

Use of Meperidine in Patient-Controlled Analgesia and the Development of a Normeperidine Toxic Reaction

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Hypothesis: Intravenous patient-controlled analgesia (IV PCA) meperidine hydrochloride can be used with a reasonable margin of safety.

Design: A retrospective review was performed of 355 medical records of patients receiving IV PCA meperidine treatment. Four groups of patients were defined, based on daily meperidine dose and the presence or absence of central nervous system excitation adverse effects. Use of more than 600 mg/d of meperidine hydrochloride was considered a high dose.

Setting: University tertiary care hospital.

Participants: Postoperative patients from general, orthopedic, neurosurgical, gynecological, and urologic procedures receiving IV PCA.

Interventions: If patients were judged to have consumed significant amounts of meperidine, the analgesic regimen was modified to (1) discontinue meperidine therapy, (2) substitute hydromorphone hydrochloride, or (3) decrease the use of meperidine by adding oral methadone hydrochloride or transdermal fentanyl citrate to the regimen.

Main Outcome Measures: Patients who received less than 10 mg/kg per day of IV PCA meperidine hydrochloride therapy were unlikely to experience central nervous system excitatory adverse effects and maintain adequate analgesia.

Results: The mean meperidine hydrochloride consumption for those patients classified as high dose, asymptomatic was 13.3 mg/kg per day (95% confidence interval, 12.1-14.4 mg/kg per day). This differed statistically significantly ($P < .05$) from the mean meperidine hydrochloride dose in patients classified as high dose, symptomatic, which was 16.9 mg/kg per day (95% confidence interval, 14.7-19.2 mg/kg per day). The duration of meperidine use did not differ among the 4 patient groups. The incidence of a central nervous system toxic reaction associated with IV PCA meperidine therapy was 2%.

Conclusions: We recommend 10 mg/kg per day as a maximum safe meperidine hydrochloride dose by an IV PCA device for no longer than 3 days. Daily patient evaluation is mandatory. Care must also be taken when using this dose to ensure the absence of renal dysfunction or enhanced hepatic metabolism of meperidine.

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MEPERIDINE hydrochloride is an opioid frequently used to treat acute pain. Normeperidine is its only metabolite that has significant pharmacologic activity.¹ Accumulation of normeperidine can occur and is strongly associated with central nervous system (CNS) excitation.²⁻⁶ Signs and symptoms of normeperidine-related CNS excitation include delirium, irritability, tremors, myoclonus, muscle twitches, shaky feelings, and generalized seizures.⁷

Central nervous system excitation is linked to plasma normeperidine levels and also to an elevated serum normeperidine-meperidine ratio.⁴ Such elevations are likely to occur with high doses of meperi-

dine, prolonged administration of meperidine, decreased excretion of normeperidine in patients with impaired renal function, and increased hepatic metabolism of meperidine in patients receiving medications that induce hepatic enzyme systems. Central nervous system toxic reactions related to normeperidine have been reported to occur with most routes of meperidine administration, including intravenous patient-controlled analgesia (IV PCA).⁸⁻¹⁰

The University of Massachusetts Medical Center has had an aggressive acute pain management service in place for more than 8 years. This study was performed to investigate retrospectively the use of IV PCA meperidine therapy in a large population of patients receiving IV PCA opi-

MATERIALS AND METHODS

The files of 5432 patients who received IV PCA opioids between January 1, 1988, and December 31, 1994, were reviewed. Four hundred twelve patients were identified as having been given IV PCA meperidine therapy at any time. Of these patients, the medical records of 355 were available for review. The discharge summary, physicians' orders, progress notes, and medication profiles were examined in all patients to determine (1) the reasons for starting or switching to IV PCA meperidine therapy; (2) the medical or surgical conditions necessitating analgesic treatment by IV PCA meperidine therapy; (3) the amount and duration of meperidine use; (4) the presence of signs and symptoms of CNS excitation; and (5) if high doses of meperidine therapy were used or CNS excitation was observed, what alternative methods were then initiated to achieve satisfactory analgesia.

