■ CASE REPORTS

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Successful Treatment of a Massive Intrathecal Morphine Overdose

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THE use of intrathecal and epidural opioids is becoming increasingly popular for the treatment of acute and chronic pain. Patients with chronic pain states can have intrathecal infusion pumps placed subcutaneously for prolonged outpatient opioid administration. Morphine commonly is chosen for neuraxial application because of its relatively long duration of action, low cost, and extensive history of safe and effective clinical use. Occasional intrathecal morphine overdoses have been reported. Overdoses of the magnitude that occur when an intended epidural dose is injected directly into the subarachnoid space because of catheter malplacement or migration are not life-threatening if the patient receives ventilatory support during the anticipated period of prolonged respiratory depression.

Morphine pumps can deliver small volumes of drug accurately. Therefore, concentrated morphine solutions are used to extend the time the pump can be used before requiring a refill. Commercial morphine preparations in concentrations of 10 and 25 mg/ml (Infumorph 200 and 500, respectively) are available. Until recently, errors in the use of these concentrated forms of morphine have not been published but have resulted in at least two deaths that were reported to Medtronics and resulted in the issuance of an urgent medical safety device alert in June 1992. These deaths occurred during pump reservoir refilling when the concentrated solution was mistakenly injected into an access port connecting directly to the cerebrospinal fluid (CSF). Death resulted despite respiratory support in these cases. We present a case of successful management of a patient in whom a massive (250 mg) intrathecal morphine overdose occurred.

Case Report

The patient is a 56-yr-old woman with severe reflex sympathetic dystrophy of the lower extremity whose chronic pain was managed successfully with an intrathecal morphine pump until the spinal catheter malfunctioned. She was admitted in March 1994 as an outpatient for catheter revision under monitored anesthesia care.

Her medical history is significant for hypertension and a fusion of the L1–L2 intervertebral space after a motor vehicle accident in 1976. Since then, she has been unable to work because of chronic back and hip pain. Attempts at nerve blocks, oral medication, and intravenous buprenorphine all failed. The patient underwent surgical insertion of a continuous intrathecal pump and catheter in January 1994, and pain relief was obtained from 5 mg intrathecal morphine per day.

Her admission medications included oral morphine, diazepam, furosemide, metoclopramide, naproxen, and propranolol. She is allergic to prochlorperazine and penicillin.

In the operating room, after a new intrathecal catheter was placed, the surgeon flushed the line with 10 ml of what was thought to be saline. Immediately after injection, the flush solution was identified as 25 mg/ml morphine intended to fill the reservoir of the pump. The patient received 250 mg morphine intrathecally. Surgery was rapidly completed. The pump was not refilled or turned on, and the patient was taken to the postanesthesia care unit approximately 10 min after the intrathecal injection.

In the postanesthesia care unit, the patient was noted initially to have an adequate respiratory rate (18–20 breaths/min) and was hemodynamically stable. However, blood pressure gradually decreased to 60 systolic; this condition responded to 25 mg intravenous ephedrine and initiation of a naloxone infusion at 100 μg/h. An arterial blood gas obtained while the patient breathed 40% O_2 revealed a *p*H of 7.32, Pa_{O_2} of 89 mmHg, and P_{CO_2} of 50 mmHg. During the next 90 min, the patient maintained a respiratory rate of greater than 10 breaths/min and was hypertensive with systolic blood pressures in the 200-mmHg range. Vigorous myoclonic activity was seen in the patient's legs. The patient soon became short of breath, restless, agitated, and incoherent, and tracheal intubation with mechanical ventilation was initiated. Blood pressure remained greater than 200 mmHg despite treatment with 30 mg labetalol and 20 mg hydralazine. Six milligrams midazolam was given to treat the myoclonus but was ineffective. A thiopental infusion at 160 mg/h greatly reduced the duration and frequency of the myoclonic activity seen in the lower extremities. The naloxone infusion was stopped, because it was con-

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sidered a possible cause of the hypertension.[1] The blood pressure decreased to 160/82 mmHg within 20 min of this intervention. Arterial blood gas during ventilation with an $F_{I_{O_2}}$ of 0.4 revealed a *p*H of 7.39, Pa_{O_2} of 91 mmHg, P_{CO_2} of 39 mmHg, and HCO_3 of 24 mmol/l. The patient was transferred to the surgical intensive care unit.

On arrival to the intensive care unit (5 h after the event), the patient's physical examination differed significantly from what was expected with a morphine overdose. Her pupils were dilated to 6 mm bilaterally, she was extremely agitated despite the thiopental infusion; and myoclonic activity in her legs had resumed. A literature review at that time was negative for reports of intrathecal morphine overdoses of this magnitude or on the neurotoxic effects of a large dose of intrathecal morphine. A phone call to Medtronic (the pump manufacturer) and Wyeth-Ayest (Infumorph distributor) revealed that two patients who had large intrathecal injection of morphine had died subsequently. Both patients had received less than 250 mg intrathecal morphine, and their lungs had been ventilated. Additional information could not be obtained.

