The use of epidural opioids as an adjunct for postoperative pain relief has increased steadily since the 1980s.1 Epidural opioids provide profound segmental antinociception that can be achieved with a smaller dose of opioid than would be used systemically. In addition, epidural opioids can provide pain relief without adding profound motor blockade.1 The use of epidural opioids may result in a variety of non-nociceptive side effects. The 4 most common side effects observed are: (1) pruritis, (2) nausea and vomiting, (3) urinary retention, and (4) respiratory depression.2

Respiratory depression appears to be the most serious side effect. Respiratory depression, secondary to epidural opioids, may be differentiated as early and late. The early form occurs within 2 hours of the opioid administration and is hypothesized to result from systemic absorption of the narcotic. Early respiratory depression typically occurs when lipophilic opioids, such as sublimaze or sufentanil, are used. The use of epidural opioids may result in a variety of non-nociceptive side effects. The 4 most common side effects observed are: (1) pruritis, (2) nausea and vomiting, (3) urinary retention, and (4) respiratory depression.2

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Delayed respiratory depression, which is linked to the use of hydrophilic opioids, occurs more than 2 hours after the initial administration, which is when the patient is no longer in the PACU. Hydrophilic opioids (morphine, hydromorphone) are not quickly absorbed systemically and may accumulate in the cerebral spinal fluid. Cephalad spread of the opioid and subsequent interaction with opioid receptors located in the ventral medulla will occur.3 It is this pharmacodynamic property that places a patient at risk for delayed respiratory depression. Delayed respiratory depression can present up to 24 hours postopioid administration. Although clinically delayed, respiratory depression will typically present at 6 to 12 hours after opioid administration.3

The following case report describes a 61-year-old woman who underwent a right arthrotomy and total knee replacement with an epidural approach and eventually experienced delayed respiratory depression after receiving epidural hydromorphone. A review of the literature revealed scant information on the use of epidural hydromorphone and its possible side effects. However, because hydromorphone is a hydrophilic opioid, the following discussion extrapolates from the literature published on morphine.
inserted on the first attempt, midline at L3-4 using the loss of resistance technique. Approximately 5 minutes after placement of the epidural, a 3-mL test dose of 1.5% lidocaine with epinephrine (1:200,000) was administered. Once it was confirmed that the epidural was not intravascular or intrathecal, 10 mL of 2% lidocaine with epinephrine (1:200,000) was incrementally injected. A sensory block at T8 was achieved. The T8 block was maintained with 3-mL boluses of 2% lidocaine with epinephrine (1:200,000) approximately every 30 minutes. In addition to the local anesthetic, epidural sublimaze (50 µg) was administered prior to incision, and an additional dose of 25 µg was administered at approximately 2.5 hours after the original dose. Total intravenous sedation administered intraoperatively included 6.5 mg of midazolam and 100 µg of sublimaze over a period of 5.5 hours. Upon arrival in the recovery room, the patient had a T12 sensory level and was placed on a continuous epidural infusion of bupivacaine (0.125%) with hydromorphone (20 µg/mL) at 6 mL/hr.

Approximately 30 minutes into the PACU stay, the patient complained of incisional pain, rating it 7/10 on the visual acuity scale. The continuous epidural infusion was then increased to 9 mL/hr, and an additional 50 µg of sublimaze was given through the epidural (the total amount of epidural sublimaze was 125 µg over approximately 6 hours). The patient spent a total of 2 hours in the PACU. She was transferred to a surgical ward at which time she was alert, oriented, had stable vital signs: blood pressure, 108/55 mm Hg; heart rate, 84 beats per minute; respiratory rate, 18 breaths per minute; and SpO2, 97% on room air. Sensory blockade was at T10, and she rated her incisional pain 1/10 on the visual acuity scale.

The patient remained hemodynamically stable, comfortable, and slept during the next 5 hours. Approximately 7 hours into the postoperative period, the nurses’ assessment noted the patient as unresponsive to verbal stimuli. Vital signs recorded at that time was a heart rate of 118 beats per minute; blood pressure, 137/71 mm Hg; respiratory rate, 10 breaths per minute; and SpO2, 77% on room air. Sensory blockade was at T10, and she rated her incisional pain 1/10 on the visual acuity scale.

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Approximately 3 minutes after administration of the naloxone, the patient became responsive to verbal stimuli, the respiratory rate improved to 14 breaths per minute, and SpO2 increased to 94% on 10 L/min of oxygen (continuously rising). The patient was then transferred back to the PACU for closer observation and continuous monitoring of vital signs. The continuous epidural infusion was changed to bupivacaine (0.125%) at 6 mL/hr without the addition of opioids.

