Epidural and Intravenous Opioid-induced Neuroexciitation

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Epidural and intrathecal opioids have been used to treat both chronic and acute postoperative pain. Common side effects of this therapy include pruritus, nausea, vomiting, and urinary retention. Rarely, respiratory depression, dysphoria,1 and infection2 occur. Even less commonly, myoclonus has been described as a side effect of intraspinal morphine,6 hydromorphone,1 and dicaeylmorphine.5 It has not been reported to have occurred with epidural morphine at a dose less than 25 mg/h. Apparent seizure activity without electroencephalographic monitoring has been reported with intravenous meperidine,7 morphine,7 and dicaeylmorphine.8 Seizure activity from intravenous hydromorphone has not been described. We report the occurrence of myoclonus induced by epidurally administered morphine that progressed to grand mal seizure activity after a large dose of intravenous hydromorphone.

Case Report

A 47-year-old, 47-kg woman with metastatic breast cancer presented to the pain management center for control of pain in her left arm and axilla. Her pain was inadequately controlled with rapidly increasing doses of intravenous fentanyl and was accompanied by increasingly severe nausea and vomiting. At a fentanyl infusion of 600 µg/h, the decision was made to place an epidural catheter with the goal of decreasing side effects and improving analgesia. A temporary epidural catheter was placed, and an epidural infusion of preservative-free morphine (0.2% solution) at 6 mg/h was begun. The intravenous fentanyl infusion was converted to demand-mode patient-controlled analgesia. An oral tricyclic antidepressant and nonsteroidal anti-inflammatory drug were added to augment her pain control. Daily patient-controlled analgesia fentanyl use was calculated, converted to morphine equivalents, and added to the epidural infusion. Over 2 days the patient experienced significant pain relief. A Du Pen long-term epidural catheter (Davol, Cranston, RI) was therefore placed. The catheter entered the epidural space at L1 with the tip at T10. The patient was discharged home, without pain, receiving 50 mg oral amitriptyline every hour, 500 mg oral naproxen twice daily, and epidural morphine (0.2% solution) at 12 mg/h.

Five days after instituting the epidural morphine, the patient began to experience mild myoclonic contractions of her lower extremities. She had no history of involuntary muscle contractions or seizure. These spasms would last 2–3 s and occurred once every few hours. The myoclonus increased in intensity and frequency over the next few days, by which time the patient was evaluated in the pain clinic. Physical examination results remained unchanged from baseline. Radiographic contrast was easily and painlessly injected through the Du Pen catheter. The catheter tip was confirmed to be in good position on fluoroscopy. Magnetic resonance imaging did not reveal an abscess or mass lesion in her thoracoabdominal spine. Electrolytes, magnesium, and calcium were within the normal laboratory range. Because myoclonus can be associated with use of adjuvant medications, the amitriptyline and naproxen were stopped.

Over the next 9 days, the myoclonic episodes increased in frequency and intensity to the point that she could no longer walk or sleep normally. The myoclonus spasms lasted about 3–5 s and occurred approximately once every 5–10 min. They caused significant pain and were exhausting. She continued to have excellent pain relief in her left arm. Physical examination results remained unchanged. She did not exhibit hypothermia or allodynia, nor did she experience spasms in her upper extremities. The patient was admitted. 14 days after instituting epidural morphine infusion, her control of myoclonus.

A single dose of 0.5 mg oral clonazepam followed by 10 mg diazepam failed to change the character of the myoclonus, although the patient became sedated and was able to sleep. Morphine was discontinued, and epidural hydromorphone (0.1% solution) at 1.5 mg/h was instituted. Intravenous fentanyl patient-controlled analgesia 50 µg/injection, demand only, was started to facilitate the transition of morphine to hydromorphone. The myoclonus resolved 12 h after stopping the epidural morphine infusion.

Over the next few days, the patient's pain recurred and became difficult to control. The epidural hydromorphone dose was increased to 12 mg/h. The fentanyl patient-controlled analgesia was changed to intravenous hydromorphone. Three days after initiating hydromorphone therapy, the lower extremity myoclonus returned. The patient was receiving epidural hydromorphone (1% solution) at 12 mg/h and had self-administered 874 mg intravenous hydromorphone over 24 h. Her laboratory data were unchanged. She also had her physical examination with 5 mg intravenous hydromorphone to decrease the intensity of her pain. Unfortunately, she experienced a seizure the following day.

