Prevalence of Meperidine Use in Older Surgical Patients

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Hypothesis: The unique toxic and adverse effects of meperidine hydrochloride have prompted a number of expert panels convened by national health care policy organizations to recommend that meperidine not be used in older patients. We hypothesized that the prescription of meperidine was less likely to reflect these recommendations in older surgical patients than in older medical patients. The current study examined the use of meperidine in 2 urban hospitals as 1 quality indicator of the care of older adults, measuring the prevalence of its use and characteristics of the patients to whom it is administered.

Design: Retrospective analysis.

Setting: Two urban hospitals: a large private tertiary care teaching hospital and a smaller academically affiliated Veterans Affairs medical center.

Patients: Patients 65 years or older and hospitalized on medical and surgical services between February 19, 2001, and February 14, 2003.

Main Outcome Measures: Patient demographics, medication administration, and department of admitting physician.

Results: Meperidine was administered to approximately 1 in 8 older surgical patients at both institutions. Surgical patients were more likely than medical patients to receive a dose of meperidine (hospital A, 12.2% vs 4.3%, $P<.001$; hospital B, 12.9% vs 1.9%, $P<.001$). Of those administered meperidine, surgical patients were also more likely than medical patients to receive multiple doses (hospital A, 86.0% vs 65.5%, $P=.045$; hospital B, 73.8% vs 48.4%, $P=.02$).

Conclusions: Contrary to national recommendations, meperidine continues to be administered to many hospitalized older adults, particularly those on surgical services. Several alternatives to meperidine exist that provide equal or better pain relief with fewer toxic effects. Hospitals and, in particular, departments of surgery should address this cause of preventable morbidity in this vulnerable population.

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THE UNIQUE TOXIC AND adverse effects of meperidine hydrochloride[1] have prompted a number of expert panels convened by national health care policy organizations to declare meperidine an inappropriate medication in the elderly population.[2-5] Among the opioids, meperidine has uniquely been shown to be less likely to achieve pain control and more likely to produce delirium (**Table 1**). Additionally, its major metabolite, normeperidine, is associated in a dose-dependent manner with twitches, myoclonus, and seizures.[13,20] Normeperidine is renally excreted and accumulates in those with renal insufficiency, including many older adults who have a normal serum creatinine level. In contrast to other opioid adverse effects, the neurologic excitation from normeperidine is not reversible and may be enhanced with naloxone hydrochloride.[21]

For more than a decade now, the Beers criteria, a consensus-based list of drugs to avoid in the elderly, has designated meperidine an inappropriate medication in patients 65 years and older.[5,22] The American College of Surgeons[23] describes meperidine as a suboptimal analgesic and specifically cautions against its use in the elderly. Major national health care organizations such as the Centers for Medicare and Medicaid Services,[5] Joint Commission on Accreditation of Healthcare Organizations,[3] and Agency for Health Care Policy and Research (now the Agency for Health Care Research and Quality)[2] discourage the use of meperidine in older patients. Use of meperidine in persons 75 years or older requiring analgesia is considered an indicator of poor care by the Assessing Care of Vulnerable Elderly project, a RAND initiative that developed an evidence-based set of 236 quality-of-care process indicators to evaluate the care provided to vulnerable elders.[4] The Joint