The following 4 groups of patients were defined. Group 1 (low dose) consisted of 291 patients who used less than 600 mg/d of meperidine hydrochloride and had no CNS excitatory signs or symptoms. Patients in this group, therefore, received a clinically acceptable dose of meperidine without adverse effects. The total daily amount of 600 mg of meperidine hydrochloride therapy used to separate groups of patients was based on the longstanding practice of intramuscular administration meperidine (100 mg every 4 hours as needed). Group 2 (high dose, asymptomatic) consisted of 51 patients who used more than 600 mg/d of meperidine hydrochloride and had no CNS excitatory signs or symptoms. Group 3 (high dose, symptomatic) consisted of 7 patients who used more than 600 mg/d of meperidine hydrochloride and had CNS excitatory signs or symptoms. Group 4 (other) consisted of 6 patients who experienced symptoms of CNS excitation that either were idiosyncratic or were confounded by the patient's medical history or the presence of other medications. One patient had a history of seizures and had a subtherapeutic phenytoin level. Another patient had a transdermal fentanyl citrate patch added to

the regimen prior to developing confusion and irritability. The remaining 4 patients had a low meperidine dose administered only for a few hours. Central nervous system toxic reaction due to accumulated normeperidine was very unlikely in patients in this group.

Each patient in this study was visited daily by members of the acute pain management service. The total daily meperidine dose was calculated for the previous 24 hours. If the patient was judged to have used a high dose of meperidine or if signs or symptoms of CNS excitation were present, the analgesic regimen was modified. Such modifications included the following: (1) substitution of IV PCA hydromorphone hydrochloride therapy for IV PCA meperidine therapy; (2) discontinuation of use of a continuous meperidine infusion (if such administration was used); (3) reduction in the amount of meperidine required by the use of supplemental analgesics (eg, oral methadone or transdermal fentanyl); or (4) discontinuation of usage of the PCA device followed by the administration of oral morphine sulfate (immediate or sustained release) or a combination of acetaminophen and oxycodone or codeine.

Records of patients in groups 2 and 3 (high dose, asymptomatic and high dose, symptomatic, respectively) were examined in detail. For each of these patients, their age, sex, weight, medical history, concurrent use of other medications (eg, phenothiazines, barbiturates, benzodiazepines, or phenytoin sodium), and serum creatinine level were noted. Additionally for patients in group 3, electrolyte, glucose, serum urea nitrogen, creatinine, calcium, and magnesium levels also were noted to be within normal limits. Serum meperidine and normeperidine levels were also available for 2 patients in group 3.

For groups 2 and 3, the arithmetic mean and 95% confidence interval (CI) for patient meperidine dose per day normalized to body weight was calculated in milligrams per kilograms per day. The mean and 95% CI for the duration of meperidine administration was also determined. After determination of the F ratio, the *t* test was used to determine the statistical significance. The frequency of the CNS toxic reactions in patients receiving IV PCA meperidine therapy was determined.

oids. Specifics relating dose and duration of meperidine administered by PCA devices were determined. As defined earlier the incidence of CNS excitation was estimated. Recommendations for the safe use of IV PCA meperidine therapy are proposed.

RESULTS

REASONS FOR USE OF IV PCA MEPERIDINE THERAPY

Of the 5432 patients who received IV PCA opioids 89% were initially administered morphine and continued to receive this opioid. When a history of allergy or adverse effect to morphine was present, either meperidine or hydromorphone was prescribed instead. These other opioids were also used if adverse effects developed once treatment with morphine by IV PCA was started. Four hundred twelve patients (7.6%) were administered IV PCA meperidine; 185 patients (3.4%) were administered IV PCA hydromor-

phone. Of the 23% who either had a history of allergy or had an adverse reaction to morphine therapy, 43% experienced nausea or vomiting, 20% had pruritus, and 14% had dysphoria, constipation, hallucinations, or urticaria.

DEMOGRAPHICS OF GROUPS 1 THROUGH 3 FOR MEDICAL OR SURGICAL CONDITION

Table 1 gives the breakdown of groups 1 through 3 as differentiated by broad medical or surgical condition. Patients with gastrointestinal disease or who underwent abdominal surgery demonstrated a tendency to use high doses of IV PCA meperidine therapy more often than patients with other painful processes.