Postoperatively, the patient complained of double vision and back pain. An infusion of 5 mg/h did not control the postoperative pain well, but the patient tolerated the neck and shoulder pain of 50–150 mg intravenous hydromorphone every 30–45 min as needed in an attempt to avoid the need for nonsteroidal anti-inflammatory drugs or nonsteroidal anti-inflammatory drugs.

These spasms became more frequent with intravenous boluses (1 mg) of morphine. The patient also reported new findings of light sensitivity and myoclonus.

The patient received 100 mg intravenous diazepam every 30 min versus phenytoin three times per day for the past three days. The patient exhibited further seizures, and myoclonus increased significantly to keep the patient from being administered phenytoin every 8 h. The patient was on a phenobarbital protocol. The patient remained on phenobarbital for 2 weeks and was not re-operated, at which time the patient was discharged.

Discussion

Opioid-induced hyperesthesia have been reported in animal models. Mueller et al. examined the etiology of opioid receptor-mediated excitatory and inhibitory responses. Metabolic pathways have been implicated as a mechanism to modulate opioid-induced hyperesthesia. Shiotani et al. showed that morphine is a specific α2 adrenergic agonist and is the receptor with the highest affinity for α2 receptors. The authors concluded that the use of morphine in patients with morbid obesity is associated with increased risk of myoclonus and seizures. The authors also suggested that the use of alternative opioids, such as fentanyl, may be associated with a lower incidence of myoclonus and seizures.

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morphine over 24 h. Her laboratory study results had not significantly changed nor had her physical examination results. The patient was sedated with 5 mg intravenous diazepam every 2 h as needed. This appeared to decrease the intensity and frequency of the myoclonus. The patient underwent a selective dorsal rhizotomy at C4–T3 on the following day.

Postoperatively, the patient complained of severe incisional as well as shoulder and back pain. An intravenous infusion of hydromorphone 50 mg/h did not control the pain. Epidural infusion was associated with intolerable neck and shoulder pain and was discontinued. Boluses of 50–150 mg intravenous hydromorphone were given every 10–15 min as needed in an attempt to control her pain. Nonsteroidal anti-inflammatory drugs were not used because of concern of causing postoperative bleeding. Postoperative myoclonus involved all of her extremities. These spasms became diminished in intensity and frequency with intravenous boluses of 10–30 mg diazepam. The patient also reported new findings of allodynia and hypersensitivity over her face and extremities. After receiving 3,600 mg intravenous hydromorphone and 270 mg diazepam over a 7-h period, the patient experienced a grand mal seizure that responded to 150 mg thiopental divided doses. The patient’s laboratory data were normal. After a brief postictal period, she was awake, alert, and responsive. Phenytoin (1 g) was administered intravenously to prevent further seizure activity.

The patient received 100 mg/h intravenous hydromorphone, 10 mg intravenous diazepam every 2 h as needed, and 100 mg intravenous phenytoin three times daily. The myoclonic jerks continued. She did not exhibit further seizure activity. Because it was becoming increasingly difficult to keep her comfortable, 300 mg intravenous phenobarbital was administered, followed by a dose of 150 mg intravenously every 8 h. The myoclonus decreased in intensity and frequency with the phenobarbital, although it did not resolve completely. The patient remained sedated and comfortable. Cardiac arrest occurred approximately 32 h after starting the phenobarbital therapy. She was not resuscitated at the family’s request.

Discussion

Opioid-induced hyperalgesia, myoclonus, and seizures have been reproduced and extensively studied in animal models. Much controversy, however, surrounds the etiology of this neuroexcitatory. Direct opioid receptor-mediated and nonopioid receptor-mediated excitatory and inhibitory mechanisms have been explored. Metabolic products and preservatives have been implicated as well.

Animal models have demonstrated the reversibility of opioid-induced neuroexcitation by specific opioid agonists. Shoham et al. reported myoclonus from intrathecal morphine in rats, which was partially reversible with intraperitoneal and intrathecal naloxone. Specific 2 agonists morphine and morphicin and 2 agonists-DAla2-D-Leu5-enkephalin (DADL) and Tyr-D-Ala-Gly-Phe-Leu-NH2 (biscuculline) (specific GABA antagonist) can duplicate this allodynia21 or amplify it in hyperalgesia models.

These effects were not blocked with baclofen but were with ketamine and MK-801. Moreover, myoclonus-induced glycine and GABA antagonism is associated with paroxysmal depolarizations in cultured spinal cord neurones.

Armstrong et al. and others have written on the neuroexcitation effects of normeperidine, a metabolic product of meperidine. Glare et al. found plasma normorphine in two patients receiving a large dose of morphine and suggests this metabolite may be responsible for some of morphine’s neurologic side effects. 

