative pain control can be achieved in many obstetric buprenorphine patients if supplemental opioids are carefully chosen and regional anesthesia is used appropriately.

DISCLOSURES

Name: Barbara L. Leighton, MD.

Contribution: This author helped care for all 4 patients, obtained consent for publication from the patients, wrote the first draft of the article, and did the final editing of the manuscript.

Name: Lara W. Crock, MD, PhD.

Contribution: This author helped review the literature summarized in Table 1, created Table 1, and prepared an intermediate draft of the article.

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