Meperidine (Demerol®) safety issues

By Christine Koczmar, RN, BScPsy, Dan Perri, BScPhm, MD, FRCPC, Sylvia Hyland, BScPhm, MHSc(Bioethics), and Lin Rousseaux, RN, BA SDS

There is a move in hospitals to restrict the use of meperidine as a result of adverse events such as neurotoxicity from the normeperidine metabolite, delirium in elderly patients, and serotonin syndrome. In addition, reports of medication errors with meperidine have prompted a review of its place in therapy. In this column, we will review the safety of meperidine for a variety of indications in critical care and help to identify those patients at high risk of adverse events. We also provide recommendations and strategies to reduce the risks associated with meperidine use in hospitals and critical care units.

Background

Meperidine (Demerol®) was synthesized 65 years ago as an anticholinergic agent (ASHSP, 2002; Latta, Ginsberg & Barkin, 2002). Preliminary clinical use led to the discovery of its analgesic properties that were initially perceived to be more favourable than morphine. Meperidine became a commonly used analgesic that remains in general clinical use today, even though its perceived benefits over other opioids have never been clearly demonstrated (Latta et al., 2002).

Medication errors

In 2002, MedMARx, a national database in the United States, received reports of 1,528 errors related to meperidine (Borden, 2002). Numerous substitution errors involving meperidine/morphine and meperidine/hydromorphone have been published (ISMP, 2002; ISMP, 2003; U, 1999; USP, 1995). A fatal mix-up occurred in a Canadian hospital in June, 1998 when an 11-month-old infant was mistakenly administered morphine 10 mg instead of meperidine 10 mg after elective surgery (U, 1999). Another sentinel event occurred in a post-operative patient who was inadvertently ordered and administered Dilaudid® (hydromorphone) 50 mg IM instead of Demerol 50 mg IM (USP, 1995). The patient suffered permanent anoxic brain damage from the ensuing narcotic-induced respiratory arrest (USP, 1995). In 2002, ISMP Canada received an error report of morphine 25 mg IV administration in response to a verbal order of “Demerol 25 mg IV” (ISMP, 2002). The patient was harmed as a result of the error. Patient acuity and urgency of the clinical situation, a scenario common to critical care environments, is often cited as a contributing factor to such errors.

Normeperidine neurotoxicity

The following preventable adverse event was reported to ISMP Canada (ISMP, 2004):

A patient who had been taking meperidine 200 mg orally every four hours for acute pain was admitted to hospital and the same dose was continued intramuscularly. Shortly after admission, the patient developed disorientation and confusion, initially attributed to the presenting medical condition. Meperidine 200 mg IM q4h continued to be given for approximately 48 hours. On the third day, the patient experienced a grand mal seizure and was transferred to the intensive care unit. The accumulation of the active meperidine metabolite, normeperidine, was suspected as the cause of the seizure. Within 48 hours of discontinuing meperidine, the confusion and disorientation resolved and the patient subsequently recovered without further incident.

In this case, the 48 hour maximum for meperidine duration of administration and the maximum dosage of 600 mg meperidine per day were exceeded (AHCPR, 1994; APS, 2003; ICAHO, 2001). When converting from the oral to the parenteral route, doses should be reduced (the bioavailability of oral meperidine is 40 to 60%) (CPA, 2004). Institutions are removing oral meperidine from formularies because of the poor bioavailability, increased risk for normeperidine toxicity with higher oral dosing requirements, potential for error when converting to parenteral dosage forms, and on increased awareness that meperidine is a poor analgesic for chronic pain.

Repeated administration of meperidine can lead to an accumulation of normeperidine and predispose patients to neurotoxicity (ASHSP, 2002; Jirak, 1992; Latta et al., 2002; Waitman, McCaffery, & Pesaro, 2001). Two different hepatic pathways metabolize meperidine with the most clinically significant result of conversion to normeperidine (CPA, 2004; Latta et al., 2002). Normeperidine has half the analgesic potency of meperidine, but has two to three times the neurotoxic potential (Latta et al., 2002). It is excreted by the renal system with a half-life of 14 to 48 hours. The half-life is prolonged in patients with renal dysfunction (Latta et al., 2002). Normeperidine toxicity is often under-recognized (Latta et al., 2002). Doses as low as 260 mg per day have been reported to cause grand mal seizures and doses as low as 46 mg per day have been reported to elicit muscle twitches or tremors, suggesting wide variability and

<table>
<thead>
<tr>
<th>Table One:</th>
<th>Signs and symptoms of normeperidine toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>Agitation</td>
</tr>
<tr>
<td>Tremors</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Muscle twitches</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Disorientation</td>
<td>Grand Mal Seizures</td>
</tr>
</tbody>
</table>

(Note that some of these signs can be misinterpreted as inadequate pain management and lead to further meperidine administration.)

| Table Two: Ideal characteristics of opioids for administration in critical care |
|-----------------------------------------------|-----------------------------------------------|
| Effective analgesic properties               | No accumulation of active metabolites         |
| Low side-effect profile                     | Cost-effective                                |
| Rapid onset of action                       |                                              |
unpredictability of patient response (Latta et al., 2002). Table One outlines the clinical presentation of normeperidine toxicity.