Table 1. Trials Comparing Meperidine With Other Analgesic Medications

Source	Study Design	Drugs Compared	Study Population	No.	Outcome
			Efficacy: Pain Control		
Plummer et al[6]	DB, RCT	Meperidine hydrochloride, morphine sulfate	Postoperative patients with major abdominal surgery	102	Patients using meperidine PCA had more pain on sitting and experienced more confusion, hallucination, and dry mouth
Tarradell et al[7]	DB, RCT	Meperidine, tramadol hydrochloride	Postoperative patients with total hip or knee replacement	48	Patients receiving meperidine had more sedation and respiratory depression
Jasani et al[8]	DB, RCT	Meperidine, hydromorphone hydrochloride	Patients with ureteral colic in emergency department	73	Patients receiving meperidine achieved less pain relief, required more rescue medication, and were admitted to hospital more frequently
Pellegrini et al[9]	Chart review	Meperidine	Nonobstetric inpatients	157	Many patients primarily prescribed meperidine for analgesia had inadequate pain control and there was increased incidence of confusion in elderly
			Adverse Events: Delirium/CNS		
Adunsky et al[10]	Retrospective cohort	Meperidine, morphine	Consecutive orthogeriatric ward patients with hip fracture	181	Exposure to meperidine was significantly and independently associated with delirium
Marcantonio et al[11]	Nested case-control within prospective cohort study	Meperidine, other opioids, benzodiazepines, anticholinergics	Postoperative general, orthopedic, and gynecologic patients	245	Delirium was significantly associated with administration of meperidine
Morrison et al[12]	Prospective cohort	Meperidine, morphine	Patients with hip fracture	541	Patients receiving meperidine were at increased risk of developing delirium
			Adverse Events: Seizure/Myoclonus		
Kaiko et al[13]	2 Prospective cohort studies	Meperidine	Postoperative patients with cancer	143	Excitatory effects from twitching to seizures were correlated with accumulation of normeperidine; repeated administration of meperidine was associated with adverse changes in mood
			Adverse Events: Biliary Colic*		
Radnay et al[14]	RCT	Meperidine, morphine	Postoperative patients with cholecystectomy	40	Meperidine raised common bile duct pressure more than morphine
Thune et al[15]	RCT	Meperidine, morphine	Patients undergoing elective cholecystectomy	36	Intraoperative manometry showed no statistically significant change in SO basal pressure or amplitude between meperidine and morphine; phasic wave frequency increased with morphine and decreased with meperidine
			Adverse Events: Nausea/Vomiting		
Ezri et al[16]	DB, RCT	Meperidine, morphine	Postoperative patients with elective gynecologic surgery	200	Patients receiving meperidine had significantly higher rates of vomiting
Cepeda et al[17]	Retrospective cohort	Meperidine, fentanyl citrate, morphine	Inpatients with normal renal function at 35 Philadelphia-area hospitals	8855	During short-term use (<48 h), meperidine caused less nausea and vomiting than fentanyl or morphine

Abbreviations: CNS, central nervous system; DB, double-blind; PCA, patient-controlled analgesia; RCT, randomized controlled trial; SO, sphincter of Oddi.
*Using endoscopic retrograde cholangiopancreatography, 2 more recent studies evaluated meperidine alone (Elta and Barnett,[18] N = 18; Sherman et al,[19] N = 47). Both studies documented significant increases in SO phasic wave frequency and no change in basal pressure with meperidine. The study by Sherman et al did show a small but significant decrease in duration of contraction.

Commission on Accreditation of Healthcare Organizations recently adopted this indicator and extended it to postoperative patients 65 years or older who meet the criteria for "vulnerable elderly."[3]

This study examines the current use of meperidine in 2 urban hospitals as 1 quality indicator of the care of older adults, measuring the prevalence of its use and characteristics of the patients to whom it is administered.

METHODS

Meperidine use in medical and/or surgical inpatients was measured at 2 hospitals, one a large private tertiary care teaching hospital (hospital A), the other a smaller academically affiliated Veterans Affairs medical center (hospital B). The attending staffs of the 2 hospitals have little overlap in medicine, but all hospital B attending surgeons also attend at hospital A. Medi-

Table 2. Patient Characteristics

	Hospital A	Hospital B
No. of subjects	1144	2117
Median age, y (interquartile range)	74 (69-80)	75 (70-80)
Sex, % male	44.9	98.7
Length of stay, mean ± SD, d	7.37 ± 11.1	9.18 ± 13.6
Surgical admissions, %	41.3	22.4
Possible dementia, %*	4.9	7.4

*At hospital A, possible dementia was determined by self-reported memory problems during the screening interview or based on medical record abstraction. At hospital B, it was determined on the basis of *International Classification of Diseases, Ninth Revision* coding.

