

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Meperidine Criteria for Use
1/2005

Recommendations:

The American Medical Association, Joint Commission on Accreditation of Health Care Organizations, American Pain Society and the Agency for Health Care Policy and Research strongly recommend restricting meperidine in both the intravenous and oral forms.

Normeperidine, a metabolite of meperidine, is neurotoxic, especially in the elderly and renally impaired. Patients with creatinine clearance less than 20 ml/min (serum creatinine greater than 2 mg/dl) are particularly at high risk. Normeperidine can cause serious side effects such as seizures, tremulousness, confusion, agitation, and myoclonus. In addition, when taken in combination with MAO inhibitors fatal cardiac events have been reported.

Meperidine (Demerol) usage is restricted except for the following:

1. Allergy or sensitivity to morphine, hydromorphone (Dilaudid), and fentanyl. More than one first-line opioid should be tried and failed before using meperidine.
2. Treatment or prevention of drug or blood induced rigors
3. Treatment of postoperative shivering
4. Peri-procedural in short duration procedures such as endoscopic, surgical or other interventional procedures
5. Emergency department use
6. One-time orders for a single dose

When meperidine is used for approved indications it is recommended that the duration be limited to 48 hours and dose to 600 mg per 24 hours.

Oral meperidine will be removed from the formulary. Oral meperidine is not recommended for pain management due to extensive first-pass metabolism, requiring a dose three times higher than injectable for equivalent analgesia. Conversion to the toxic metabolite, normeperidine, is increased with oral use. When outpatient therapy with meperidine is continued in house the pharmacist will contact the physician to assist in alternative product selection.

Other safer opioids should be generally used for analgesia instead of meperidine, particularly in persons 65 years of age or older and those with creatinine clearance less than 20 ml/min (serum creatine greater than 2 mg/dl) who are at increased risk for normeperidine toxicity. Renal clearance of normeperidine is equivalent to creatinine clearance and it accumulates in patients receiving hemodialysis, CAVH, and CAPD.

Long-term pain management with parenteral meperidine is inappropriate, increases risk of adverse events, and is to be avoided.

The recommended opioids for PCA administration are: morphine, hydromorphone (opioid of choice in renal impairment, no active metabolites, small percent excreted renally as hydromorphone), and fentanyl. Fentanyl is recommended for patients truly allergic to morphine.

Pharmacy will assist physicians in providing a safe and effective analgesic regimen. Patients receiving PCA meperidine will be monitored by pharmacy.

The policy requires that no orders for meperidine PCA, intermittent prn, or scheduled frequency orders (Q3H) will be filled unless the physician's order form indicates both dosage and reason for exception. One-time orders for a single dose do not require a reason for exception.

Findings:

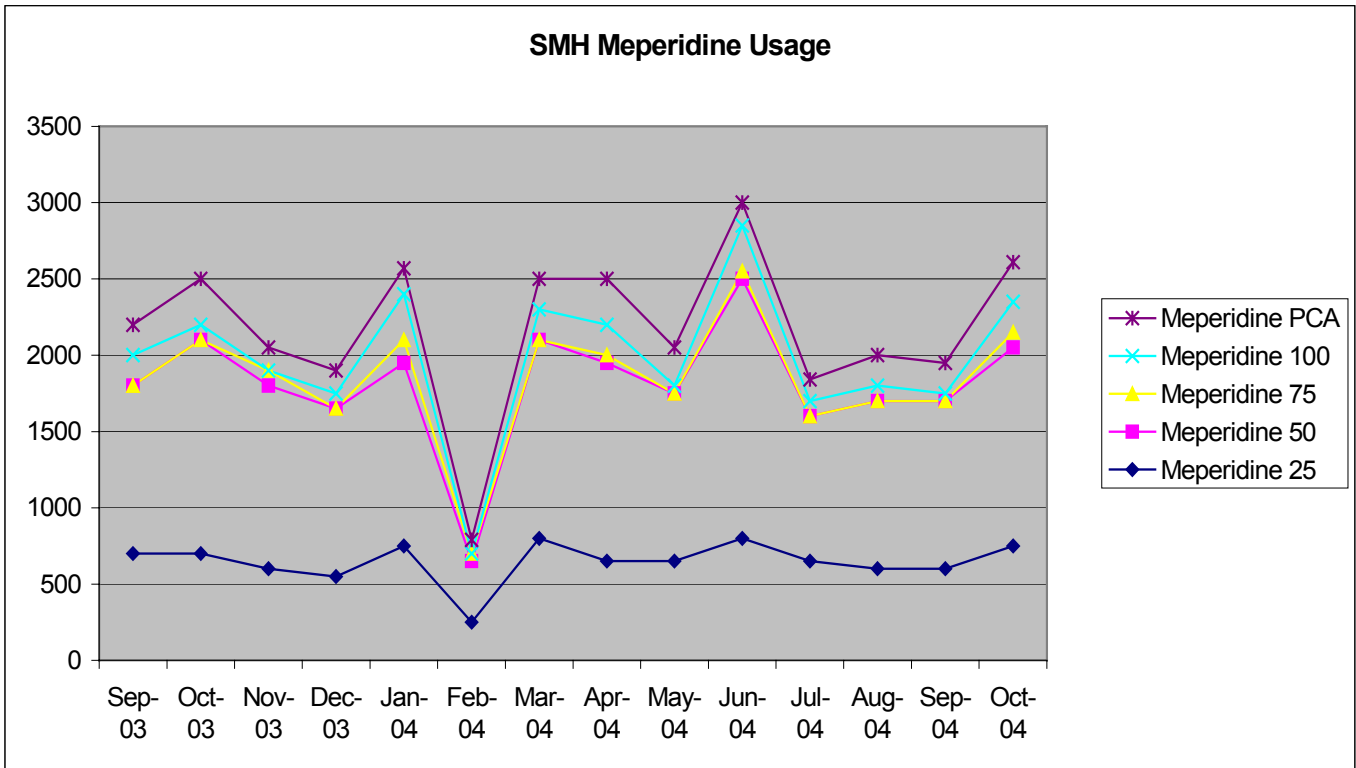
The American Medical Association recommends that meperidine should be avoided in the elderly, as renal excretion of normeperidine, a neurotoxic metabolite, is often delayed in this population. Normeperidine can cause tremulousness, dysphoria, myoclonus, and seizures. In addition, when taken in combination with monoamine oxidase inhibitors, fatal cardiac events have been reported. Because of these potential toxic effects and the availability of alternative opioid analgesics, meperidine is not recommended for either acute or chronic pain management. Meperidine is generally not recommended for pediatric use when other opioids are available because of the potential for seizures due to its metabolite, normeperidine.

The Agency for Health Care Policy and Research recommends that oral meperidine not be used for pain management and that injectable meperidine be restricted to patients who have a true allergy or intolerance to other opioids.