An electroencephalogram (during the thiopental infusion) showed synchronous recurring spike discharge bitemporally that correlated with the lower extremity myoclonus suggesting seizure activity. Because this situation previously proved fatal, aggressive management was planned. A neurosurgeon was consulted about placing a cisternal or cervical spinal catheter so that the CSF could be irrigated. A catheter was placed in the C1–C2 interspace, a CSF sample was taken, and 900 ml of warmed Ringer's lactate was infused over 1 h into the cervical CSF and drained through two lumbar spinal needles. Seizures were controlled during this period with thiopental and vecuronium. After the irrigation of CSF was complete and a postirrigation cervical CSF sample was obtained, a pentobarbital-induced coma was instituted with a loading dose of 250 mg followed by an infusion of 140 mg/h. The seizure activity ceased, but blood pressure and urine output decreased. Urine output, which had been greater than 40 ml/h, decreased to 24 ml/h, and the systolic blood pressure decreased to 80 mmHg. Dopamine ($3.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$) was started, and urine output increased to 200 ml the next hour and remained greater than 80 ml/h for the next day. Systolic blood pressure increased to 125 mmHg and remained stable throughout the rest of the patient's intensive care unit stay. After 6 h, the pentobarbital infusion was discontinued and a neurologic examination was performed. The patient opened her eyes to command and was following complex commands when awake. She was quite somnolent and made no effort at spontaneous respirations when separation from mechanical ventilation was attempted. Electroencephalogram showed no seizure activity, and myoclonic movements were seen rarely. The patient gradually improved, and her trachea was extubated on the 3rd day after the intrathecal morphine injection. She was discharged from the hospital after 10 days complaining only of short-term memory loss. Follow-up at three weeks showed no subjective signs of current memory impairment, and her morphine pump has been started with good results at 2 mg per day.

The CSF specimens taken from the C1–C2 intervertebral space demonstrated a 97% reduction in morphine concentration (before irrigation 122,893 ng/ml; after irrigation 4,063 ng/ml).

Discussion

Immediate recognition of the significance of a massive intrathecal morphine injection probably would have led to immediate attempts to remove this drug from the CSF by the surgeon. The information about two patient deaths from massive intrathecal morphine overdoses is not well known. Many physicians feel that morphine is a safe drug for intrathecal use and overdose will result only in the need for prolonged mechanical ventilation. This does not appear to be true for massive overdoses. Two hundred fifty milligrams resulted in a patient who had circulatory depression requiring inotropic support, dilated pupils, and seizures.

Opioid effects on the central nervous system appear to be related to the route of administration and the dose. Bowdle and Rooke[2] report a case of myoclonus on emergence related to intravenous sufentanil use that was relieved by 40 μg naloxone. They also cite seven other case reports of opioid-induced muscle rigidity that were treated quickly and successfully with naloxone. This is in contrast to a report of two cancer patients,[3] in whom increasingly large doses of intrathecal morphine eventually induced myoclonus that did not respond to naloxone and was thought to be mediated by nonopioid receptors. This result has been experimentally induced in rats[4] and was seen in our patient, who continued to have myoclonic seizures while receiving a naloxone infusion. This suggests different mechanisms for myoclonus and rigidity if induced by intravenous *versus* peridural opioids.

Our patient's myoclonic seizures were greatest in the lower extremities. This is similar to a report by Parkinson *et al.*[3] describing two patients who died within 48 h after the development of lower extremity myoclonic seizures. The authors suggest that this could be a preterminal event associated with a large dose of peridural opioids. Coombs *et al.*[5] exposed ewes to large doses of epidural morphine and noted flank irritation and hind limb weakness. Shohami[4] reports myoclonus affecting the hind limbs of rats after a large dose of intrathecal morphine, and Kaiser and Bainton[6] reported a patient who complained of leg pains and cramps after 5 mg intrathecal morphine. Whether the predilection of a large dose of intrathecal morphine to affect the lower extremities is a function of the drug's effect on the central nervous system or location of injection (usually lumbar) remains unanswered.

Direct toxicity of high-dose intrathecal opioids has not been well explored. Ewes given Infumorph epidurally in increasing doses to 100 mg/day over 30 days demonstrated the development of eosinophilic and fibrogranulomas with dural breakdown.[5] Ewes given placebo *via* epidural catheters injected with saline did

not develop these neurologic sequelae. Rawal *et al.*[7] demonstrated profound neurologic injury in sheep after high doses of intrathecal sufentanil that also was not present at lower doses.

After reports of two patient deaths and the questionable neurotoxicity of a large dose of intrathecal morphine, aggressive management was followed in this patient. The patient was kept supine, because Infumorph 500 is isobaric, and spread would not be influenced by patient position. Although 5 h had elapsed since the drug had been given, irrigation of the CSF was undertaken. Morphine is hydrophilic, and in smaller doses, delayed respiratory depression often is seen much later than 5 h. It was hoped that a large percentage of the injected morphine was still in the spinal CSF. Success in treating a 5-mg intrathecal injection of morphine has been reported[6] after 4 h by the removal of 50 ml of CSF from the lumbar area and its replacement with saline. That patient's somnolence and obtundation improved, and postprocedure mechanical ventilation was not necessary.