Table 3. Meperidine* Use

	No. (%) of Patients	
	Hospital A (n = 1144)	Hospital B (n = 2117)
Overall prevalence	87 (7.6)	**92** (4.3)†
Prevalence on surgical service	58/471 (12.2)	61/474 (12.9)
Prevalence on medical service	29/673 (4.3)	31/1643 (1.9)
No. of doses received		
1-2	44 (51)	44 (48)
3-4	18 (21)	13 (14)
≥5	25 (29)	35 (38)

*Given as meperidine hydrochloride.
†$P<.001$.

cal and surgical house staff from hospital A rotate through hospital B, but hospital B also has its own internal medicine residency program.

At hospital A we took advantage of data that had already been collected for a prospective study evaluating pain management interventions. Subjects were selected on the basis of a 25% random sample of patients admitted between February 19, 2001, and February 14, 2003, to 9 medical and/or surgical units that were considered representative of the institution as a whole. Patients were excluded if they had evidence of significant cognitive impairment (determined by either the screening interview or the medical record), or if they met the Confusion Assessment Method criteria for delirium.[24] At hospital B, all medical and surgical patients admitted for acute care during the foregoing dates were included in the data analysis, regardless of cognitive function. In addition, *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes were accessed from this database to determine whether the patient had a diagnosis that indicated memory-related problems. At both sites, all patients were 65 years or older and hospitalized between February 19, 2001, and February 14, 2003.

During the last 6 months of the study, physicians at hospital A had access to a passive clinical decision support system consisting of "pain management help" and an "opiate titration calculator" that was linked to the computerized medication ordering system. Whenever an opioid was selected, the next screen presented the prescribing physician with specific opioid doses as well as the option of using the decision support system. The physician could choose to order a specific opioid dose without triggering the decision support system, and the screen did not prompt use of the system when meperidine was the opioid ordered. A hospitalwide education effort encouraged nurses and physicians to avoid meperidine use. No attempt was made to change meperidine prescribing patterns at hospital B.

Medical records were abstracted for date of birth, sex, date of admission, discharge date, and department of admitting physician. Data on medications administered during the hospitalization were obtained from the hospital pharmacy database and included dose, route of administration, and date and time administered. Medications administered in the emergency department were not included in the database. If a patient had more than 1 inpatient admission during this period, data from only the first hospitalization were included. The number of times meperidine was administered was measured, since the risk of normeperidine accumulation increases with repeated dosing.

Data were analyzed with SPSS 11.0 statistical software (SPSS Inc, Chicago, Ill), and logistic regression was used to investigate the relationships among meperidine prescription and sex, length of stay, age, and whether the admission was to a medical or surgical attending physician.

RESULTS

The median age of study patients was 74 years at hospital A and 75 years at hospital B (**Table 2**). As expected, most patients at hospital B were male. Surgical admissions accounted for 41.3% of study patients at hospital A and 22.4% at hospital B. At hospital A, 4.9% of patients were found to have a history of dementia by medical record review or screening interview. At hospital B, 7.4% of patients carried a diagnosis of dementia based on *International Classification of Diseases, Ninth Revision* codes.

Meperidine was prescribed to 7.6% and 4.3% of all study patients at hospital A and hospital B, respectively (**Table 3**). All doses were parenteral. The number of doses administered was similar at both sites. Among the elderly patients receiving meperidine, about half received 1 or 2 doses and half received 3 or more. About one third of patients (28.7% at hospital A and 38.0% at hospital B) received 5 or more meperidine doses. There was no significant difference in meperidine prescribing at hospital A after implementation of the clinical support decision system in the computerized medicine ordering program (data not shown).