AMOUNT AND DURATION OF IV PCA MEPERIDINE USE

Group 2 (high-dose, asymptomatic) patients (n=51) received meperidine hydrochloride therapy at a mean dose

Table 1. Demographics of 355 Patients Who Received Intravenous Patient-Controlled Analgesia Meperidine Characterized by Broad Medical or Surgical Conditions*

Type of Medical or Surgical Condition	Total No. of Patients	No. (%) of Patients		
		Group 1 (n = 291)	Group 2 (n = 51)	Group 3 (n = 7)
Gastrointestinal (inflammatory bowel disease or pancreatitis) or abdominal surgery	60	34 (57)	24 (40)	2 (3)
Orthopedic	180	146 (81)	29 (16)	5 (3)
Neurosurgical	32	28 (88)	4 (12)	0
Gynecological	26	26 (100)	0	0
Cancer	25	25 (100)	0	0
Urologic	22	22 (100)	0	0
Other†	10	10 (100)	0	0

*In a retrospective review between 1984 and 1994, 355 medical records of patients who received intravenous patient-controlled analgesia meperidine hydrochloride were classified into the following 4 groups based on the total daily dose received and the presence of central nervous system (CNS) excitatory signs and symptoms: group 1 (low-dose) patients received less than 600 mg/d with no CNS excitatory signs or symptoms; group 2 (high-dose, asymptomatic) patients received more than 600 mg/d with no CNS excitatory signs and symptoms; group 3 (high-dose, symptomatic) patients received more than 600 mg/d and had CNS excitatory signs and symptoms.

†This category includes sickle cell disease; idiopathic thrombocytopenic purpura; and otolaryngologic, thoracic, and human immunodeficiency-related conditions.

Table 2. Characteristics of Patients Using More Than 600 mg/d of Meperidine Hydrochloride

Variable	Group 2 (n = 51)	Group 3 (n = 7)
Age, y	49 ± 16	44 ± 8
Sex, M/F†	21/30	3/4
Creatinine clearance, mL/min†	116 ± 19	114 ± 13
No. of patients receiving phenothiazines, phenytoin, or barbiturates	0	0

*Data are given as mean ± SD unless otherwise indicated. Group 2 (high-dose, asymptomatic) patients received more than 600 mg/d of meperidine hydrochloride with no central nervous system (CNS) excitatory signs or symptoms; group 3 (high-dose, symptomatic) patients received more than 600 mg/d of meperidine hydrochloride with CNS excitatory signs or symptoms. There were no statistically significant differences in these variables between the 2 high-dose meperidine therapy groups.

†Creatinine clearance = [(140 - age) × lean body weight] / (72 × plasma creatinine level). For women, this equation is multiplied by 0.85.¹⁹ To convert creatinine clearance values to the Système International Unit milliliters per second, multiply by 0.01667.

of 13.3 mg/kg per day (95% CI, 12.1-14.4 mg/kg per day) for a mean of 1.7 days (95% CI, 1.4-2.0 days). Group 3 (high-dose, symptomatic) patients (n=7) received meperidine hydrochloride therapy at a mean dose of 16.9 mg/kg per day (95% CI, 14.7-19.2 mg/kg per day) for a mean of 2.2 days (95% CI, 1.5-3.0 days). There were no statistically significant differences for age, sex, and renal function (**Table 2**). None of the patients in either group were prescribed phenothiazines (including antiemetics), barbiturates, phenytoin, or benzodiazepines. Renal function was intact in both groups.

Specific signs and symptoms of CNS toxic reactions for each patient in group 3 are listed in **Table 3**. At the time of the CNS toxic reaction, all patients had serum electrolyte, glucose, calcium, and magnesium levels within normal limits, and renal function was within normal limits. There was no history of seizures or neurologic disease. Computed tomographic scan of the head in 2 of the 7 patients did not demonstrate any focal abnormalities to explain the observed neuroexcitatory symp-

toms. Serum meperidine and normeperidine levels were obtained in 2 patients, as listed in Table 3.

The mean dose rate of group 3 (high-dose, symptomatic) patients differed significantly ($P < .05$) from the mean dose rate of group 2 (high-dose, asymptomatic) patients. The duration of IV PCA meperidine use did not differ between the 2 groups. In our study, the overall incidence of CNS toxic reactions resulting from IV PCA meperidine use was 7 (2%) of 355 patients. The apparent incidence rises sharply and significantly to 7 (12%) of 58 patients as more than 600 mg/d of meperidine hydrochloride is used.

