CASE STUDY

Low-dose intrathecal naloxone to enhance intrathecal morphine analgesia: A case report

Scott Hamann, MD, PhD
Paul Alexander Sloan, MD
William Witt, MD

ABSTRACT

Ultra low doses of opioid antagonists such as naloxone block excitatory opioid receptor pathways may paradoxically enhance morphine analgesia. This case study reports safety and efficacy of ultra low-dose intrathecal (IT) naloxone added to IT morphine for the treatment of severe refractory chronic low back pain. A 56-year-old man with a history of severe chronic low back pain (postlaminectomy syndrome) was evaluated. Extensive multidisciplinary therapies had all failed. Initial treatment at our clinic was a lumbar IT trial of morphine (unsuccessful) up to 50 mg/day. We administered an IT bolus of morphine 2 mg combined with IT naloxone of 20 ng with the patient's consent and approval. The onset of pain relief was within 20 minutes and peaked at 1 hour with a 50 percent reduction in VAS pain score. There were no signs of adverse drug toxicity or hemodynamic compromise. An IT infusion of daily morphine 5 mg and naloxone 50 ng was started. Throughout the 3-year follow-up period, the patient maintained pain reduction of 60 to 80 percent, with a return to daily activities and no further hospitalizations.

Key words: intrathecal naloxone, intrathecal morphine, analgesia, spinal analgesics

INTRODUCTION

Clinical problems

The traditional analgesic management of chronic nonmalignant pain includes nonsteroidals and adjuvant analgesics such as muscle relaxants, antidepressants, and antiseizure drugs.[1] When traditional analgesic therapies have been exhausted, opioids in oral and spinal routes of administration have been recommended in selected patients.[2] There remain, however, a subset of patients for whom even aggressive spinal or oral analgesics do not provide adequate pain relief. It is for these patients that clinicians search for novel pharmacological approaches to provide adequate pain relief with a minimum of side effects. One such novel therapy is the combination of ultra low-dose opioid antagonists with opioids to enhance the opioid agonist analgesic activity.[3]

Paradoxical pharmacology

Opioids activate stereospecific opioid receptors on cell membranes throughout the central nervous system producing profound analgesia but also with opioid-related side effects.[4] More than 60 years ago, it was suggested that the opioid antagonist nalorphine had analgesic properties in man.[5] Since that time, conflicting/paradoxical opioid effects have emerged in both human and animal studies, in part, because of the wide variation in dosing regimens for opioid agonists and antagonists, as well as experimental pain paradigms. Recently, dose-dependent inhibitory-analgesic and excitatory-hyperalgesic actions of opioid agonists have emerged from animal and isolated neuronal cell culture experiments.[6] Although the dominant effect of opioids in the usual clinical doses is to inhibit opioid receptors, opioid agonists simultaneously activate excitatory opioid receptors on sensory neurons.[7] These findings have led to proposals that ultra low doses of opioid antagonists, such as naloxone or naltrexone, may selectively block the excitatory effects of opioid agonists to enhance analgesia.[8] Several clinical studies and case reports have suggested the enhancement of opioid analgesia with concurrent use of low doses of naloxone.[9] A recent pilot clinical trial found that among patients with chronic back pain receiving chronic intrathecal (IT) morphine analgesia, the addition of low-dose oral naltrexone tended to result in the enhancement of morphine analgesia.[10]

Although the enhancement of opioid agonist analgesia by low doses of opioid antagonists given orally or intravenously has been published, there are no clinical reports of combining IT opioid antagonists with IT opioid

agonists to enhance clinical analgesia. This case reports apparent efficacy and safety of ultra low-dose IT naloxone added to IT morphine for the treatment of severe refractory chronic low back pain.

CLINICAL CASE

Patient history and pain diathesis

Our patient is a 56-year-old man with a history of severe refractory chronic low back pain who was referred for evaluation and pain management. His previous medical history was significant only for hypertension and depression. His relevant pain diagnoses included postlaminectomy syndrome, right leg radiculopathy, and mild depression. The most severe clinical pain was located in the low back radiating down the right leg to the toe. This pain pattern had been present for many years, originating with a herniated lumbar disc related to strain at work. The pain was constant, which worsened with activity, rated at 9/10 on a numeric pain rating scale and greatly interfered with the activities of daily living.

