CASE STUDY

Epidural haloperidol enhances epidural morphine analgesia: Three case reports

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ABSTRACT

Epidural opioids provide significant postoperative analgesia; however, their use is often limited by side effects such as nausea and pruritus, or they require the addition of epidural local anesthetics with possible side effects of motor block and hypotension. Adjuncts to epidural opioid analgesia would benefit pain management. There is evidence that epidural butyrophenones may enhance opioid analgesics and reduce side effects. The authors present the first reported use of epidural haloperidol to enhance epidural morphine analgesia in three individuals. Pharmacodynamic interactions of haloperidol, which may explain its analgesic efficacy, are summarized.

Key words: epidural haloperidol, epidural morphine, analgesia, epidural analgesics

INTRODUCTION

The traditional management of postoperative pain includes medications in the "analgesic ladder" that can be administered parenterally, such as cyclooxygenase inhibitors and acetaminophen. When these cannot provide sufficient analgesia, parenteral opioids are added. Systemic opioids are effective for the treatment of postoperative pain; however, they are associated with typical side effects such as nausea, vomiting, itching, and somnolence.[1] With the discovery of specific opioid receptors in the spinal cord in the early 1970s, spinal administration of opioids for pain relief was first applied to patients[2] in 1979 and has been advocated for the relief of postoperative pain for the past 25 years. Although the analgesia obtained from epidural opioids is significant, side effects such as pruritis sometimes limit its use[3] or often require the addition of epidural local anesthetics. Local anesthetics may cause orthostasis and hypotension, inhibit ambulation, delay removal of bladder catheters and cause "numbness" that may be unpleasant for patients, and mask injury.[4] Improving analgesia while reducing drug side effects remains a primary goal of anesthesiologists providing postoperative pain management.

In addition to traditional epidural analgesics of opioids and local anesthetics, other substances, such as clonidine and ketamine, have been found to provide epidural analgesia.[2] There is a growing body of evidence to suggest that epidural butyrophenones may enhance epidural opioid analgesics and is the subject of these case reports. The butyrophenones were discovered by Janssen 50 years ago during attempts to synthesize opioids.[5] Greene noted in 1972 that droperidol was capable of potentiating both the analgesic and respiratory depressant effects of fentanyl.[6] Maltbie noted that haloperidol, meperidine, and morphine shared a "phenylpiperidine" structural configuration and that oral haloperidol was effective in the management of intractable pain syndromes.[7] A more recent prospective, randomized, observer-blinded clinical trial of epidural droperidol added to epidural fentanyl/bupivacaine improved postsurgical analgesia with less nausea and vomiting compared with epidural fentanyl/bupivacaine alone.[8] Because droperidol use has been given a "black box" warning by the FDA,[9] we investigated the use of epidural haloperidol to enhance epidural opioid analgesia in patients with postoperative pain.

We present three patients with postoperative pain managed with a mixture of epidural haloperidol and morphine. All patients demonstrated a significantly decreased requirement (or complete elimination) for additional postoperative analgesics.

CASES

Patient 1 was a 63-year-old female with a past history of smoking and lung cancer palliated with prior surgical

resection. Her medications were lanosprazole, atenolol, and loratadine daily. She presented for resection of gastric adenocarcinoma. Prior to surgery, a mid-thoracic epidural catheter was placed under local anesthesia supplemented by midazolam 2 mg IV. A 3-mL epidural test dose of 1.5 percent lidocaine with epinephrine 5 μg/mL was administered and was negative. General endotracheal anesthesia and surgery proceeded uneventfully, with the exception that extensive abdominal exploration required more than 4 hours and a xiphoid to pubis incision. Her only intraoperative analgesic was 200 μg of intravenous fentanyl. No epidural local anesthetic was administered. One hour prior to conclusion of surgery, epidural haloperidol 1 mg mixed with epidural preservative-free morphine 2 mg was administered. Upon awakening in the operating room the patient was alert, communicated easily, and denied any pain. With 45° head elevation in the postanesthesia care unit (PACU), she expressed mild abdominal discomfort and was given 3 mg morphine IV and 4 mL of epidural bupivacaine 0.25 percent. She required no further analgesics of any kind during her 6-hour PACU stay while she waited for a floor bed to become available. She was given an epidural patient controlled analgesia (PCA) device containing a solution of bupivacaine 0.125 percent with hydromorphone 0.02 mg/mL. Because of her unusually low pain level, she was given a basal epidural infusion rate of 0.5 mL/h instead of our standard 2 mL/h. Despite this reduction in basal rate, she accessed on-demand (PCA) doses only 9 times (9 mL) during the subsequent 30 hours. Her verbal pain scores (0 = no pain; 10 = worst pain) were assessed every 4 hours during the first 24 hours postoperatively and never exceeded a rating of "1."