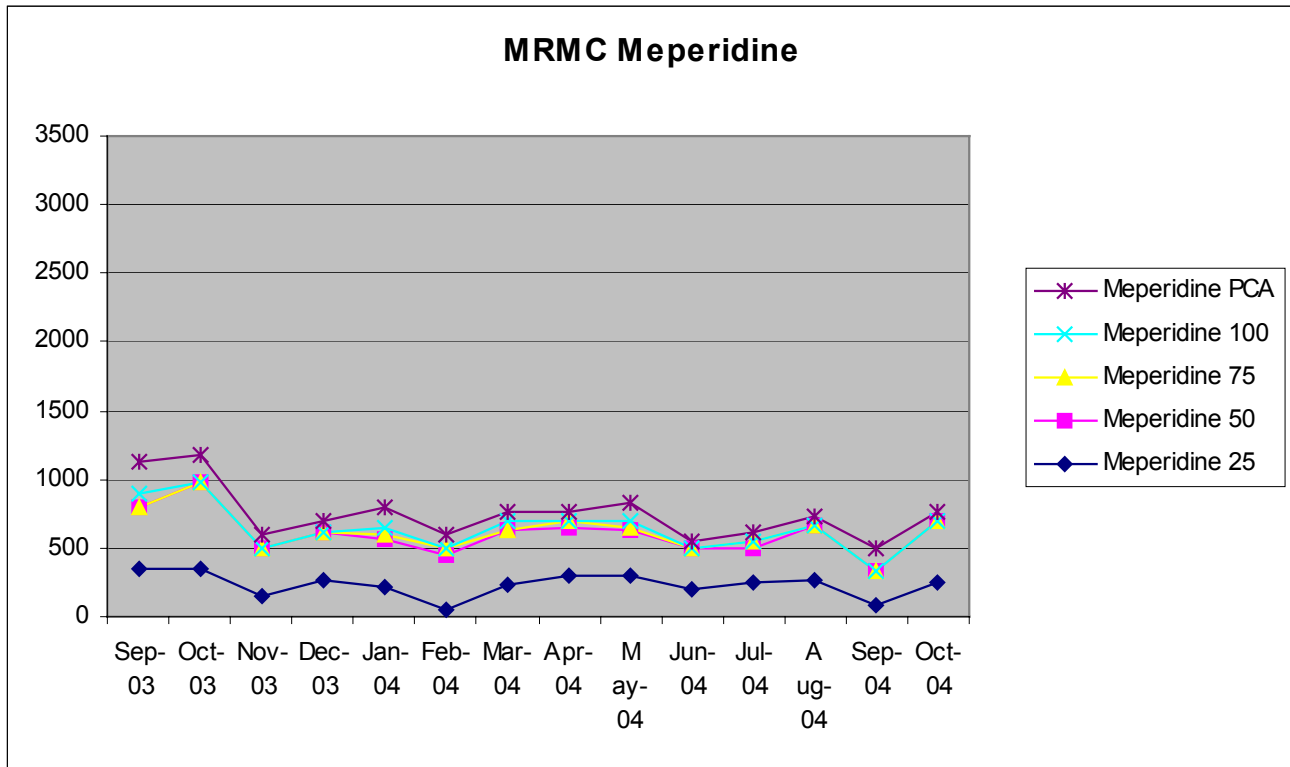
The Joint Commission on Accreditation of Health Care Organizations (JCAHO) recommends that meperidine not be used for management of chronic pain due to accumulation of the toxic metabolite (normeperidine). The toxic metabolite limits use to less than

48 hours or 600 mg in 24 hours. Oral administration is not recommended for severe pain. Use with care in patients with renal insufficiency, convulsive disorders, and cardiac arrhythmias.

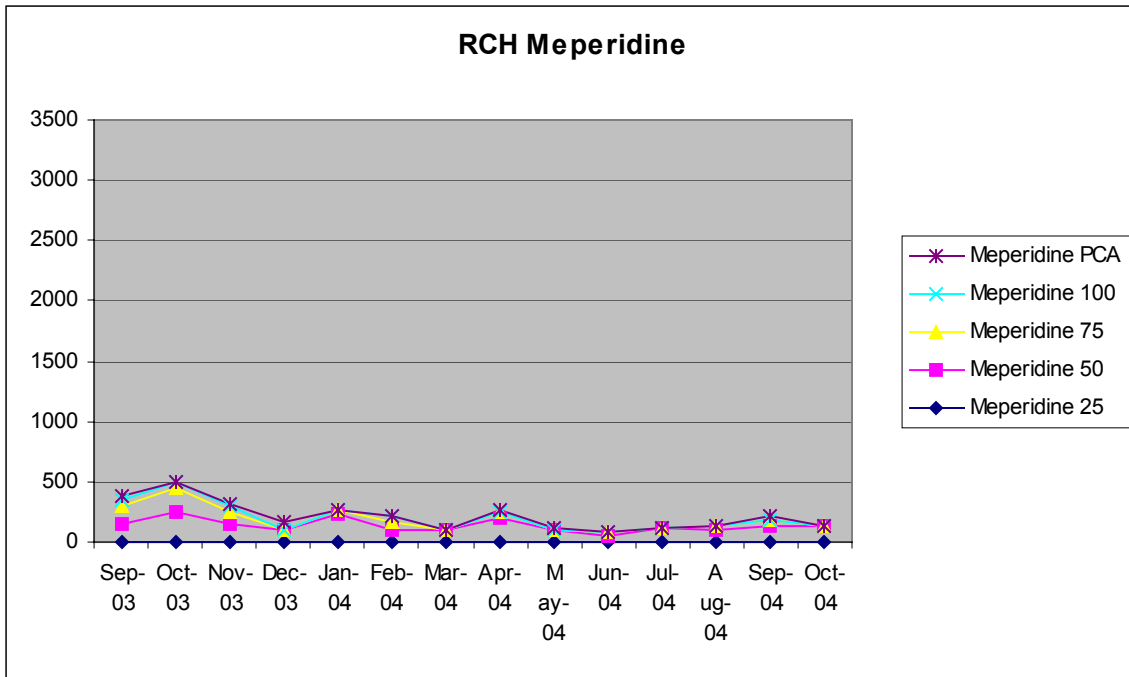
The American Pain Society recommends that meperidine should not be used orally. Injectable meperidine should not be used for more than 48 hours for acute pain in patients without renal or CNS disease, or at doses greater than 600 mg/24 hours, and should not be prescribed for chronic pain.