Failed pharmacologic and invasive therapies

Previous pain therapies included physical therapy, TENS, antidepressants, oral opioid analgesic trials, adjuvant analgesics, steroid epidural injections, lumbar laminectomy, and spinal cord stimulation (SCS). Of note, stimulation of the SCS was obtained below the knee; however, this did not provide any degree of pain relief. Aquatic physical therapy helped to increase the activity level and strength but did not relieve his pain. A lumbar epidurogram revealed absence of any filling in the right L5 or S1 nerve root distribution. At presentation, the patient was being treated with sustained and immediate release analgesics (fentanyl patch 100 mcg/hr and oxycodone tablets PRN) along with an antidepressant (sertraline). Evaluation by our psychologist found no psychopathology, and the patient was consented for IT pharmacologic treatments using multiple spinal analgesics.

A lumbar IT catheter was placed under fluoroscopy and a trial of IT morphine up to 50 mg/day was initiated but with no reduction in pain scores. The addition of IT clonidine (up to 75 mcg) and IT ketamine (6 mg) were seemingly without benefit. A single dose of IT fentanyl 200 mcg was also not helpful in relieving his pain. A bolus dose of IT bupivacaine produced motor block in the lower extremities but did not affect his pain.

Intrathecal morphine/naloxone trial

After almost every possible treatment for his chronic and severe back pain, our patient was becoming discouraged with life and despondent that any hope of pain relief was possible. Because of the failure of all traditional spinal analgesics to relieve this patient's debilitating pain, we decided to briefly withdraw further pain therapy (oral and IT drugs) in prelude to treating the patient with a combination of IT morphine and ultra low-dose IT naloxone. Although our primary purpose was to provide this patient with desperately needed pain relief, the clinical problem provided a unique opportunity to test the concept that selective antagonism of excitatory opioid receptor function may enhance IT morphine's pain relief for this patient with chronic pain.

We administered an IT bolus of morphine 2 mg combined with IT naloxone 20 ng with the patient's consent and approval. The mechanistic rationale for this dose selection was based upon preclinical dose-response studies in isolated sensory neurons and rodents, which have shown that when opioid antagonists (eg, naloxone, naltrexone) are combined with opioid agonists (eg, morphine), the resultant effects on sensory function and nociception are dependent upon the antagonist/agonist dose ratios, with greatest analgesia produced when antagonist doses are many times lower than doses of opioid agonist.[11,12] Opioid antagonists/agonist dose ratios of $1/10^4$ down to $1/10^6$ have demonstrated enhanced analgesic efficacy.[13] The selection of the initial naloxone/morphine IT bolus dose ratio of $1{:}10^5$ was based upon convincing preclinical research and scientific concepts, together with clinical anecdotal experience in postoperative pain settings. To prepare the treatment solution used for this case, an ampule of naloxone (40 mcg/ml) was diluted under sterile conditions with saline 1:10 four times, and then in half, to produce a final solution of 20 ng/ml naloxone, which was injected intrathecally with 2 mg morphine.

The onset of pain relief was within 20 minutes and peaked at 1 hour with a 50 percent reduction in VAS pain score. The patient reported pain relief over the right foot, which had previously been totally refractory to all pain management techniques. The initial IT morphine 2 mg with naloxone 20 ng dose was repeated and the patient was followed up in hospital overnight. There were no signs of adverse drug toxicity or hemodynamic compromise. Under close clinical observation, an IT infusion of morphine 5 mg with naloxone 50 ng per day was initiated and continued for several days with 50 percent pain reductions reported by the patient. All other opioid therapy (fentanyl patch, oral oxycodone) was weaned and discontinued over a 1-week period.

Clinical pain management/follow-up

Following these initial therapeutic successes and with patient's clinical consent, a programmable infusion pump was surgically implanted, which delivered the IT morphine/naloxone infusion at a constant ratio of 10 ng

of naloxone per 1 mg of morphine. The implanted pump was refilled every 3 months. Throughout the 3-year follow-up period, the patient maintained pain reduction of 60 to 80 percent, with a return to daily activities, no further hospitalizations, and only a modest increase in IT analgesics to morphine 8 mg with naloxone 80 ng daily.

DISCUSSION

Clinical case report

We present the use of ultra low doses of IT naloxone infusion to enhance IT morphine infusion analgesia in a patient with severe and otherwise refractory chronic low back pain. The addition of ultra low doses of IT naloxone to IT morphine resulted in significant pain relief in a patient who had been refractory to combinations of IT opioids with IT clonidine and IT ketamine. The pain relief was rapid in onset, profound and sustained over a 3-year follow-up period.