Monitoring for normeperidine toxicity is required for patients who receive meperidine, particularly after repeated administration (Hagmeyer, Mauro, & Mauro, 1993; Waitman et al., 2001). In addition to monitoring for signs and symptoms of toxicity, if patients are able, ask them to extend their arms and check for tremors and ask patients if they are experiencing any involuntary jerking or twitching movements, particularly when sleeping (Simopoulos, Smith, Peeters-Asdourian, & Stevens, 2002; Waitman et al., 2001).

**Increased risk of delirium with meperidine use in elderly patients**

It has been shown that meperidine is poorly tolerated in the elderly and is the narcotic most often associated with delirium in the geriatric surgical population (Marcantonio et al., 1994). Meperidine can predispose patients to delirium due to its anticholinergic properties, and the risk of normeperidine neurotoxicity with renal function changes with age (Latta et al., 2002).

**Serotonin syndrome**

Meperidine possesses complex pharmacodynamics not found with first-line opioids including the inhibition of the re-uptake of the neurotransmitter serotonin. This can lead to serotonin syndrome (Hubbard & Wolfe, 2003), which is a potentially fatal condition that presents with mental status changes, myoclonus, muscle rigidity, tremors, diaphoresis, and hyper-reflexia. It occurs as a result of excessive serotonin levels, usually resulting from interactions between drugs that increase serotonin levels. Given the “striking” similarity to the signs and symptoms of normeperidine toxicity, serotonin syndrome should be considered in the differential diagnosis of normeperidine toxicity (Ener, Meglathery, Van Decker, & Gallagher, 2003; Latta et al., 2002). Treatment includes discontinuation of serotonergic agents “with 70% of patients recovering within 24 hours, 40% requiring ICU admission, and 25% requiring intubation” (Ener et al., 2003, p.66). Serotonin syndrome can progress to severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation and life-threatening tachyarrhythmias (Ener et al., 2003). Fatal outcomes due to serotonin syndrome have occurred when even a single dose of a monoamine oxidase inhibitor was ingested within 14 days of meperidine administration (CPA, 2004; Hubbard & Wolfe, 2003; Latta et al., 2002).

**Meperidine use in critical care**

Meperidine does not possess many of the ideal characteristics of an opioid for administration in critical care as outlined in Table Two (Jacobi et al., 2002). Critically ill patients are particularly at risk for meperidine-related adverse events due to their comorbidities and the need for multiple medications (see Table Three).

A stated allergy to morphine (or other opiates) may lead to meperidine use. However, immune-mediated allergy to

---

**Table Three:**

<table>
<thead>
<tr>
<th>Critical care patient attributes and risk of meperidine adverse events</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Renal dysfunction/ insufficiency (patients with ↓ cardiac index are at risk (e.g., MI, septic shock)</td>
<td>↑ risk of normeperidine toxicity</td>
</tr>
<tr>
<td>2. Require doses exceeding 600 mg/ 24 hours for adequate pain relief</td>
<td>↑ risk of normeperidine toxicity</td>
</tr>
<tr>
<td>3. Require pain therapy beyond 48 hours</td>
<td>↑ risk of normeperidine toxicity</td>
</tr>
</tbody>
</table>
| 4. Drug history may include:  
  - overdose/ recent use of stimulants such as amphetamines, cocaine (↑ serotonin levels)  
  - alcohol withdrawal | ↑ risk of serotonin syndrome  
  ↑ risk of seizures (normeperidine further reduces threshold) |
| 5. Seizure disorders | ↑ risk of seizures (normeperidine further reduces seizure threshold) |
| 6. Concomitant medications that reduce seizure thresholds (e.g., neuroleptics [haloperidol], fluoroquinolones [ciprofloxacin]) | ↑ risk of seizures (cumulative effect on reducing seizure threshold) |
| 7. Increased age | ↑ incidence of delirium |
| 8. Concomitant medications that increase serotonin levels:  
  - by monoamine oxidase inhibition (e.g., phenylzine, tranylcypromine) (Should not be administered within 14 days of one another due to synergistic effect)  
  - other medications which lead to increased serotonin levels (e.g., SSRIs [Selective Serotonin Reuptake Inhibitors], venlafaxine, tricyclic antidepressants, dextromethorphan, “triptane” migraine medicines) | ↑ risk of serotonin syndrome  
 ↑ risk of serotonin syndrome |
opioids is rare and, often, what is stated as an allergy, may be an intolerance or a histamine-related side effect (Anibarro, Vila, & Seoane, 2000; CPA, 2004; Tucker, 2002). Communication of allergy information has been identified as a general problem in health care (Netescu, Hunt, & Teeters, 1998). Therefore, careful history taking, documentation and communication of findings related to past adverse reactions is imperative to ensure the safest and most effective pain management treatments are used. Fentanyl can be considered as an alternative to meperidine in patients with a true allergy to phenanthrenes (like morphine, codeine, hydromorphone, or hydrocodone).

