Demerol: Is It the Best Analgesic?

One of the most commonly used opioid analgesics on the market is meperidine (DEMEROL). Eisendrath, et al., claimed in 1987 that meperidine was the most widely used opioid analgesic in the US, prescribed by approximately 60% of physicians for acute pain and by 22% for chronic pain.2 Of the top 10 drugs mentioned by general surgeons in 2004, based on projected data from a survey of general surgeons, Demerol injection was third on the list.3

Meperidine is considered to be an inappropriate medication for patients over the age of 65 based on the Beers criteria,4 yet a 2006 study that examined the use of meperidine in patients over the age of 65 in two urban hospitals found that meperidine was administered to approximately one in eight older surgical patients at both institutions. In addition, surgical patients were more likely than medical patients to receive a dose of meperidine.5

Meperidine was initially produced in 1939 for its anticholinergic effects, but its analgesic properties were discovered soon thereafter. Morphine, at that time, was associated with many problems such as constipation, urinary retention, potential for dependency and respiratory depression while meperidine was thought to be an analgesic without these problems.6 But initial studies demonstrating the analgesic efficacy of meperidine were mostly case reports and not double-blind, randomized, controlled trials in specific populations. Subsequent comparative studies failed to demonstrate any advantages of meperidine over comparable doses of other analgesics.7 In fact, studies found that the analgesic effects of meperidine are not pronounced, and that meperidine has unique side effects including serotonergic crisis and toxicity by its metabolite, normeperidine.

Central Nervous System Effects
Meperidine is a phenylpiperidine opioid agonist analgesic with anticholinergic, serotonergic, and noradrenergic effects. Meperidine is metabolized in the body by two different pathways. The predomi-
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on the floor, face down and seizing. The patient was not responsive to verbal or physical stimuli, was turned over and placed in bed. Oxygen was applied and the patient slowly began responding after 3-5 minutes. Patient had a suspected history of seizures possibly associated with higher doses of Demerol.

A patient was ordered meperidine 100 mg I.M. every 3 hours as needed. Over a period of three days the patient received a total of 1900 mg of meperidine, which led to the patient developing seizures.

After receiving meperidine for a procedure, the parents of a pediatric patient reported to the recovery room nurse that the patient was twitching. They stated that the patient was not doing this before. The nurse observed rapid eye movement and seizure-like head movements. The patient’s arms were rigid and he was unable to extend his arms voluntarily, but was able to follow verbal commands. Approximately 30 minutes later no seizure like activity noted.

Clinically, the predominant side effect that differentiates meperidine from the other opioids is its neurotoxicity. Meperidine has been implicated in “Serotonin Syndrome.” Serotonin Syndrome (SS) is thought to be caused by high levels of serotonin (5-HT) in the CNS. Most cases of SS reported in the literature were associated with patients taking two or more medications that increase CNS serotonin levels by different mechanisms such as monoamine oxidase inhibitors (MAOI) used in conjunction with meperidine, tricyclic antidepressants, or Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants. Examples of commonly used SSRI antidepressants, also known as 5-HT-selective reuptake inhibitors, include fluoxetine (PROZAC), paroxetine (PAXIL), sertraline (ZOLOFT), and citalopram (CELEXA).

Common symptoms of SS that are similar with toxicity due to normeperidine evident in adverse drug reaction reports involving meperidine submitted to PA-PSRS include: altered mental status, agitation, shaking, tremors, dystonic cramping in legs, and restlessness. A more extensive list of common SS symptoms is presented in Table 1.

The Institute for Safe Medication Practices (ISMP) has reported on a case in which a 59-year-old woman experienced Serotonin Syndrome after meperidine PCA was discontinued due to hallucinations and agitation. When her symptoms worsened with IV lorazepam, a pharmacist investigated treatment options for what he thought was normeperidine metabolite accumulation, but he could find little information. He then called the Poison Control Center. After learning that the patient also was taking ZOLOFT (sertraline), Poison Control suggested that the patient might be suffering from Serotonin Syndrome. The nurse confirmed that the patient had several telltale symptoms (hyperreflexia, diaphoresis, diarrhea, disorientation, confusion, hallucinations). Cyproheptadine 4 to 8 mg orally every four hours was recommended, and the patient improved dramatically within the next several hours after receiving the drug.

In a study to determine the cumulative doses of opioid agonists, Walker and Zacny called meperidine the most intoxicating of the narcotics tested. Meperidine had the largest mean peak ratings of “confused,” “high,” “drunk,” “floating,” “coasting,” and “difficulty concentrating.” They stated that meperidine had the most intense effects, but they were short lived, lasting approximately 5 minutes.

Another problem with meperidine is the anticholinergic effect of meperidine owing to its blockade of muscarinic/acetylcholine receptors. Common side effects of anticholinergics include blurring of vision, constipation, agitation, confusion, delirium, and disorientation.

Analgesic Effects

Despite its popularity as an analgesic, numerous studies have shown the ineffectiveness of meperidine compared to other medications used for pain relief. Austin, et al., demonstrated the limitations of a scheduled dose of 75 mg of meperidine every 6 hours, with patients not achieving significant levels of pain relief for more than 24 hours after surgery. During the initial post-dose 4-hour period, patients only received partial pain relief for 30 minutes.

