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Myoclonic Seizure Activity with Chronic High-Dose Spinal Opioid Administration

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High doses of intrathecal morphine have been noted to induce myoclonic seizures in rats.[1,2] Krames *et al.* reported myoclonic jerking in two patients during infusion of high concentrations of intrathecal morphine.[3] Myoclonic seizure activity from the use of intrathecal hydromorphone or epidural morphine has not previously been reported in humans. We present two cases of myoclonic seizure activity with high-dose spinal opioid therapy for cancer pain—one case involving intrathecal hydromorphone and one epidural morphine.

CASE REPORTS

Case 1. A 58-yr-old, 60-kg man was evaluated by the Pain Clinic for control of pain from metastases (prostate cancer) to multiple ribs, pelvis, and femur. His pain medications included 900 mg/day of sustained release oral morphine, 20–40 mg/day of oral hydromorphone, a nonsteroidal analgesic, and a tricyclic antidepressant. Because of his poorly controlled pain, a permanent epidural catheter was inserted at T10 and his pain brought under control with a regimen of morphine 15 mg bid *via* the epidural catheter. His oral morphine was continued and the oral hydromorphone was used as needed. This regimen was effective for approximately 1 month until the catheter became disconnected at the subcutaneous junction. Because his epidural morphine dose had increased to 45 mg tid during the previous month, the catheter was removed and replaced with a permanent intrathecal catheter. His medication was changed to intrathecal hydromorphone and the dose stabilized over the next month to 10 mg (1 ml) every 4–6 h. His wife noticed that a few minutes after each dose of the hydromorphone, uncontrollable, rhythmic jerking of his legs would commence. This would generally subside after 1–2 h, only to begin again after his next dose. The patient was alert, yet comfortable, except for the periods of the myoclonic contractions. In an effort to decrease the requirement for the intrathecal hydromorphone, the patient was admitted for upper-body radiation therapy. Baclofen 10 mg po tid was also started in an attempt to control the myoclonus. His intrathecal hydromorphone was changed to an infusion of 2 mg/hr (1% solution). For the next two days his myoclonus became progressively more difficult to control. Therefore, the intrathecal infusion was stopped and an iv infusion of morphine, 100 mg/h, begun. Lorazepam, 1–2 mg im every 6–12 h, proved effective in stopping the lower extremity myoclonus. The patient, sedated from the lorazepam but without myoclonic contractions, expired 36 h after cessation of the intrathecal infusion.

Case 2. A 51-yr-old, 48-kg woman with squamous cell cancer of the lung with metastases to multiple ribs was referred to the Pain Clinic for assistance in pain control. Her pain medications at that time included 1080 mg/day of sustained-release oral morphine, 40–60 mg/day of oral hydromorphone, a nonsteroidal analgesic, and a tricyclic antidepressant. Her pain was poorly controlled by the above medications and radiation therapy had already been maximally used. We were able to initially achieve significant pain relief using neurolytic (10% phenol) intercostal nerve blocks, along with the same oral medications. After 3 months her pain had progressed to include her right upper extremity (from a large tumor mass in the apex of the right lung and metastases to cervical vertebral bodies) as well as her chest wall. A permanent epidural catheter was inserted at T10 with the catheter tip at T6 and the patient's pain was well controlled with a basal infusion of 12.5 mg/h of preservative-free morphine (2.5% solution) with patient-controlled boluses of 2.5 mg every 15 min as needed. She was discharged to home with the epidural catheter infusion and a combination of oral medications similar to that which she had been receiving for several months. During the next 3 weeks her epidural morphine infusion was incrementally increased to 25 mg/h (with the same patient-controlled bolus and time interval) to achieve continued pain control.

After receiving the infusion of 25 mg/h of epidural morphine for 1 day she began to experience what her daughter described as "frequent, spastic contractions of her stomach and legs." Baclofen 10 mg po tid was begun with no change in the patient's status other than the patient became somewhat somnolent. The uncontrollable myoclonic jerking persisted, much to the discomfort of the patient. She was subsequently admitted to the hospital for control of her myoclonus.

Five milliliters of 0.25% bupivacaine was injected through the epidural catheter, the morphine infusion was stopped, and a sufentanil and bupivacaine epidural infusion at 1 ml/h (25 μg and 1.25 mg/h, respectively) begun. Her myoclonic jerking stopped with the onset of the epidural anesthesia from the bupivacaine. Because of persistent hypotension the infusion solution was changed to sufentanil alone at 25 μg/h. The myoclonic activity of the lower limbs rapidly returned after the epidural anesthesia had resolved in spite of the continued epidural sufentanil infusion. We found we could achieve good control of the myoclonus with iv midazolam (although creating a heavily sedated patient) and started administered diazepam 5 mg po every 6 h. After receiving the first dose of diazepam she became extremely somnolent (almost unarousable), but the myoclonus was minimal. Her sufentanil infusion was then decreased to 15 μg/h. When the effects of the diazepam receded, she began again to have the uncontrollable, repetitive contractions of the muscles of the lower abdomen and proximal lower extremities. These were brought under control again, this time using haldol 1–2 mg im every 2–4 h as needed. The epidural sufentanil infusion was stopped and an iv infusion of hydromorphone, 1 mg/h,

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begun. The patient expired 38 h later, requiring continued heavy sedation with intermittent haldol to control the myoclonic contractions.

Discussion

Intrathecal morphine has been found to induce myoclonic seizures in the hind limbs of rats when given in high doses.[1,2] This myoclonic seizure activity is not reversible with naloxone. Intrathecal methadone, meperidine, fentanyl, ketamine, and D-ala2-methionine-enkephalinamide (DALA) were devoid of myoclonic activity, although meperidine and ketamine produced paralysis of the lower limbs at higher doses.