Despite longstanding anecdotal use of meperidine (e.g., for Sphinicter of Oddi dysfunction), there is no more benefit with its use when compared to other opioids at equianalgesic doses for biliary colic (Latta et al., 2002; Lee & Cundiff, 1998), pancreatitis (Latta et al., 2002) or renal colic (O’Connor, Schug, & Cardwell, 2000). The potential for neurotoxicity and anticholinergic effects with repeated administration makes meperidine an inferior choice in many conditions, including Sickle Cell (APS, 2003; Latta et al., 2002).

Meperidine is not recommended for patient controlled analgesia (PCA) since the maximum dosage can easily be exceeded leading to normeperidine-related neurotoxicity and seizures (Hagmeyer et al., 1993; Seifert & Kennedy, 2004). In a 12-month study, researchers at a university hospital reviewed 185 charts of patients taking meperidine who were at high risk for seizures (Hagmeyer et al., 1993; Seifert & Kennedy, 2004). The study found that 14% of patients experienced an adverse drug reaction and 80% of these patients had received meperidine by PCA. The researchers found that dosages were poorly documented and believe that such adverse events are under-reported.

In a six-year study of 5,432 patients who had received PCA at a university hospital, 412 patients were administered PCA meperidine due to history of allergy or new onset adverse reaction to PCA morphine (Simopoulos et al., 2002). Researchers found a 2% rate of CNS toxic reactions in those patients despite the long-standing use of a pain service and active promotion of meperidine safety initiatives. They concluded that adverse events were related to dosage and length of time meperidine was administered (Simopoulos et al., 2002).

The use of meperidine to treat shivering and rigors, however, is one of the few indications where the benefits of treatment may outweigh the risks. The mechanism of action for meperidine treatment of shivering is complex and not fully understood. It includes a multifaceted interaction of the thermoregulatory centre in the hypothalamus, CNS receptors (muscarinic, opioid) and neurotransmitters (serotonin, norepinephrine, dopamine) in the ascending and descending CNS pathways (De Witt & Sessler, 2002). When compared to other opioids at equianalgesic doses, meperidine possesses distinct and effective anti-shivering properties. Shivering is a post-operative complication that may require pharmacological treatment to reduce complications such as increased metabolic and oxygen demand, increased intracranial pressure, generalized discomfort, and increased surgical site pain (Kranke, Eberhart, Roewer, & Tramier, 2002). In a 2002 review of placebo-controlled trials of pharmacological interventions for treatment of shivering, meperidine was shown to be one of the most effective agents.

Table Four: Recommendations for meperidine safety (AHCPR, 1994; APS, 2003; JCAHO, 2001)

1. Remove oral meperidine from the hospital formulary.

2. Review and revise pre-printed order sets to discourage the use of meperidine.

3. Restrict the use of meperidine to:
   a. the prevention and treatment of drug-induced or blood product-induced rigors (e.g., amphotericin B, platelets),
   b. treatment of post-operative shivering, and
   c. short-term pain management in individuals with normal renal, hepatic and CNS function
      where alternative opioids are contraindicated (e.g., allergy), and
      i. do not exceed 600 mg/24 hours,
      ii. limit the duration of use to 48 hours.

4. Avoid use of meperidine in elderly patients since adverse effects are associated with increasing age.

5. Consider an automatic review by a pharmacist (e.g., clinical ICU pharmacist) of meperidine orders to verify that the daily dose and duration of therapy comply with recommended guidelines.

6. Have information about meperidine restrictions, maximum dosing, treatment duration, and signs of toxicity readily available at the point of care (e.g., monitoring forms, guidelines).