The patient’s vital signs and level of consciousness returned to baseline within an hour of the hypoxic incident and remained stable throughout the night with adequate pain control (visual acuity score of 1-3). She was transferred back to the surgical ward the next morning (20 hours postoperatively). The epidural infusion and catheter were discontinued at 24 hours postoperatively. The patient remained in the hospital for scheduled physical therapy and was discharged at home on postoperative day 4 with no sequelae.

**Discussion**

Side effects of epidural opioids are caused by the presence of the drug in either the cerebral spinal fluid or the blood. The propensity of epidural opioids to cause side effects, particularly respiratory depression, is largely related to the dose and the pharmacokinetics of the specific opioid. The epidural space contains an extensive venous plexus, therefore, vascular reabsorption is extensive. A highly lipid soluble drug is absorbed relatively quickly, thus accumulation and cephalad spread is uncommon. However, a high blood concentration as a result of extensive vascular reabsorption is more likely to occur and increase the risk of early respiratory depression, thus early respiratory depression is likely to occur when using such opioids as sublimaze and sufentanil. The less lipid soluble opioids, morphine and hydromorphone, tend to accumulate. Cephalad spread of the opioid occurs with bulk flow of cerebrospinal fluid as it diffuses through the dura. This physiologic event can increase the risk of delayed respiratory depression. Our patient exhibited respiratory depression at approximately 7 hours postoperatively, which suggests delayed respiratory depression secondary to accumulation and cephalad spread of the hydromorphone that was contained in the continuous epidural infusion.

Although dose and pharmacokinetics play a large role in the extent of side effects, there are other contributing factors. The obese and elderly patient may have exaggerated cephalad spread and require decrease doses or volume. Nishimura et al documented cephalad spread of lidocaine in patients older than 50 years, suggesting that decreased volumes of...
epidural agents be used in this population.6 Bromage also suggested that the anatomical changes that occur in the elderly epidural space causes cephalad spread.7

The obese patient should be evaluated extensively for the evidence of sleep apnea syndrome. Ostermeier et al performed a review of a series of 18 cases of patients with sleep apnea syndrome. The review focused on the development of postoperative respiratory complications from any mode of analgesic therapy. Of the 18 cases reviewed, 5 involved the administration of epidural narcotics.8 Delayed respiratory depression was the most common presentation and was reported up to 48 hours after the start of the epidural infusion. Similar to our experience, 3 of the 5 cases involved titration to a larger dose, because patients were uncomfortable and experiencing pain. In another striking similarity to our experience, all 3 patients failed to demonstrate the usual signs of respiratory depression. The postoperative respiratory event appeared rather acutely and without prior evidence of decreased ventilatory frequency or dyspnea. The absence of the normal warning signals may represent a critically significant difference between obese patients with sleep apnea syndrome and normal healthy patients being treated with epidural opioids. Concomitant use of other opioids and sedatives also may represent a potential cause for postoperative respiratory depression. The synergistic effect of the neuraxial and parenteral drugs normally tolerated by most patients may not be tolerated in the obese patient with sleep apnea syndrome. The combination of medications was not a problem for our patient because she did not receive additional analgesic therapy.

Our patient did experience delayed respiratory depression. The cause was multifactorial; she was an obese, elderly patient receiving a continuous infusion of a less lipid soluble opioid. This patient’s risk of respiratory depression may have been reduced with the use of alternative opioids in the local anesthetic or even a local anesthetic infusion alone. The avoidance of administering additional medications or increasing the infusion rate through the epidural may represent a conservative but ultimately safer postoperative pain management plan. Ostermeier et al recommend establishing the lowest possible epidural infusion rate to maintain a patient’s pain at mild (≤ 3 on a scale of 0 to 10). Increased vigilant monitoring and 24 to 48 intensive care unit admissions should be considered when patients are identified as high risk for the development of postoperative respiratory depression.

The advantage of epidural opioids normally supersedes the possible side effects that can occur. While it is true that the aforementioned side effects are more common with intrathecal opioids, the probability of their occurrence in epidural opioids is clinically relevant and warrants close observation.1 Respiratory depression represents the most serious side effect. Vigilant monitoring is recommended in order to avoid devastating events.

As a result of the scant information in the literature regarding the possible side effects of epidural hydro-morphone, we recommend that it be cautiously used in the elderly. In addition, we recommend that hydrophilic opioids not be administered to the obese patient with evidence of sleep apnea syndrome.

REFERENCES

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