Seizures Following Meperidine Use

Case Study

M.T. is a 28-year-old male with sickle cell anemia who was admitted to the emergency department in sickle cell crisis. His pain affected his lower back, knees, and ankles while “moving from place to place,” aching, and throbbing. M.T. reported his pain, whether resting or moving, as a 10 on a scale from 0–10, with 10 being the maximum level of pain. According to M.T., IV push (IVP) meperidine (Demerol) is the only medication that helps control his pain during a crisis. He listed allergies to morphine, codeine, and prochlorperazine. His past medical history includes five sickle cell crises in the past 12 months. He has no history of seizures or strokes. He takes 1 g of hydroxyurea orally every day to help prevent crises.

His hemoglobin on admission was 8 g/dl, his reticulocytes were 5%, his white blood cell count was 4,000/mm³, and his serum creatinine level was 1.9 mg/dl. His pulse oximetry on room air was 92%, and his chest x-ray was negative. The emergency room physician wrote the following orders and transferred M.T. to the inpatient unit.

• IV of 5% dextrose and 0.45% normal saline at 150 ml/hour
• Meperidine 125 mg IVP every two hours as needed
• Promethazine 12.5 mg IVP every six hours as needed for nausea

M.T. received meperidine every two hours and reported his pain intensity as ranging from 4–9 on the 0–10 scale. Six hours after admission, he was found having a seizure. His seizure was managed with phenytoin (Dilantin®, Parke-Davis, Morris Plains, NY). The meperidine was stopped, and M.T. was started on hydromorphone 4 mg IVP every two hours around the clock with 2 mg IVP every hour for breakthrough pain. His serum meperidine level was 400 ng/ml, and serum promethazine level was 450 ng/ml. M.T. was diagnosed with normeperidine toxicity as a result of receiving 800 mg of meperidine over 12 hours.

Clinical Problem Solving

Responding to this clinical challenge are Chris Pasero, MS, RN, and Margo McCaffery, MS, RN, FAAN. Pasero is a pain management educator and consultant in Rocklin, CA, and McCaffery is a consultant in the nursing care of patients with pain in Los Angeles, CA.

This patient experienced seizures as a consequence of the inappropriate prescribing of meperidine. Why was meperidine a poor choice for this patient, and how should this patient’s pain have been managed?

Meperidine no longer is recommended as a first-line opioid analgesic for the treatment of any pain because its active metabolite, normeperidine, can cause central nervous system toxicity and seizures (Acute Pain Management Guideline Panel, 1992; American Pain Society [APS], 1999; Jacox et al., 1994). This drug is a particularly poor choice for patients with sickle cell disease because they often require doses much higher than the recommended total daily dose of 600 mg and longer than the recommended limit of 48 hours. Furthermore, most patients with sickle cell disease have renal dysfunction and cannot easily eliminate normeperidine. Many also have a low seizure threshold, putting them at even a higher risk for normeperidine seizures (APS).

Promethazine is another poor choice for patients with pain because it does not relieve pain or potentiate opioid analgesia (APS, 1999). In addition, the drug is a poor antiemetic (Ernst, Weiss, Park, Takakuwa, & Diercks, 2000). It also lowers the seizure threshold, making it a dangerous choice in patients with sickle cell disease.

IV hydromorphone is a better alternative for M.T. because the drug has no clinically relevant metabolites. A dose of 2.5 mg hydromorphone is roughly equal to 125 mg of meperidine and can be administered by IVP over 5–10 minutes (Pasero, Portenoy, & McCaffery, 1999). It is often necessary to repeat the bolus dose in patients who are experiencing severe pain. After M.T. achieves a level of comfort, a patient-controlled infusion of hydromorphone can be started to allow him to manage his ongoing pain. A nonsteroidal anti-inflammatory drug, such as ibuprofen or rofecoxib, can be given in scheduled doses around the clock to provide additional analgesia. A dose of ondansetron or dolasetron at the time of the initial bolus dose of hydromorphone can help to prevent nausea (Korttila et al., 1997; Zarate et al., 2000).

Because M.T. believes that only meperidine can relieve his pain, switching to another opioid may cause anxiety. Ideally, the need to avoid meperidine and use another morphine-like opioid should be discussed when the patient is not in crisis (e.g., after a crisis is resolved, during a clinic visit). When the change is made, the clinician must titrate the new analgesic aggressively to convince the patient that it will be effective (Brookoff & Polomano, 1992).