At both institutions, surgical patients were more likely than medical patients to receive meperidine (hospital A, 12.2% vs 4.3%, $P<.001$; hospital B, 12.9% vs 1.9%, $P<.001$). Of those administered meperidine, surgical patients were also more likely than medical patients to receive multiple doses (hospital A, 86.0% vs 65.5%, $P=.045$; hospital B, 73.8% vs 48.4%, $P=.02$). Both general and specialist surgeons (mainly orthopedists, otolaryngologists, and urologists) used meperidine considerably more often than nonsurgeons (ie, internists and neurologists) (**Figure**). Of all patients who received 3 or more doses of an opioid at hospital A (N=240), meperidine was twice as likely to be the opioid prescribed if the patient was on a surgical service rather than a medical service (18.8% vs 8.9%; $P=.03$).

After adjusting for length of stay, age, and sex, surgical patients at both institutions were still more likely than medical patients to receive meperidine (hospital A: odds ratio, 3.58; 95% confidence interval, 2.12-6.02; hospital B: odds ratio, 7.40; 95% confidence interval, 4.64-11.80) as well as multiple doses of meperidine (**Table 4**).

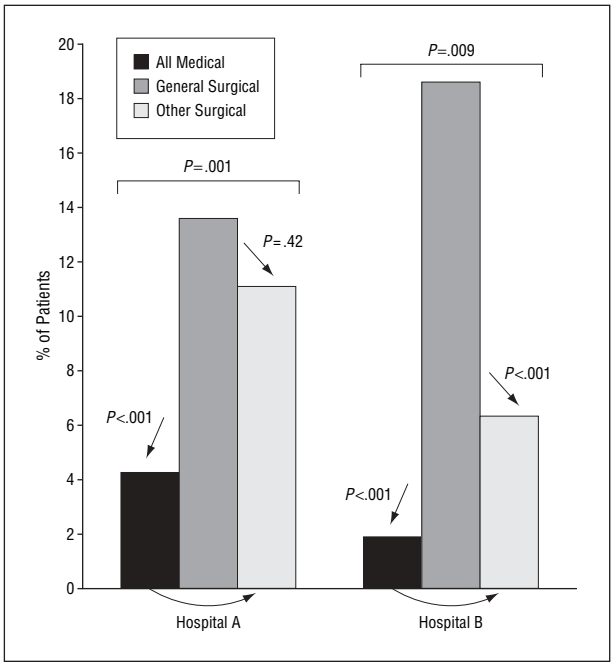

Figure. Meperidine hydrochloride use by department.

There were no statistically significant relationships between administration of meperidine and age, dementia, sex, or race.

COMMENT

This study found that, contrary to national recommendations, meperidine continues to be administered to hospitalized older adults. At both institutions, parenteral meperidine was administered to approximately 1 in 8 older surgical patients. The difference in meperidine prescribing at the 2 hospitals (7.6% vs 4.3%) can be almost entirely explained by the lower surgical admission rate at hospital B. Surgical patients were more likely to receive the drug in both single and multiple doses. At hospital A, the odds were about 4 times greater, and at hospital B, almost 8 times greater that meperidine would be administered to a surgical than to a medical patient. Of patients who received 3 or more doses of an opioid, and were therefore at greater risk of accumulating the toxic metabolite normeperidine, meperidine was twice as likely to be the opioid prescribed when patients were on a surgical service than when on a medical service. Both admission to a surgical attending physician and length of stay were independent predictors of receiving meperidine at both institutions. From these data it is not possible to say whether the increasing length of stay was secondary to meperidine use. However, several other studies have found a significant increase in length of stay associated with meperidine-induced adverse drug reactions.[25-27]

The percentage of patients who received meperidine on surgical services at both institutions was nearly identical and quite considerable (12.2% and 12.9%). The lower overall prevalence of meperidine use at hospital B, 4.3%, is most likely because of the fewer patients on a surgical service at this hospital. If patients at hospital B were admitted to surgical and nonsurgical units in proportions similar to those at hospital A, the use of meperidine at hospital B would climb to 6.5%, close to the 7.6% at hospital A.