ALTERNATIVE METHODS OF ANALGESIA CHOSEN

Using the alternative analgesic regimen described earlier, no patient in group 2 had any CNS adverse effects. Group 3 patients had these modifications made after the CNS excitatory signs or symptoms had begun. The 1 patient who experienced a seizure sustained a right temporal lobe contusion when the patient fell during the seizure. The patient also experienced hallucinations for 5 days after the right temporal lobe injury. All other patients had resolution of the CNS excitatory signs or symptoms within 3 days after discontinuing meperidine therapy.

COMMENT

The management of acute pain has been substantially improved by the use of IV PCA when compared with conventional intramuscular therapy.¹¹ Morphine is the opioid most commonly used when IV PCA is administered. This study indicates that IV PCA morphine provides satisfactory analgesia without intolerable adverse effects in 89% of patients treated. However, 11% of our patients required an alternative opioid.

Hydromorphone is an alternative to morphine, which is most often used for IV PCA in patients with adverse effects and/or problems (but not true allergic reactions)

Table 3. Signs and Symptoms of Central Nervous System (CNS) Excitation in Group 3 (High-Dose, Symptomatic) Patients*

Patient No.	Diagnosis	Symptoms of CNS Excitation	Meperidine Hydrochloride Level, µg/mL	Normeperidine Level, ng/mL	Meperidine-Normeperidine Ratio
1	Pancreatitis	Muscle twitches	920	630	0.68
2	Ankle fracture	Jitteriness	760	850	1.12
3	Crohn disease	Muscle twitches	NA	NA	NA
4	Femur fracture	Hallucinations, agitation, and jitteriness	NA	NA	NA
5	Femur fracture	Muscle twitches and agitation	NA	NA	NA
6	Rotator cuff tear	Jitteriness, hallucinations, and seizures	NA	NA	NA
7	L1 burst fracture	Hallucinations, agitation, and jitteriness	NA	NA	NA

*The levels of meperidine and normeperidine are provided when they are available from the patient's medical record. NA indicates not available.

†To convert the serum meperidine level to the Système International units of micromoles per liter, multiply by 4.04.

from morphine therapy.¹² In general the use of IV PCA meperidine therapy is considered by some to be ill advised; however, there may be occasions when IV PCA meperidine therapy remains a reasonable option. Additionally, dosing principles of meperidine most probably apply to intramuscular bolus administration, which remains a popular and effective perioperative analgesic regimen with some surgical teams.

There are special potential problems associated with meperidine administration. The biotransformation of meperidine involves either hydrolysis to meperidinic acid, or *N*-demethylation to normeperidine.¹³ Normeperidine in turn undergoes hydrolysis to normeperidinic acid.¹⁴ The metabolites of meperidine are primarily eliminated in urine. If the rate of hepatic formation of normeperidine exceeds its renal elimination, CNS excitation may result from the accumulation of normeperidine in plasma.⁴ Enhanced metabolism of meperidine resulting from induction of microsomal enzymes by chlorpromazine, phenobarbital, and phenytoin may predispose the patient to a CNS toxic reaction.¹⁵⁻¹⁷ Renal clearance of normeperidine has been correlated with creatinine clearance,¹⁸ which accounts for the susceptibility of patients in renal failure to CNS excitation due to normeperidine accumulation. Increasing the dosage and duration of meperidine administration has also been linked to a CNS toxic reaction.⁴

In this study, group 2 (high-dose, asymptomatic) patients used a statistically significantly lower ($P < .05$) mean dose of 13.3 mg/kg per day (95% CI, 12.1-14.4 mg/kg per day) than did group 3 (high-dose, symptomatic) patients. The mean meperidine hydrochloride dose rate leading to CNS excitation was 16.9 mg/kg per day (95% CI, 14.7-19.2 mg/kg per day), which was in the absence of renal impairment and of medications promoting normeperidine formation. The duration of IV PCA meperidine use was 2.2 days (95% CI, 1.5-3.0 days). From these data, it becomes apparent why previously reported cases of a CNS toxic reaction associated with IV PCA meperidine therapy occurred.⁹ The 3 patients described in that report used IV PCA meperidine hydrochloride at a dose of 24 to 25 mg/kg per day for approximately 2 days. In our study, if a CNS toxic reaction was noted, it was manifest after approximately 2 days in all cases.