Patient 2 was a 56-year-old female with a previous medical history of smoking and uncontrolled hypertension. Her medications were hydrochlorothiazide, lisonopril, atenolol, and buspirone 10 mg. Clonidine was started for hypertension and administered twice the day before surgery. She presented for radical abdominal hysterectomy with bilateral salpingo-oopherectomy and lymph node sampling for the treatment of cervical cancer. Prior to surgery, a low-thoracic epidural catheter was placed under local anesthesia after midazolam 2 mg IV. A 3-mL epidural test dose of 1.5 percent lidocaine with epinephrine 5 μg/mL was administered and was negative. Just prior to induction of anesthesia, epidural haloperidol 1 mg mixed with epidural morphine 2 mg was administered. General endotracheal anesthesia and surgery then proceeded uneventfully. No epidural local anesthetics or IV opioids were given during the surgery. Anesthesia was maintained with isoflurane and no intraoperative opioids were given. The patient denied any pain after awakening and continued to deny any pain during her PACU stay. She was given an epidural PCA device for rescue epidural analgesics (no basal infusion) but did not administer any injections during her hospital stay. She was questioned every 3 hours and she denied any pain for the first 36 hours postoperatively. No postoperative opioids were given. It was noted, however, that she experienced discomfort when she coughed. Her only request for pain medication came at 36 hours after surgery and ibuprofen 600 mg gave adequate pain relief.

Patient 3 was a 51-year-old male with hip osteoarthritis presenting for hip arthroplasty. He was 5 ft, 6 in tall and 146 kg with a previous history of gastric bypass surgery. His medical conditions included poorly controlled hypertension, sleep apnea requiring continuous positive airway pressure (CPAP), hyperlipidemia, and coronary artery disease treated with a coronary artery stent. His medications included doxazosin, artorvastatin, lisonopril/hydrochlorothiazide, and hydromorphone. He had discontinued clopidogrel several days prior to surgery. A high lumbar epidural catheter was inserted prior to surgery. After a negative epidural test dose with 1.5 percent lidocaine with epinephrine, an epidural mixture of haloperidol 1 mg with morphine 2 mg was administered. General endotracheal anesthesia was uneventful, with fentanyl 100 μg IV given on induction. No other intraoperative opioids were given. No epidural local anesthetics were administered. The patient awakened from surgery pain-free and denied any pain upon questioning in the PACU. His nurse noted that he was able to move himself without assistance and without any discomfort while postoperative X-rays were taken. His epidural PCA solution (no basal infusion) was bupivacaine 1.25 mg/mL with morphine 200 μg/mL. Per orthopedic surgeon protocol, he received ketorolac 30 mg with acetaminophen 325 mg every 8 hours postoperatively. At 33 hours postoperatively, he had used only 12 mL of PCA epidural solution. He consistently denied having any pain and was always alert and oriented when awake.

DISCUSSION

We present three cases of epidural haloperidol administration, which appeared to greatly enhance epidural morphine analgesia. Despite receiving a basal epidural infusion, which was 25 percent of our customary dose, Patient 1 required only 9 mL of PCA epidural solution during her first 30 hours postoperatively. This is far less than typical incremental dosing which averages a total epidural dose of approximately 2 mL/h. Except for epidural morphine/haloperidol, the second patient did not receive any analgesics or local anesthetic for the first 36 hours postoperatively. Although patient 3 was supplemented with ketorolac and acetaminophen once per shift, his use of 9 mL of epidural solution without a basal infusion is far below average. This is especially significant because he had a history of chronic opioid use prior to surgery. We postulate that the epidural haloperidol enhanced the initial bolus of epidural morphine with an apparent duration of action of 24 hours.

There are several possible mechanisms of action for the enhancement of epidural opioid by epidural haloperidol administration. We believe that epidural haloperidol may act produce analgesia through its effect on sigma

receptors. Sigma receptors are thought to be unrelated to opioid receptors because they bind diverse drugs such as haloperidol and phencyclidine. Butyrophenones exhibit activity on neuraxial receptors involved in nociceptive modulation including sigma receptors.[10] Although sigma receptors were originally thought to be sites of opioid activity,[11] more recent research has determined that the amino acid sequence of sigma-1 receptors does not resemble that of any other mammalian protein.[12] Unlike opioid receptors, sigma isomeric stereoselectivity is (+) rather than (−), and naloxone is ineffective against sigma ligands.[13] Sigma-1 receptors are thought to act as modulators, only becoming relevant as physiological signal amplifiers after another biological system is first activated.[14] Sigma-1 receptors can effect neurotransmitter release, ion channel regulation, nociception, and possibly neuroplasticity.[14]