Table 4. Logistic Regression Analysis of Variables Related to Meperidine* Administration

	Hospital A		Hospital B	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Increased age	0.97 (0.93-1.01)	.09	0.96 (0.93-1.00)	.03
Sex†	0.99 (0.62-1.59)	.98	0.94 (0.13-7.08)	.95
Length of stay	1.05 (1.03-1.07)	<.001	1.04 (1.03-1.05)	<.001
Surgical admission‡	3.58 (2.12-6.02)	<.001	7.40 (4.64-11.80)	<.001

Abbreviation: CI, confidence interval.
*Given as meperidine hydrochloride.
†Excluded category is female.
‡Excluded category is admission to medical service.

The unique harms of meperidine are well documented, particularly in patients receiving large doses of meperidine through patient-controlled analgesia,[26,28,29] as treatment for cancer pain,[13] or in those with renal insufficiency.[13,20] A recent case series[26] examining outcomes of meperidine hydrochloride use in 141 high-risk patients (defined as those with impaired renal function, receiving dosages exceeding 200 mg/d for multiple days, or those receiving the medication by patient-controlled analgesia) documented adverse drug reactions in 14%, with older patients being particularly vulnerable. The adverse drug reactions included confusion, anxiety, tremors, and seizures.

On the basis of these data, several national health care policy organizations have recommended that meperidine not be used in older patients, and that its use in this population be considered an indicator of poor-quality care. For this reason, meperidine use was measured as a quality-of-care process indicator in this study, and actual adverse outcomes were not determined. Process quality indicators can be used as a guide to monitor and improve services provided. They do not assume a tight correlation between the indicator (here, use of meperidine) and poor patient outcomes, but they also consider the relative risks and benefits to patients, particularly when, as with meperidine, there are feasible alternatives with equal or better efficacy and fewer toxic effects. Recently, the use of such process indicators has been advocated in the surgical setting because they are "generally actionable and link directly to quality improvement activities."[30]

The reason for the continuing popularity of meperidine, particularly among surgeons, remains unclear. Historically, meperidine has been promoted as the "opioid of choice" in patients with biliary and pancreatic pathology because of the belief that it is the only opioid that does not increase sphincter of Oddi pressures. Even if this were true, however, biliary and pancreatic surgery account for less than 4% of all surgical procedures performed nationally on patients 65 years or older,[31] making it unlikely that this is the major indication for its high use in surgical patients. Recent studies using both endoscopic retrograde cholangiopancreatography and

sphincter of Oddi manometry have demonstrated that all opioids, including meperidine, interfere with peristalsis and increase sphincter of Oddi pressure.[32] No studies have directly compared clinical outcomes with meperidine and other opioids in patients with biliary colic or pancreatitis. For this reason, a recent review[32] suggests that it is time for a randomized controlled trial to compare meperidine and morphine sulfate in this population. Despite the lack of evidence supporting the use of meperidine for biliary and pancreatic disease, many of the most popular student teaching texts continue to teach the next generation of physicians and surgeons that meperidine is the preferred agent in such circumstances.[33,34]

There are scant current published data about the national use of meperidine in older hospitalized patients. In 1995 and 1997, 11% and 12%, respectively, of all patients admitted to the University of Wisconsin Hospital, Madison, were prescribed meperidine.[35] Titler and colleagues[36] found that in 709 patients hospitalized for hip fracture in 1999 (mean age, 83.3 years) in 12 hospitals, meperidine accounted for almost one third of the opioids administered within the first 72 hours of hospitalization and that more than 56.8% received at least 1 dose of meperidine during that time. Data from a 2003 study of inpatients at 35 hospitals in the Philadelphia, Pa, area showed that meperidine was prescribed to nearly 3 times as many patients as morphine and nearly 12 times as many as fentanyl citrate.[17]