High-dose intrathecal morphine and multiple morphine-related compounds (including hydromorphone) have also been found to result in allodynia (hyperesthesia) in both the rat and the cat.[4-6] This, too, was not reversible with naltrexone. This nonopiate receptor-mediated response can be readily mimicked by intrathecal administration of the glycine antagonist, strychnine.[7,8] Glycine has been shown to mediate a postsynaptic inhibition on dorsal horn neurons.[9] It appears that high-dose intrathecal morphine and its related compounds or metabolites act *via* a spinal antiglycinergic effect to decrease postsynaptic inhibition, resulting in allodynia and/or myoclonus. There is some evidence that the allodynia and the myoclonic activity may be manifestations of the same nonopiate receptor-mediated response as strychnine administered in submotor convulsive doses produces a behavioral phenomenon comparable to the allodynia of high-dose morphine.[10]

Documentation of spinal morphine "toxicity" in humans has been rare. Krames *et al.* noted myoclonic jerking in two patients during infusion of high concentrations of intrathecal morphine.[3] Stillman *et al.* observed what was termed "paradoxical hyperalgesia," accompanied by autonomic signs and hyperesthesias of the lumbosacral dermatomes, in three patients receiving high-dose boluses (4–45 mg) of intrathecal morphine.[11] Our report is the first involving intrathecal hydromorphone and appears to be the only one to date involving epidural morphine.

Our patients differed from what has been seen in laboratory animals with high-dose spinal morphine or hydromorphone in that there was no apparent allodynia. Neither patient showed any abnormal response to tactile stimuli and pain only occurred as a result of the contractions themselves, not as a precipitating event or stimulus. Between myoclonic contractions the patients noted no change in sensory perception of the lower extremities.

Some salient points and questions for the clinician dealing with chronic spinal opioids for cancer pain are:

1) Mechanism of action.—The myoclonic activity is apparently a nonopiate receptor response to morphine and its related compounds. Is it a spinal antiglycinergic effect, similar in mechanism to the allodynia and hyperesthesia seen with high-dose spinal morphine in laboratory animals?

Does it correlate directly with the CSF concentration of morphine or its conjugated metabolites? Regrettably, we did not obtain CSF samples in either patient before or after the commencement of the myoclonic seizures. Our patients' problems continued up to 36 h after stopping the infusion of the hydromorphone and the morphine.

Is this a manifestation of altered spinal cord physiology seen with spinal cord lesions or a preterminal event? Both of our patients expired within 48 h of the onset of the uncontrollable myoclonic jerking and one had known metastases to the cervical vertebrae. Both patients were neurologically intact just prior to the onset of the myoclonic seizures; however, neither had an autopsy to determine the presence of spinal cord or cerebral pathology.

2) Treatment.—Oral baclofen, an agonist of γ-aminobutyric acid that inhibits both monosynaptic and polysynaptic reflexes at the spinal level, was of little benefit for our patients. However, it was only used for 1–2 days in either case. Krames stated that the myoclonic spasms secondary to the intrathecal morphine were fairly well controlled with oral baclofen, but the dose and duration of treatment are not mentioned.[3] Although it is not currently commercially available, would intrathecal baclofen[12] have been useful?

Diazepam, lorazepam, and haldol seemingly proved useful in stopping the myoclonus for our patients, but at the expense of significant sedation. Would a relatively nonsedating antiepileptic such as dilantin have been more beneficial to treat the seizure activity?

Local anesthetics (*i.e.*, spinal or epidural anesthesia) will eliminate the problem, but concerns with hypotension and other local anesthetic effects (paresis, loss of sensation, *etc.*) become paramount.

3) Alternative spinal opioids.—If the assumption is correct that the problem stems from a nonopiate receptor effect due to the morphine or morphine-related compounds, then using nonmorphine-related opioids for those patients requiring high doses of spinal opioids seems prudent. In our experience, doses less than 20 mg/h of epidural morphine have not caused a problem with morphine toxicity. We noted the problem with intrathecal hydromorphone at bolus doses of 10 mg and also with an infusion of 2 mg/h. The doses of intrathecal morphine received by Krames' patients who experienced the myoclonus were 19 and 38 mg/day.

High-dose spinal methadone, diacetylmorphine, fentanyl, alfentanil, and sufentanil are devoid of nonopiate receptor effects in laboratory animals. However, difficulties may arise with some of these if one is attempting to use highly concentrated solutions for home-use pumps with small reservoirs. Diacetylmorphine (a crystalline

powder), not commercially available in the United States, is deacetylated to monoacetylmorphine and then to morphine,[13,14] which may cause nonopiate receptor-mediated difficulties with chronic use, a problem not seen in the animal studies (perhaps because of the short time frame involved).

4) Nonopioid therapy.—In the future, concomitant use of α-$_2$ adrenergic agonists[15,16] or related agents may decrease the total dose of spinal opioid needed, or at least delay the onset of tolerance. Currently these solutions are not commercially available in the United States. It is also apparent to those who deal with cancer pain that spinal opioids are not a cure-all nor the first step in pain management. Judicious use of oral medications, subcutaneous and iv infusions, transcutaneous electrical nerve stimulation, and neurolytic and neurosurgical ablative procedures is warranted and frequently necessary.

In summary, we presented two patients who had myoclonic seizure activity of the lower extremities with high-dose spinal opioid therapy involving hydromorphone and morphine. Previous animal research indicates that spinal morphine toxicity is a nonopiate receptor-mediated phenomenon. Because the exact mechanism of the myoclonic seizure activity in humans is unclear, treatment of spinal opioid toxicity remains anecdotal. It is hoped that the use of α-$_2$ agonists (when available) and nonmorphine-related opioids will avoid the onset of this problem in patients requiring high doses of chronic spinal opioid therapy.

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