The signs and symptoms of CNS excitation from a normeperidine toxic reaction are nonspecific, making the chances of detection somewhat difficult (especially

retrospectively). Although grand mal seizures can occur without apparent mild to moderate symptoms of CNS excitement; in general, shaky feelings, tremors and/or twitches, and multifocal myoclonus precede seizure activity.

The symptoms of CNS excitement due to a normeperidine toxic reaction are irreversible and may even be exacerbated by opioid antagonists (eg, naloxone). Naloxone will reverse the respiratory depression of a meperidine overdose but may potentially precipitate seizures. The approach to a meperidine overdose or a toxic reaction is generally to support respiratory function (while protecting the airway by intubation with a cuffed endotracheal tube and/or mechanical ventilatory assistance), to treat any seizure activity with benzodiazepines or other anticonvulsants, to immediately discontinue meperidine therapy, and lastly, to substitute another opioid for pain (eg, morphine).⁴

Based on the dose ranges for symptomatic and asymptomatic patients, 10 mg/kg per day is proposed as a maximum dose. This value probably offers a reasonable safety margin in most patients and is simple to recall. With the institution of 10 mg/kg per day as a cutoff limit for 5 years, there were no instances of CNS excitation except in 2 cases (included in group 3) where the limit was ignored and meperidine therapy was continued. Also, before using maximum doses, one should carefully ensure that renal disease is absent as well as any other factors that might predispose to a CNS toxic reaction (ie, seizure disorder or concurrent administration of medications that increase meperidine metabolism by hepatic enzyme induction).

The plasma half-life of meperidine in normal subjects is roughly 3½ hours.³ The half-life of normeperidine may vary considerably (eg, approximately 14-21 hours in patients with cancer vs 34 hours or longer in patients with renal failure), and does not approach steady state until 3 to 6 days after the start of meperidine administration.³ Normeperidine is believed to exert an excitatory effect on the CNS, while meperidine itself is a depressant. When normeperidine levels rise, and concomitantly meperidine levels decline, CNS excitement can occur. In general, a normeperidine-meperidine ratio of greater than 1 represents a potential for CNS excitation.⁴ However, there is no direct predictive correlation in that seizures can occur at low normeperidine-meperidine ratios (ie, <1).^{3,4}

A maximum dose of 10 mg/kg per day for a 3-day period will obviate normeperidine-induced CNS excitation. Our data limit us from commenting on additional duration of IV PCA meperidine use, since most devices are discontinued between days 2 and 3. The length of time a patient receives meperidine therapy is an important factor leading to the development of a CNS toxic reaction.^{4,7} This point is supported by 4 asymptomatic patients in the present study (in group 2) who received doses of IV PCA meperidine hydrochloride of more than 20 mg/kg per day, but for only 1 day or less (specific data not shown). These patients did not develop CNS excitation, presumably because they did not accumulate enough normeperidine in their short duration of exposure to meperidine to have a toxic reaction. However, smaller doses of meperidine given over a longer period can lead to normeperidine accumulation and a potential toxic reaction.

The frequency of adverse effects in hospitalized medical patients receiving parenteral meperidine therapy has been estimated in the Boston Collaborative Surveillance Program Study.⁵ Adverse effects were preponderantly neuropsychiatric and occurred in 3.1% of patients.⁵ This is similar to the 2% incidence of a CNS toxic reaction observed in our study patients receiving IV PCA meperidine therapy. This incidence may change significantly when doses exceed 14 mg/kg per day for longer than 2 days.

Daily evaluation of each patient using IV PCA meperidine therapy should include determination of a 24-hour dose, as well as the presence or absence of signs and symptoms of CNS excitation. It is recommended that the dose of meperidine hydrochloride should be limited to 10 mg/kg per day in patients with normal renal function who are not also taking medications that induce hepatic metabolism of meperidine. If the daily dose of meperidine exceeds this level, alternative methods of analgesia should be used.

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