Meperidine-Induced Seizure In A Sickle Cell Patient Using A Patient-Controlled Analgesia Pump

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Meperidine is indicated and frequently used for the relief of moderate to severe pain associated with various disease states and procedures, including sickle cell crisis pain, postoperative analgesia, and migraine headaches. Additionally, the parenteral form is approved for preoperative medication. The use of meperidine for analgesia should not be considered benign. Common adverse reactions caused by meperidine are similar to those found with other narcotic analgesics and include dizziness, sedation, nausea, vomiting, constipation, euphoria, dysphoria, and disorientation. The major hazards with meperidine use include respiratory tract depression, respiratory arrest, shock, and cardiac arrest. Several reports of seizure activity during meperidine therapy have been described.[1-8] This seizure activity is rarely experienced with other narcotic analgesic use. Most of these seizures have occurred in patients with underlying renal insufficiency; however, in four case reports there was documented meperidine-induced seizure activity in patients without renal disease.[5-8] Only one case involved a patient receiving meperidine by means of a patient-controlled analgesic pump.[8] Furthermore, in many of these case reports other causes of seizures were not ruled out.

This case report re-emphasizes the potential for meperidine-induced seizures in patients who have normal renal function while receiving the drug through a patient-controlled analgesic pump. Although this patient did have sickle cell anemia, there was no history of any seizures or other neurological problems.

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Case Report

A 34-year-old black woman with a history of sickle cell anemia was hospitalized for analgesic treatment of a sickle cell crisis and painful tibial cellulitis. This hospitalization was one of many that occurred while she was under the care of the same group of family physicians. The patient was thin and in moderate distress because of her cellulitis and sickle cell crisis. Upon admission her blood pressure was 133/90 mmHg, heart rate 82 beats per minute, temperature 99.9°F, and respiratory rate 22/min. Serum creatinine was 0.4 mg/dL, and blood urea nitrogen (BUN) was 5 mg/dL. All serum electrolytes were within their normal ranges with the exception of a serum bicarbonate level, which was 15 mEq/L. The patient did have an elevated gama-glutamyltransferase (GGT) of 246 U/L and lactic dehydrogenase of 299 U/L, but aspartate aminotransferase was normal at 25 U/L. These elevated enzyme levels were believed to be the result of the vaso-occlusive sickling process and long-term, high-dose acetaminophen intake by the patient as an outpatient. Serum albumin and total protein were also low at 3.1 g/dL and 6.3 g/dL, respectively. The patient had a normal white cell count but was anemic with a hemoglobin of 8.8 g/dL and hematocrit of 25.2 percent.

Upon admission, the patient was prescribed meperidine in doses varying from 50 to 100 mg every 3 to 4 hours to be given either intravenously or intramuscularly. Total meperidine administered as a result of these orders was 750 mg during the course of 33 hours. Additionally, the patient was given fluid therapy with 5 percent dextrose-0.45 percent sodium chloride at a rate of 125 mL/h, promethazine 25 mg intravenously every 4 hours as needed for nausea, co-trimoxazole 240 mg (trimethoprim) orally every 12 hours, and vancomycin 1000 mg intravenously every 12 hours. The latter two agents were prescribed for her tibial cellulitis. The patient's home medications of acetaminophen 650 mg orally every 4 hours, hydrozyurea 500 mg orally

every morning, and doxepin 10 mg orally three times daily were also continued on admission, but acetaminophen with codeine, which had been prescribed for the patient as an outpatient, was not. On hospital day 2, the meperidine administration was changed to a patient-controlled analgesic pump (Bard MedSystems, Harvard PCA device) for improved pain control.

After using the patient-controlled pump for 45 hours, during which time the patient self-administered 3070 mg of meperidine, she had a focal tonoclonic seizure and loss of consciousness. During this seizure the patient became unresponsive for approximately 90 seconds. After regaining consciousness, she remained confused for an additional 3 to 5 minutes and had no memory of the seizure episode. Following the seizure her temperature was 100.2°F, blood pressure 120/74 mmHg, heart rate 68 beats per minute, and respirations 18/min.

The meperidine was immediately discontinued, and analysis of a blood sample obtained 5 hours after the seizure revealed a meperidine level of 0.19 μg/mL and normeperidine level of 0.39 μg/mL. The normal analgesic range for meperidine is 0.1 to 0.6 μg/mL and less than 0.5 μg/mL for normeperidine.