7. On an ongoing basis, evaluate the contents of narcotic stock to assess which products and which concentrations should be readily available. Review of narcotic stock can also identify if look-alike packaging might pre-dispose to medication errors. If so, the pharmacy department can assist with error-prevention strategies.

8. Implement an Acute Pain Service to promote best practices.

9. Make pain management care (i.e., best practice guidelines for use of analgesia and sedatives) a priority for critical care practitioners. Include discussions of error reports (including external reports and near-miss reports) in education programs to promote a safe culture.
Recommendations for meperidine safety
ISMP Canada recommends health care facilities evaluate their use of meperidine to improve its safety as outlined in Table Four.

Conclusion
The use of meperidine in pain management should be restricted, and careful evaluation of the risk-benefit ratio should be made before it is used in any critically ill patient. In the United States, there has been a move away from meperidine use (APS, 2003; Gordon, Jones, Goshman, Foley, & Bland, 2000; Latta et al., 2002). The Joint Commission on Accreditation of Health Care Organizations published pain management guidelines (JCAHO, 1999), standards (JCAHO, 2001), and quality indicators (JCAHO, 2003) that discourage the use of meperidine. The pain guidelines were based on a two-year collaboration with the University of Wisconsin-Madison (UW-Madison. 2002) and previous guidelines, including those by the Agency for Health Care Policy and Research (AHCPR, 1994) and the American Pain Society (APS, 2003). Many U.S. organizations now view meperidine use as an inverse indicator of quality of care (Gordon et al., 2000; JCAHO, 2003; Pelligrini, Paice, & Faut-Callahan, 1999).

About the authors
Christine Kozmara, RN, BScPsy, is a staff member at ISMP Canada. She also holds a part-time position as a bedside nurse in the intensive care unit (ICU) at St. Joseph’s Health Centre, Toronto. Dan Perri, BScPhm, MD, FRCPC, is a drug safety fellow at ISMP Canada and is undertaking combined subspecialty fellowships in clinical pharmacology at the University of Toronto and critical care medicine at McMaster University. Sylvia Hyland, BScPHM, MHSc (Bioethics), is vice-president of ISMP Canada. She is also a member of the pharmacy department at both Sunnybrook and Women’s College Health Sciences Centre and University Health Network, Toronto, Ontario. Lin Rousseaux, RN, BA SDS, CON(C), is in private practice.

References


references continued on page 12...


Question to the Board

Why should I become certified in critical care?

CACCN response:

Nurses working in critical care areas face ongoing challenges with new treatments and technology, different modalities in the delivery of health care, and the vast diversity in the patient population. They also have to deal with the increased acuity of the patients, the ongoing nursing shortage, and budget shortfalls. As health care providers in this specialty area, we need to increase our scope of knowledge and competence in order to provide the level of safe and effective care required by our patients.

Certification is a voluntary endeavour which nurses pursue to build on their basic knowledge and clinical skills. Acquiring certification demonstrates a nursing commitment to career development and dedication to patient care. It increases competency in skills, accountability, confidence and self-esteem. A nurse who has met the national standards of practice through certification validates that they have the specialized knowledge, skills, clinical judgment and experience to care for the most vulnerable and sickest of patients.

From the clinical editor

In this issue of *Dynamics: The Official Journal of the Canadian Association of Critical Care Nurses* we are pleased to publish three original articles and our regular ISMP column.

Fu discusses a possible alternative treatment for constipation among critically ill patients: neostigmine. Fu describes how neostigmine was used to treat acute colonic pseudo-obstruction in a patient with ALS. This medication is not without risk and side effects, however, and precautions should be taken. This treatment may have important implications for clinical nursing practice.

A nursing practice frequently observed in critical units, especially with intubated patients, is the practice of using restraints to prevent patients from injuring themselves (e.g., self-extubation). Hurlock-Chorostecki and colleagues looked at the recent literature to discover whether this practice was well-grounded. Their literature search revealed some surprises and led the authors to develop their own innovative program: *Knot So Fast*.

Critical care nursing has long been recognized as a specialty nursing area. The acquisition of the required knowledge and skills to practise in this area is an important topic. Pooler et al. describe a unique partnership that is occurring in Alberta to prepare critical care nurses and meet the needs of employers for critical care nurses.

Finally, we would like to run a regular column that includes a review and critique of a recent research article on any topic in critical care nursing. We know there are many journal clubs active across the country as well as many nurses taking courses and programs where critiquing research articles is a necessary activity. Why not publish some of the work you are doing. Look for our Call for Research Reviews in this issue.

Glenda Roy, CNCC(C), CCN(C), Treasurer, CACCN BOD

Paula Price, RN, PhD, Clinical Editor