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Perhaps a metabolite of hydromorphone, hydromorphone-3-glucuronide\(^{21}\) is neuroexcitatory, as is morphine-3-glucuronide in animal models.\(^{15,20,26}\) It would seem unlikely, however, that a metabolite produced in the liver would produce isolated myoclonus in the lower extremities of patients receiving intraspinal opiates. These metabolites could be implicated with systematically administered opioids, although the parent compounds have their own neuroexcitatory features. Rarely, the preservative sodium bisulphite has been suggested as the cause of myoclonus and seizures when administered with intravenous morphine in large doses.

Our patient experienced lower extremity myoclonus from epidural morphine at 12 mg/h, less than half the dose reported by Parkinson et al.\(^{4}\) and seizure activity from high-dose intravenous hydromorphone. A brain computed tomography scan was not performed; therefore, intracranial pathology cannot be excluded. It seems most likely, however, that the lower extremity myoclonus resolved with discontinuation of epidural morphine and then reappeared with high-dose intravenous hydromorphone, that it was caused by the opioids. Moreover, the isolation of myoclonus to the lower extremities suggests a spinal action of the epidurally administered morphine.

The preliminary attempt to treat this patient’s myoclonus, as suggested by Potter et al.,\(^{27}\) was to discontinue treatment with an antidepressant and nonsteroidal antiinflammatory drug adjuvant medications. This proved ineffective. Benzodiazepine and phenobarbital therapy were useful only at doses that caused profound sedation. Baclofen was not used, but it has been reported to be ineffective at 10 mg orally three times daily.\(^{1}\) Dilantin therapy did not affect the frequency or intensity of the myoclonus, a question raised by Parkinson et al.,\(^{3}\) although no further seizure activity was noted after its institution. In all of the case reports referenced and in our patient, the only means of clinically resolving opioid-induced neuroexcitation has been either to change the type of opioid (perhaps to a nonmorphine-related opioid, as suggested by Sogren et al.)\(^{28}\) or to significantly decrease its dose. This has been accomplished most frequently by decreasing afferent pain impulses through neurolytic procedures or through the addition of intraspinal local anesthetic. In our patient, simply switching from epidural to intravenous opioid administration did not provide resolution of the neuroexcitation. Instead, it changed the character of the neuroexcitation from regional, lower extremity myoclonus to global myoclonus, progressing finally to a grand mal seizure.

The progression of myoclonus to frank seizure activity suggests that these phenomena reside on a continuum. The appearance, therefore, of myoclonus in a patient receiving a large dose of opioids should be considered a sign of possible impending seizure. It would be reasonable to consider using a means of resolving opioid-induced myoclonus. Such therapy may avert the development of a grand mal seizure.

References

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Severe Neurologic Deficit after Nitrous Oxide Anesthesia

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The interaction of nitrous oxide and vitamin B12 is well known from experimental studies in animals and anecdotal clinical reports. Nitrous oxide oxidizes cobalamin in vitamin B12 and disrupts several pathways involved in one-carbon chemistry. The result is an irreversible inactivation of the enzyme methionine synthase, which requires vitamin B12 in the +1 oxidation state to act as its coenzyme. The clinical syndrome associated with oxidation of vitamin B12 develops after prolonged exposure to nitrous oxide and consists of megaloblastic erythroidosis and subacute combined degeneration of the spinal cord. We present the case of a patient who developed a severe neurologic deficit 6 weeks after anesthesia with nitrous oxide.

**Case Report**

A 47-year-old previously healthy former ballet dancer underwent elective cosmetic surgery of the face and scalp. Her preanesthesia assessment disclosed a history of thyroidectomy at age 16 and a remote history of anemia. The patient did not remember the exact indications for the operation or the type of anesthesia that she received in her home country (Russia) but denied any difficulties perioperatively. She denied smoking or alcoholism and claimed to be an occasional vegetarian. There was no history of intake of vitamins or other medications. Her hematocrit was 41% with a mean corpuscular volume of 99 femtoliters (fl., normal 81–99 fl.). The surgical procedure lasted 8 h, during which the patient was anesthetized with fentanyl (200 µg) and isoflurane (0.27–0.7%) in a mixture of oxygen and 70% N2O. Intraoperative blood loss was less than 100 ml. Her intraoperative and immediate postoperative course was uneventful, and she was discharged home in good condition. Six weeks later, the patient was readmitted to the hospital with complaints of paresthesia in the extremities and unsteady gait. On admission, she gave a history of loss of balance, frequent falling, and worsening numbness and weakness.

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