Historically, the most familiar clinical effects produced by common doses of opioid agonists result from direct activation of neuronal opioid receptors, causing sustained inhibition of sensory stimulus transmission (antinociception) and pain perception (clinical analgesia). Less familiar, and long recognized as paradoxical, clinical actions of opioid agonists have been recently shown to result from simultaneous direct activation of highly sensitive neuronal opioid excitatory receptors causing sustained enhancement of sensory stimulus transmission (pronociception) and clinical pain perception (hyperalgesia).[8] Such bimodal actions of opioid agonists on neuronal sensory function has been demonstrated at both supraspinal and spinal sites[14] and serve to explain how dose selective antagonism of neuronal excitatory receptors by opioid antagonists (eg, naloxone, naltrexone) may produce profound enhancement of opioid agonist analgesia. Although the efficacy of extremely low doses of opioid antagonists suggest a high degree of neuropharmacologic selectivity, alternative explanations for the analgesic effect of IT opioid antagonists need to be considered including the effect of naloxone on nonopioid chemokine receptors[15] or the interaction of naloxone with glial cells in the spinal cord.[16] Clearly, additional studies into the mechanism of action of spinal opioid antagonists to enhance spinal opioid agonist analgesia are indicated.

Our patient was resistant to a large bolus of IT fentanyl (200 mcg) with no apparent analgesic effect. It is possible that increased doses of fentanyl would have provided some pain relief as was recently described in case reports of four patients with otherwise intractable chronic pain who responded to escalation of IT fentanyl as high as 20 times usual doses.[17] The safety and efficacy of using extremely high-dose spinal opioids needs further study among patients with chronic pain refractory to standard opioid doses.

Safety precautions

For several important reasons, our case report therapy should not be considered appropriate for clinical pain management practice. First, ultra low-dose opioid antagonists therapy in a patient on chronic opioid therapy has the potential to precipitate serious opioid withdrawal and/or other side effects such as hypertension. Our patient was kept in hospital for close observation while the IT naloxone therapy was initiated. There was no evidence of drug toxicity or opioid withdrawal related to IT naloxone therapy. Other case reports have demonstrated similar apparent safety of ultra low-dose oral naltrexone used to potentiate the analgesic effect of oral methadone in a patient with chronic nonmalignant neuropathic pain.[18] In this one patient with chronic pain, the use of IT naloxone combined with IT morphine infusion appeared to be safe and without obvious side effects. However, patient's safety and risk/benefit must take priority and mandate restricted clinical applications.

Second, our case report describes novel off-label use of IT naloxone in the treatment of a patient with severe, chronic, and unrelenting pain. Naloxone is not approved for neural-axial clinical therapies, and preclinical data from spinal toxicology studies of naloxone are not available. Until IT naloxone is appropriately evaluated and approved by the FDA, its clinical use as an IT therapy must remain cautionary. Nonetheless, it is doubtful that extremely low doses of IT naloxone would exhibit spinal cord toxicity based upon chemical characteristics and animal research. Except for two relatively minor moiety substitutions at positions 6 and 17 of morphine's chemical structure, naloxone's chemical structure is virtually identical to morphine, which is approved for IT use at several fold higher doses. Further, rodent studies using IT naloxone to enhance morphine analgesia have not demonstrated complications or signs of spinal cord toxicity.[15,17,19] Finally, a considerable animal literature actually suggests that IT naloxone may offer antitoxicity protection against neural tissue damage following ischemic injury.[20] When chemical characteristics, animal study data, and extremely low dose ranges are considered together, it seems improbable that IT naloxone would produce spinal cord toxicity. However, standard precautions and informed patient consent are mandated for IT naloxone, and all treatments involving novel, but unproven, spinal analgesic agents.

Third, the long-term stability of IT naloxone is currently unknown. Our patient had the pump solution refilled every 3 months without seeming loss of analgesic efficacy during this time period. Two studies among rodents suggest that naloxone may be stable within the body: (1) an implanted naloxone delivery system in rats showed that

naloxone was stable for 4 weeks[21] and (2) a transdermal delivery system of naloxone in rats showed the naloxone formulation was stable for up to 3 months of administration.[22] A clinical report from Australia states that naloxone appears stable at extremes of both cold and heat.[23] However, until additional naloxone stability studies are conducted in animals, this case report should not be considered appropriate for clinical pain management practice.

SUMMARY

Most patients with chronic cancer and nonmalignant pain can be treated with a variety of opioid and nonopioid analgesics. For the selected patient with pain refractory to all traditional analgesic therapy, the use of spinal naloxone to enhance spinal morphine analgesia may be an option. Clinical caution is warranted until safety and efficacy profiles of spinal naloxone/morphine combination are available from further animal and controlled human trials.

Scott Hamann, MD, PhD, Department of Anesthesiology, University of Kentucky, Lexington, Kentucky.

Paul Alexander Sloan, MD, Department of Anesthesiology, University of Kentucky, Lexington, Kentucky.

William Witt, MD, Department of Anesthesiology, University of Kentucky, Lexington, Kentucky.

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