Because our patient continued to have electroencephalographic activity suggestive of seizures, a pentobarbital-induced coma was initiated. This was done to terminate the seizures, reduce the cerebral metabolism and oxygen demand, and inhibit postsynaptic excitatory amino acid activity, all of which could worsen cerebral function.[8] Also, the metabolism of morphine by the brain may be reduced. Sandouk *et al.*[9] has identified morphine 3-glucuronide and a more potent morphine 6-glucuronide as cerebrally produced metabolites. Both of these substances are not well studied and may be responsible for some of the neurotoxicity seen.

After this patient was treated, a case report was published describing the intrathecal injection of 450 mg morphine into the access port of a continuous morphine infusion pump.[10] Treatment consisted of 8 mg intravenous naloxone given immediately and the placement of a lumbar CSF drain, which removed approximately 10 ml/h of CSF by gravity drainage for 2.5 days. The patient had an extremely high blood pressure after the naloxone of 250/150 mmHg. As with our patient, myoclonic movement confirmed to be seizure activity by electroencephalogram required continuous pentobarbital infusion.

Unlike our patient, this patient received naloxone during her entire treatment and required intravenous nitroprusside to control blood pressure. A left frontal parenchymal and subarachnoid hemorrhage developed in this patient and was thought to be related to the hypertension. Intracranial pressure was monitored but not increased. Sauter *et al.*[10] advises caution in the early use of naloxone in massive intrathecal morphine overdose. They believe this could have been the cause of their patient's hypertension. We concur, because in our patient, hypertension resolved soon after the naloxone infusion was discontinued.

Our patient had active irrigation and drainage of the CSF in a cephalic to caudal direction. This resulted in a 97% decrease in cerebrospinal morphine concentration in 1 h. With the passive drainage described by Sauter *et al.*[10] this level of cerebrospinal morphine reduction was obtained only after 15 h. It is our belief that, had cerebrospinal irrigation and drainage been started immediately in our patient, some morbidity might have been avoided. We believe irrigation is a faster and ultimately safer way to prevent the cephalad spread of morphine in the CSF and would advocate its use should this type of overdose occur again.

We have described our treatment of massive intrathecal morphine overdose, which resulted in complete recovery of the patient. All peridural drugs should be labeled and identified by the operator before injection. When refilling a pump, the proper template must be used to find the opioid reservoir. Emptying the pump before refilling (until there are air bubbles in the extension tubing) will confirm that needle placement is not subcutaneous[11] or in an access port that connects directly to the CSF. If an error is made, attempts to remove as much drug as possible from the CSF by aspiration and, if necessary, irrigation should be started immediately unless it is known that the drug, its concentration, and dose is harmless. If delayed, irrigation of the CSF in a cephalic to caudal direction can be useful, especially with hydrophilic substances.

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Reactivation of Phantom Limb Pain after Combined Interscalene Brachial Plexus Block and General Anesthesia: Successful Treatment with Intravenous Lidocaine

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IT is well known that spinal or epidural anesthesia can lead to a recurrence or exacerbation of phantom pain.[1–7] Painless phantom phenomena of the upper extremity after brachial plexus anesthesia are not uncommon and usually are described as perception of the arm in an unusual position.[8]

We describe the reactivation of severe upper extremity phantom pain in a patient after combined interscalene brachial plexus block and general anesthesia, which, to our knowledge, has not been reported previously. This responded to a single dose of intravenous lidocaine.

Case Report

A 62-yr-old, 106-kg woman with peripheral vascular disease was scheduled for resection of necrotic tissue and bone from her right elbow stump. The patient's medical history was significant for an atherosclerotic lesion of the right innominate artery, which had required brachial embolectomy on two occasions—both with general anesthesia. Most recently, gangrene of the right hand and forearm required above-elbow amputation, which was performed under general anesthesia. Immediately after the amputation, severe phantom pain developed, which the patient localized to the elbow and forearm (fig. 1). She received intravenous morphine for 3 days, which resulted in complete resolution of the phantom pain.

In addition to antibiotics, the patient was receiving the following medications: albuterol inhaler, aspirin, clonidine, diphenhydramine, dipyridamole, hydrochlorothiazide, lisinopril, ranitidine, acetaminophen, and phenytoin for a seizure disorder. The patient was not receiving opioids. Laboratory investigations revealed a hematocrit of 28%, blood urea nitrogen of 22 mg/dl, creatinine of 1.6 mg/dl, and normal electrolyte values.

The patient agreed to an interscalene brachial plexus block but requested a general anesthetic in addition, because of apprehension about being awake during surgery. A right interscalene brachial plexus block was performed, and paresthesias were produced in the patient's "phantom" fingers. Thirty milliliters of a mixture of 0.33% bupivicaine and 0.5% lidocaine with 5 μg/ml epinephrine was injected. General anesthesia was induced 15 min later, at which time a partial sensory and motor block had developed in the stump. Anesthesia was induced with thiopental and maintained with nitrous oxide, oxygen, and 0.2–0.6% isoflurane. The patient also received vecuronium for neuromuscular blockade and a total of 200 μg fentanyl. The op-

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