To rule out other neurological causes, she had a computer-aided tomographic scan of her head, which showed no abnormalities. A lumbar puncture revealed no white cells, normal opening pressure, and normal glucose and normal protein levels within the cerebrospinal fluid. An electroencephalogram (EEG) was not ordered. After the meperidine was discontinued, morphine was used for analgesia. No further seizure activity occurred during the remainder of her hospitalization or during the next 6 months.

Discussion

Meperidine appears to have a more rapid onset and shorter duration of action than morphine, which makes it a very appealing analgesic to use.[9] Following intramuscular administration, peak analgesia occurs within 30 to 50 minutes and gradually declines during the next 2 to 4 hours in most patients. Meperidine exerts its seizure activity through its hepatic metabolite, normeperidine.[10-13] Meperidine undergoes extensive first-pass N-demethylation within the liver to yield normeperidine.

Approximately 33 percent of a meperidine dose is excreted in urine in the normeperidine form.[9] Less than 5 percent of a total meperidine dose is excreted unchanged in urine. Normeperidine appears to possess less analgesic activity than its parent compound but 200 percent more propensity toward induction of convulsions.[10] Normeperidine causes a progressive slowing of EEG waves with a subsequent increase in their amplitude.[11] This increased amplitude appears to be the focus for the seizure induction. To complicate matters further, the elimination half-life of normeperidine is four to seven times longer than the half-life of meperidine (14 to 21 hours versus 3.2 to 3.7 hours, respectively) in patients with normal renal function.[4] Additionally, the normeperidine half-life extends up to 34.4 hours in patients with renal dysfunction.[4] Consequently, normeperidine can accumulate in patients with renal disease.

A correlation has been made between meperidine and normeperidine levels and neurologic abnormalities. Researchers have reported cancer patients in which myoclonus or grand mal seizure activity has been attributed to mean plasma normeperidine concentrations of 0.81 μg/mL (range, 0.42 to 1.8 μg/mL).[6] These same investigators noticed tremors or twitching to occur in 18 cancer patients who had mean plasma normeperidine levels of 0.46 μg/mL (range 0.15 to 1.1 μg/mL). Furthermore, our patient was receiving promethazine concurrently in doses ranging from 50 to 150 mg/d, which has been additive in inducing seizures in animal models, although the exact mechanism behind these central nervous system excitory effects is not fully understood.[14] None of the other medications prescribed for the patient has been shown to interact pharmacokinetically with meperidine. Although our patient had a serum normeperidine level (0.39 μg/mL) below the mean normeperidine level for cancer patients who experienced seizures, the blood sample was taken 5 hours after the seizure occurred. By back-extrapolation using linear kinetic modeling, we can assume serum normeperidine concentrations exceeded 0.45 to 0.52 μg/mL in this patient at the time of the seizure.

This patient had received large doses of meperidine in the past both as an inpatient and as an outpatient for relief of sickle cell crisis pain. This admission was the first time, however, that the meperidine was administered by use of a patient-

controlled analgesic pump. This method of administration allowed for larger meperidine doses to be given in shorter time intervals than in previous hospitalizations.

In addition, both renal failure and sickle cell anemia have been linked to increased seizure potential.[15,16] This patient was not known to have any renal compromise, and there was no history of any seizure disorder. There was also no known family history of any seizure disorder.

One further note of caution is that meperidine undergoes extensive first-pass metabolism; therefore, switching from parenteral to oral administration does not lessen the chance for seizure activity. Because oral meperidine is only one-half as potent as parenteral meperidine, the oral route might actually increase the chance of seizures because larger individual doses of meperidine are given. These larger doses will lead to a greater accumulation of normeperidine because of the extensive first-pass metabolism following oral absorption.

Because meperidine has a tendency to excite the central nervous system, especially when used in large quantities, it should be avoided in patients who have underlying renal impairment or patients who have a history of seizures. In our institution it was current practice for a registered nurse working with the anesthesia service to monitor the use of the patient-controlled analgesic pumps. Although cost-effective and practical, this method is, perhaps, not ideal, particularly for patients who have certain underlying characteristics, such as renal insufficiency or a history of seizures. Based upon the work of Shimomura and Harris,[17] even for patients with normal renal function who require greater than 100 mg of meperidine every 2 hours for more than 24 hours, it might be advisable to use other narcotic analgesics, such as morphine or fentanyl.

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