Rats and mice possess tonically active anti-opioid brainstem activity which acts through sigma receptors.[15,16] In addition, sigma receptors are present in the spinal cord of rats in areas involved with nociception.[17] Thus, sigma antagonists should facilitate opioid analgesia. In a rat model, sigma antagonists such as haloperidol (and some of its metabolites) potentiate opioid analgesia.[18] Sigma antagonists enhance the analgesic activity of agents, which act at the mu, kappa-1, or kappa-3 opioid receptors.[15] Sigma-opioid interaction seems to be confined to analgesia. For example, sigma receptor blockade does not alter morphine's gastrointestinal effects.[15]

Haloperidol may also act to produce analgesia by an NMDA receptor antagonist effect. The NMDA receptor has been implicated in transmission of nociceptive input in the spinal cord, especially for the generation of neuropathic pain.[19] However, the affinity of haloperidol for sigma-1 receptors is 1,000 times higher than for NMDA receptors.[20] Sigma agonists amplify NMDA-mediated neuronal firing rates. Because haloperidol antagonizes this effect, it allows indirect NMDA inhibition.[21] In addition, the concentrations reached with the epidural administration of haloperidol may cause a direct effect on NMDA and other receptors and channels. Haloperidol can act as an NMDA receptor antagonist in cultured rat hippocampal neurons as well as cloned rat brain NMDA receptors.[22]

In addition to sigma and NMDA receptor interaction, haloperidol binds to dopaminergic, alpha-1 adrenergic, serotonergic, and muscarinic receptors. These have all been shown to affect nociception, thus the effect of haloperidol to produce analgesia may be complex.[10] In addition, haloperidol in high concentrations may produce effects similar to local anesthetic. Haloperidol and droperidol have close structural similarity with each other and also with lidocaine.[23] Droperidol reduces neural sodium influx during the action potential at a far lower concentration than required with lidocaine. Both droperidol and haloperidol have demonstrated ability to block fast sodium channels and thus may produce analgesia at the spinal cord in a manner similar to local anesthetics.[23,24]

Early studies on the use of oral or parenteral neuroleptics as adjuvant analgesics were disappointing, with little evidence from controlled clinical trials found to support their claim as analgesics.[25] However, these reports did not use the epidural route of administration, which may be important for pain relief. The more recent study of epidural droperidol[8] did show some improvement in postoperative analgesia and prompted our report to evaluate epidural haloperidol. The second generation atypical neuroleptics seem to show promise as analgesic agents[25]; however, few controlled clinical trials have been completed and their use via the epidural route of administration has not been reported.

There are several potential benefits associated with the use of epidural haloperidol for enhancement of epidural opioid analgesia. Epidural opioids are used routinely in the management of postoperative pain, but side effects such as respiratory depression are dose-related and can limit analgesia. Opioid reduction should diminish respiratory risk and also have a salutatory effect upon bowel motility, because inhibition of gut motility by epidural opioids has a positive correlation with dosing.[26] Also, eliminating the need for intraoperative epidural local anesthetic administration would simplify intravenous fluid management as well as aid in maintenance of postoperative blood pressure. Patient 2 did not require any epidural local anesthetic to achieve good pain relief. A reduction in postoperative opioid/local anesthetic should facilitate bladder catheter removal and ambulation, perhaps leading to shorter hospitalization.

This series of three case reports is obviously limited by the very small number of patients reported. There are no other reports of epidural haloperidol for analgesia in the literature and thus conclusions from our small series must be tested further. A controlled, prospective, and randomized clinical trial of the analgesic efficacy of epidural haloperidol is required following studies to ensure that spinal haloperidol has no neurotoxicity. Studies of epidural droperidol on postoperative analgesia have shown mixed results, with recent clinical trials among patients completing thoracic or abdominal surgery failing to demonstrate any analgesic effect.[27,28] Differences in opioid administered, administration method, or surgical site have all been postulated to contribute to the varied outcomes of epidural droperidol on postoperative analgesia.[8]

The possible risks of epidural haloperidol administration are unknown. The risk of extrapyramidal side effects[25] or prolongation of the QT interval from epidural haloperidol use is possible, with an unknown frequency at present. Neither epidural droperidol nor epidural haloperidol administration has been approved by the Food and Drug Administration. Our access was restricted to haloperidol which contained propyl- and methylparaben as a preservative, but parabens have been shown to lack neurotoxicity after high-dose intrathecal administration.[29] In a spinal analgesic study involving rats, intrathecal droperidol in moderate and high doses

combined with intrathecal morphine did not exert any toxic effects on the spinal cord.[30] No signs of neurotoxicity on light or electron microscopy or the spinal cord were seen when compared with saline control animals.

Adjuncts to enhance epidural opioid analgesia for postoperative analgesia would be a welcome addition to the armamentarium of the pain physician. These brief case reports, along with preliminary animal studies to support an antinoceptive function of haloperidol, provide evidence that epidural haloperidol appear to enhance epidural morphine analgesia among patients with postoperative pain. Clinical trials to determine efficacy and side effect profiles are clearly indicated.

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