25 mg decreased 3%, 50 mg decreased 5%, 75 mg same, 100 mg increase 16%, PCA decreased 12%



25mg and 50 mg utilization has decreased 30%, 75 mg and 100 mg with no usage, and PCA utilization has been reduced 50%



25mg and 100 mg have no usage, 50 mg has been reduced by 50%, 75 mg has been reduced by 75%, PCA reduced by 33%

Pharmacokinetics of Opioids						
Drug	Half life: Normal/ESRD		Adjustment for Renal Dysfunction			
			>50	10-50	<10	Supplement for Dialysis
Fentanyl	2-7/	<i>No active or toxic metabolites</i>	100%	75%	50%	
Hydromorphone	2-3/	<i>No active or toxic metabolites</i>				
Meperidine	2-7 / 7-32 Normeperidine 14-21/35	Normeperidine accumulates in ESRD causing seizures, tremors, delirium	100%	Avoid	Avoid	Avoid use in: dialysis, CAVH, & CAPD
Propoxyphene	9-15/12-20 Nor-propoxyphene 30-36/	Nor-propoxyphene Cardiac toxicity-not reversed by naloxone	100%	100%	Avoid	Avoid in dialysis, CAVH, & CAPD Not removed by dialysis Nor-propoxyphene accumulates
Morphine	1-4/ Unchanged	Morphine 6 glucuronide (active metabolite): 5 fold accumulation in ESRD, 3.7 times more potent than morphine	100%	75%	50%	Hemo: none CAPD: no data CAVH: dose for GFR 10-50 Increased sensitivity in ESRD

