EDITORIAL

Is Meperidine the Drug That Just Won't Die?

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ABBREVIATIONS CYP, cytochrome P450; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor

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Meperidine, the first synthetic opioid, was developed by German chemists as an antispasmodic; its analgesic properties were not identified until several years later in 1939.[1] Its rapid onset, short duration of action, and potential antispasmodic benefit in patients with pancreatitis or cholecystitis have long been cited as reasons for its use, but there is now substantial evidence that meperidine provides no greater analgesia or antispasmodic effect

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than other opioids. Over the past quarter century, a growing number of case reports and clinical studies describing meperidine's adverse effects have changed opinion on the role of this drug in clinical practice. The rapid onset and short duration, initially thought to be of benefit in providing prompt analgesia, are now believed to result in more rapid development of tolerance and dependence than that seen with other opioids. The ability of meperidine to inhibit dopamine and norepinephrine transporters, similar to cocaine, may not only be responsible for its greater euphoric effect and negative effects on cognition, but may also lead to a greater likelihood for abuse.[2] In addition to these drawbacks, meperidine inhibits the presynaptic uptake of serotonin, placing patients at risk for serotonin syndrome, especially in those patients receiving concomitant therapy with a selective serotonin reuptake inhibitor (SSRI), monoamine oxidase inhibitor (MAOI), linezolid, or other compounds that increase serotonin concentrations.

The most significant risk from meperidine, however, lies with its elimination. Meperidine is metabolized by N-demethylation via cytochrome P450 (CYP) 2B6, CYP3A4, and CYP2C19 to normeperidine, a potential neurotoxin.[3] Both meperidine and normeperidine are then hydrolyzed to inactive meperidinic acid and normeperidinic acid. These metabolites undergo conjugation with glucuronic acid. All metabolites, as well as a small percentage of the parent compound, are excreted in the urine. While the half-life of meperidine is only 2 to 5 hours, the normeperidine metabolite has a half-life of approximately 15 to 30 hours in adults. The half-life in patients with renal impairment is prolonged, up to 35 to 40 hours. With repeated dosing, or in patients with kidney disease, accumulation of normeperidine may produce anxiety, hallucinations, tremors, myoclonus, and seizures.

Little is known about the risk for normeperidine accumulation in pediatric patients. In 1978, Caldwell and colleagues[4] reported a slow rate of normeperidine accumulation in infants whose mothers received meperidine during delivery, possibly the result of a reduced rate of hepatic metabolism at birth. That report was supported by the work of Pokela and colleagues,[5] who found an average meperidine half-life of 10.7 hours in their sample of 21 infants.[5] With age, however, the rate of metabolism rapidly increases. In a study by Hamunen and colleagues[6] of 20 4- to 8-year-old children, meperidine pharmacokinetic parameters were found to be similar to those reported in adults, with an average half-life of 3.0 hours. Unfortunate-

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ly, normeperidine concentrations were not evaluated in either of those studies. Although we lack information about normeperidine pharmacokinetics in children, it may be assumed that any infant or child with renal dysfunction, or those treated with large doses or over a prolonged period of time, would be at risk for accumulation. Cases of normeperidine toxicity have been reported in patients of all ages, including children. It should be kept in mind, however, that neurotoxicity may be particularly difficult to assess, as early symptoms of anxiety and hallucinations are likely to be missed in preverbal and nonverbal patients and tremor or seizures may be ascribed to other causes.[7–10]

Despite its relative lack of benefit compared to other opioids and increasing reports of toxicity, meperidine continues to be used.[11] In 1992, the Agency for Health Care Policy and Research, became the first of many professional health care organizations to call for placing restrictions on prescribing meperidine.[12] Among the recommendations from these groups were setting a maximum daily dose (600 mg/day in adults) and limiting duration to 48 hours, as well as eliminating the use of oral meperidine. These policy statements, as well as early quality initiatives,[13] influenced the Joint Commission's Pain Management Standards, which recommend limiting meperidine to the short-term treatment of acute pain and the prevention or treatment of drug or blood product-induced rigors or postoperative shivering.[14] Compliance with these recommendations has subsequently become an indicator of quality care. Over the past decade, a number of health care organizations have published their experiences with monitoring and restricting meperidine prescribing in adult patient populations. In this issue of the *Journal of Pediatric Pharmacology and Therapeutics*, Benner and Durham[15] add to the literature with the first publication describing meperidine restriction in a children's hospital.

While it has been a decade since the American Academy of Pediatrics and the American Pain Society published a joint recommendation that meperidine not be used as an analgesic for infants and children, there has been a slow acceptance of this change.[16] Although most pediatric institutions have significantly reduced their use of meperidine, few institutions have completely eliminated its availability. Some of the prescribing may stem from pediatric health care providers who are reluctant to change from the routine use of meperidine for procedural sedation, as in the old "DPT cocktail" consisting of meperidine (Demerol), promethazine (Phenergan), and chlorpromazine (Thorazine), despite studies showing improved outcomes with agents like ketamine and midazolam.[17] Other providers, as described in this issue,[15] may continue to prefer meperidine for managing abdominal pain associated with pancreatitis, clinging to a belief in the superiority of meperidine in preventing spasm of the sphincter of Oddi. Clinicians may also fail to appreciate the significance of normeperidine toxicity due to the relative scarcity of pediatric case reports compared to those in adults. In addition, pediatric health care providers continue to receive mixed messages about meperidine use.[18,19] While several newer review articles on pediatric analgesics omit meperidine entirely, other articles still list it as a therapeutic option. This is illustrated by a 2009 review of postoperative analgesia in children, which highlighted the risk for normeperidine toxicity and serotonin syndrome in the text but then included recommendations for meperidine in the article's drug dosing tables.[20]

Benner and Durham[15] saw a substantial decrease in meperidine prescribing after the implementation of a restriction policy. The authors found that the need to complete even a simple request form can dissuade prescribers when the perceived advantage of the drug is small. The drop in prescribing by orthopedic surgeons suggests that that the group may not have had a strong preference for meperidine but may have been ordering it based on traditional practice patterns. In contrast, the gastroenterology service wrote fewer orders but continued to choose meperidine as an analgesic for children with abdominal pain associated with pancreatitis. Evaluating the effectiveness of their meperidine restriction policy gave the authors information about current prescribing patterns and identified areas for future health care provider education. By publishing their experience, they have provided a useful guide for other children's hospitals facing similar challenges. While meperidine use may never completely die away, with controlled prescribing and health care provider education, we may minimize the number of children who experience its adverse effects.

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