What institutional safeguards can be put in place to prevent the inappropriate use and prescribing of meperidine?

The use of meperidine should be limited to patients who are otherwise healthy and allergic to or intolerant of first-line opioid analgesics, such as morphine, hydromorphone, and fentanyl (Acute Pain Management Guideline Panel, 1992). The dose of meperidine should be limited to 600 mg in a 24-hour period and administered for no more than 48 hours (APS, 1999). In patients who are at risk for normeperidine accumulation, nurses should...
assess for central nervous system toxicity (e.g., restlessness, shakiness, tremors, twitching, jerking) every eight hours (Pasero et al., 1999). If these symptoms are present, the patient should be switched immediately to another mu agonist (morphine-like) opioid.

Several institutions have successfully reduced the use of meperidine by implementing some simple approaches. For example, the dangers and liability of prescribing meperidine (Waitman & McCaffery, 2001) can be taught during continuing-education programs, in medical newsletters, and through form letters generated by pharmacies when physicians prescribe the drug. Providing preprinted physician’s orders that offer only appropriate first-line opioids is another effective method for reducing meperidine use.

Emergency departments can use a multidisciplinary approach to establish evidence-based protocols for managing patients with recurring pain, such as those with sickle cell disease. By mandating the use of appropriate analgesics and doses, protocols promote optimal, efficient, and cost-effective pain management. In addition, triaging patients with severe pain to high priority status can help ensure their pain is brought under control within acceptable time frames (e.g., within one hour).

References


Clinical Highlights: Norineperidine Neurotoxicity

**Definition:** Accumulation of normeperidine, an active metabolite of meperidine, can lead to potentially life-threatening neurotoxicity, including seizures.

**Pathophysiology:** Meperidine is transformed into the neurotoxic metabolite, normeperidine. The half life of normeperidine (15–30 hours) is longer than that of meperidine (2–3 hours); therefore, repeated administration of meperidine can lead to the accumulation of normeperidine, even in patients with normal renal function (Pasero, Portenoy, & McCaffery, 1999). Because urinary excretion is the primary route of elimination for meperidine and its metabolite, renal dysfunction can increase the accumulation of normeperidine in the plasma. Accumulation of normeperidine can result in central nervous system excitatory effects, including tremors, seizures, coma, and death.

**Incidence:** Unknown.

**Possible risk factors:** Meperidine doses greater than 600 mg over 24 hours or use of meperidine for more than 48 hours (American Pain Society [APS], 1999), history of seizures or increased risk for seizures related to the disease process or medications (e.g., phenothiazines, imipenem), renal dysfunction, elderly patients or patients younger than six months.

**Prevention:** Risk of normeperidine neurotoxicity can be reduced by limiting meperidine doses to less than 600 mg over 24 hours and limiting the use of meperidine to less than 48 hours (APS, 1999). The healthcare team should avoid its use in patients with known risk factors.

**Clinical findings:** Anxiety, hallucinations, decreased level of consciousness, agitation, illusions, restlessness, seizures, shakiness, multifocal myoclonus, tremors, confusion, grand mal seizures, coma, and death (Kaiko et al., 1983; McCaffery & Pasero, 1999).

**Differential diagnosis:** Medication reactions and neurologic changes from disease processes (e.g., stroke, central nervous system metastases).

**Treatment:** If meperidine toxicity is suspected, halt meperidine administration. Substitute another mu agonist (morphine-like) opioid for meperidine to relieve pain, allow the normeperidine level to drop, and prevent opioid withdrawal. Manage seizures with anticonvulsants. Protect the patient from physical injury if the patient is confused, agitated, or having seizures. Serum meperidine and normeperidine levels may help aid in the diagnosis. Naloxone (Narcan®), Endo Pharmaceuticals, Chadds Ford, PA) and other opioid antagonists do not reverse the neurotoxicity from normeperidine (Kaiko et al., 1983), and, in fact, they may increase seizure activity by reversing the depressant effect of meperidine.

For additional information regarding meperidine prescribing guidelines, visit www.wisc.edu/wcp/prof/inguide.htm, the University of Wisconsin Hospitals and Clinics’ Web site for Guidelines for the Use of Meperidine.


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