Meperidine has unique interactions, toxic effects, and adverse drug effects that set it apart as an especially unsafe medication in older patients (Table 1). Its major metabolite, normeperidine, is a cerebral irritant that can cause effects ranging from dysphoria and irritable mood to convulsions.[13,20] Normeperidine is produced by cytochrome P-450 IID6 in the liver and is half as potent as the parent drug as an analgesic but 2 to 3 times more potent as a proconvulsant.[37,38] Its long active half-life, more than 3 times that of meperidine itself, and the fact that it is renally excreted results in a greater than expected steady-state concentration of normeperidine in many older patients,[39] particularly those who receive multiple doses or have renal insufficiency, which is present in more than half of older adults.[40] Serum creatinine level has been shown to be a very inadequate marker of glomerular filtration rate in this population.[39] Also potentially at high risk are patients taking substances that induce hepatic microsomal enzymes, such as phenytoin, phenobarbital, and chlorpropamide, creating higher levels of normeperidine.[40-44] Normeperidine toxic effects have been observed even in young, otherwise healthy patients given sufficiently high doses of meperidine postoperatively.[45] The Agency for Health Care Policy and Research guidelines recommend that, regardless of age, meperidine be used only for very brief courses in otherwise healthy patients who have demonstrated an unusual reaction (eg, local histamine release at the infusion site) or an allergic response during treatment with other opioids such as morphine or hydromorphone hydrochloride.[2] However, as this study and others show, enthusiasm for the widespread use of meperidine continues in the inpatient setting.

Strengths of this study include the large number (3261) of older patients, the recency of the data, and the collection of data on medications actually administered, not just ordered. A weakness is that the staff at the 2 institutions studied were not mutually exclusive. Some of the medical house staff and many of the surgical staff overlapped, although there was no overlap of medicine attending physicians. In addition, the methods of data collection differed between the 2 sites. Specifically, subjects with significant cognitive impairment were excluded from the sample in hospital A. Nevertheless, the overall rate of dementia in the 2 populations appeared quite similar.

Decreasing meperidine use could reduce preventable morbidity and possibly length of stay in older hospitalized adults.[25] To achieve this goal, education is clearly needed; however, education alone rarely changes the behavior of medical providers.[46] The best method to improve physician compliance with evidence-based best practices is still unknown.[47] However, a meta-analysis of intervention studies suggests that the most effective method is the use of active reminders to clinicians at the point of patient care delivery.[48] There is also some role for continuing education to change prescription practices. One controlled study found that individual and group education was both practical and effective in reducing the use of potentially dangerous medications in the elderly.[49]

System-based measures or active decision support systems are also likely to be successful at changing prescribing practices. Some hospitals, for instance, have restricted the use of meperidine to specific indications such as prevention of amphotericin B or postoperative rigors.[35,50,51] Meperidine prescription to older inpatients could also be reduced by making this the target of a departmental quality improvement project. The clinical decision support system that hospital A implemented, described in the "Methods" section, was likely too passive an intervention to be effective at changing physician behavior, as orders for meperidine could be entered without reviewing the content of the educational screens. However, a novel quality-improvement initiative at the University of Wisconsin, Madison, was able to successfully reduce the use of meperidine 5-fold, from 11% to 2%.[35] Implementing such a project within a department of surgery could also be used to demonstrate that residents are participating in system-based learning, one of the new required competencies of the Accreditation Council for Graduate Medical Education.[52]

There are many hazards of hospitalization for older adults that are hard to prevent.[53] Meperidine-induced morbidity does not need to be one of them. Several alternatives to meperidine exist that provide equal or better pain relief with fewer toxic effects. Hospitals and, in particular, departments of surgery should address this cause of preventable morbidity to improve the quality of care for this vulnerable population.

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