In a comparison of three equipotent doses of meperidine with morphine delivered via PCA,
Plummer, et al., found that the level of analgesia at rest following major abdominal surgery provided by both drugs was similar, but that on movement morphine provided better analgesia at the three doses that were compared in the study.\textsuperscript{15}

In another PCA study, Bahar, et al., noted that overall pain relief was similar, but that pain on movement, after deep inspiration or coughing, and at rest was better with morphine than meperidine.\textsuperscript{16} Vetter demonstrated in children using PCA devices that morphine produced significantly better pain scores than meperidine with no difference in the side-effect profiles. Further, the anxiolytic effect of morphine reduced the distress and suffering of the children when compared with meperidine.\textsuperscript{17}

Jasani, et al., compared the therapeutic effects of 50 mg of meperidine to 1 mg of HYDROmorphone for the treatment of ureteral colic and demonstrated that with HYDROmorphone, patients needed fewer breakthrough medications (31\% versus 68\%), fewer intravenous pyelograms (28\% versus 54\%), and fewer hospital admissions (25\% versus 49\%). This study also reported improved analgesia with HYDROmorphone. Clinically, patient outcomes were significantly better with HYDROmorphone, and it provided more cost-effective treatment.\textsuperscript{18}

In a study comparing the analgesic efficacy of IM doses of ketorolac, meperidine, and placebo after major orthopedic surgery, DeAndrade, et al., showed that ketorolac was significantly more effective than meperidine in duration of action and in the number of patients requiring additional medication 6 hours after the first dose. In addition, ketorolac was associated with significantly lower percentages of patients reporting adverse drug events.\textsuperscript{19}

Not only has meperidine been shown to be an inferior analgesic compared to other opioids; it is also characterized by a limited duration of action. This effect may have some utility for short-duration procedures but is less than optimal for treating situations in which pain is of longer duration.\textsuperscript{20}

**Conclusion**

Given the reports in the literature, its potential for seizures, its effects on the central nervous system, and its anticholinergic effect, meperidine may not be the optimal analgesic for the treatment of pain. The euphoric effects are reported to be more pronounced than with other analgesic agents, and it is the only agent associated with negative effects on mood. It has been shown to be a less effective analgesic than other agents with a capacity to cover mild to moderate pain.

The anticholinergic effect decreases the amount of secretions and thus enhances endoscopic procedures, and if used for moderate pain for less than 24 hours, practitioners can avoid the side-effect profile. The use of meperidine requires careful patient selection, since the Beers criteria classifies it as an inappropriate medication for individuals over 65 years of age. In addition, its use requires vigilant monitoring for neuron-excitative effects and tracking of dosage to reduce the risk of

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**Table 1. Symptoms Associated with Serotonin Syndrome**

<table>
<thead>
<tr>
<th>Mental status change</th>
<th>Motor Abnormalities</th>
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<tbody>
<tr>
<td>Confusion (51%)</td>
<td>Myoclonus (58%)</td>
</tr>
<tr>
<td>Agitation (34%)</td>
<td>Hyperreflexia (52%)</td>
</tr>
<tr>
<td>Hypomania (21%)</td>
<td>Muscle rigidity (51%)</td>
</tr>
<tr>
<td>Anxiety (15%)</td>
<td>Restlessness (48%)</td>
</tr>
<tr>
<td>Coma (29%)</td>
<td>Tremor (43%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Ataxia/ incoordination (40%)</td>
</tr>
<tr>
<td>Sinus tachycardia (36%)</td>
<td>Shivering (26%)</td>
</tr>
<tr>
<td>Hypertension (35%)</td>
<td>Nystagmus (15%)</td>
</tr>
<tr>
<td>Hypotension (15%)</td>
<td>Seizures (12%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
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<tr>
<td>Nausea (23%)</td>
<td></td>
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<tr>
<td>Diarrhea (8%)</td>
<td></td>
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<tr>
<td>Abdominal pain (4%)</td>
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<tr>
<td>Salivation (2%)</td>
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*Source: U.S. Pharmacist. Reprinted with permission.*
neurotoxicity, as well as awareness of concomitant or recent use of serotonergic drugs to prevent potentially fatal drug interactions.

Since other opioid agonist analgesics have similar analgesic efficacy, lower risk of neurotoxicity at usual therapeutic doses, and lower risk for Serotonin Syndrome due to drug interactions, your facility may want to consider limiting the use of meperidine to those situations in which the benefits outweigh the risks.

Notes
The Patient Safety Authority is an independent state agency created by Act 13 of 2002, the Medical Care Availability and Reduction of Error (“Mcare”) Act. Consistent with Act 13, ECRI, as contractor for the PA-PSRS program, is issuing this newsletter to advise medical facilities of immediate changes that can be instituted to reduce serious events and incidents. For more information about the PA-PSRS program or the Patient Safety Authority, see the Authority’s website at www.psa.state.pa.us.

ECRI is an independent, nonprofit health services research agency dedicated to improving the safety, efficacy and cost-effectiveness of healthcare. ECRI’s focus is healthcare technology, healthcare risk and quality management and healthcare environmental management. ECRI provides information services and technical assistance to more than 5,000 hospitals, healthcare organizations, ministries of health, government and planning agencies, and other organizations worldwide.

The Institute for Safe Medication Practices (ISMP) is an independent, nonprofit organization dedicated solely to medication error prevention and safe medication use. ISMP provides recommendations for the safe use of medications to the healthcare community including healthcare professionals, government agencies, accrediting organizations, and consumers. ISMP’s efforts are built on a non-punitive approach and systems-based solutions.