- Meperidine inhibits serotonin reuptake, resulting in increased CNS serotonin, particularly in the brainstem.
- ICU patients: fentanyl or hydromorphone are preferred for hemodynamic instability or renal insufficiency. Fentanyl administration for anesthesia produces remarkably few hemodynamic changes, and hypotension is rarely observed, as is seen with morphine. Fentanyl in doses of 50 to 100 mcg has no effect on cardiovascular dynamics during enflurane/nitrous oxide anesthesia. However, fentanyl 200 mcg can produce significant cardiovascular depression.
- Opioid analgesics are divided into three classes: phenanthrenes (buprenorphine, butorphanol, codeine, hydromorphone, levorphanol, morphine, nalbuphine, oxycodone, pentazocine), phenylpiperidines (anileridine, fentanyl, meperidine, sufentanil), and phenylheptanes (methadone, propoxyphene).
- Allergic and anaphylactic reactions to the opioid analgesics are rare and ill-defined. These compounds cause endogenous histamine release to varying degrees, and histamine causes a number of allergy like symptoms. The presence of cross sensitivity is questionable and the risk is extremely low if it does exist. Allergic and anaphylactic reactions are rare complications of therapy with opioid analgesics. Urticaria, pruritus, sneezing, and exacerbation of asthma are common. When any of these reactions occur, the question of CROSS-SENSITIVITY arises. Virtually all OPIOID ANALGESICS, but particularly the naturally occurring and semi-synthetic compounds, cause histamine release as a pharmacologic effect (Feldberg & Payton, 1951; Patterson, 1972; Gilman et al, 1985). This release of endogenous histamine is responsible for most cases of urticaria, pruritus, and sneezing in opioid treated patients (Gilman et al, 1985; Levy et al, 1986). Histamine also induces or exacerbates asthmatic attacks in pre-disposed patients and can lead to wheezing, bronchoconstriction, and status asthmaticus (Baum, 1974; Braunwald, 1987). These reactions to the release of histamine are not allergic or anaphylactic in nature. Anaphylactic and true allergic reactions to opioid analgesics are much rarer. In the last 12 years, the clinical literature has carried single case reports of anaphylactic reactions to MEPERIDINE (Levy & Rockoff, 1982), PENTAZOCINE (Ohkubo et al, 1980), MORPHINE (Fahmy, 1981; Rossi & Dick, 1982), and FENTANYL (Pevny & Danhauser, 1981; Bennett et al, 1986; Fukuda & Dohi, 1986). However, many of these reports suggested the possibility of the reactions resulting from other medications taken concurrently or from inert ingredients in products. None of these reports documented cross-sensitivity with other opioid analgesics. Reviews of studies involving several thousand patients receiving meperidine or morphine revealed no cases of cross sensitivity (Sagullo et al, 1983; Paddock et al, 1969; Miller & Greenblatt, 1976). As with any exogenous chemicals, opioid analgesics would be expected to cause allergic or anaphylactic reactions. However, on the basis of this literature review, they occur rarely. Furthermore, reports which do exist often point to confounding variables and none describe cross sensitivity.
- Biliary pressure is increased by meperidine, morphine, and fentanyl. Butorphanol and nalbuphine do not increase biliary pressure. Naloxone administration reduces the narcotic induced pressure increase. Gaensler et al⁵⁸ performed studies on resting intrabiliary

pressure, perfusion pain level, and pressure changes resulting from drugs. The study findings revealed that meperidine caused spasm of the sphincter mechanism of the common bile duct and that it also increased rather than relieved natural spasm. Although meperidine produced slightly less (84%) spasm than morphine when compared with codeine (53.7%), it was still significant (144 mL water versus morphine 175 mL water versus codeine 94 mL water). Similarly, 50 mg of intravenous meperidine increased the biliary pressure by an average of 93% compared with 114% for 30 mg of intravenous pentazocine. Economou and Ward-McQuaid⁶⁶ demonstrated that both meperidine and morphine caused a marked increase in biliary pressure. Equianalgesic doses of intravenous morphine (0.125 mg/kg) and meperidine (1.25 mg/kg) caused a prolonged spasm of the human biliary sphincter. Radnay et al showed that 1 mg/kg of meperidine increased biliary pressure by 52.7%, whereas 0.125 mg/kg of morphine increased the biliary pressure by 61.3%. A later study using 10 mg of morphine and 75 mg of meperidine for a 70-kg individual showed an increase of 85% with morphine and 54% with meperidine. Clinically, these repeated findings provide evidence that equianalgesic doses of meperidine cause similar effects on the sphincter of Oddi and the biliary tract, thus refuting one of the major selection criteria for using meperidine preferentially over other opioids. Direct application of meperidine to isolated guinea pig common bile duct and gallbladder revealed that lower concentrations of meperidine decreased the response to stimulation, whereas higher doses gave an increase in spontaneous contractions. This effect was not responsive to naloxone, and thus it was concluded that meperidine acts by a nonopioid mechanism. In this study, the local anesthetic effect of meperidine was not considered. Wagner et al showed conclusively that meperidine blocks sodium channels with molecular pharmacologic features of a local anesthetic. Direct application at nonphysiologic levels could affect the ability of neurons to transmit impulses to smooth muscle, thus giving a response different from what one would find with normal administration. However, elective cholecystectomy using intraoperative manometry morphine (10 mcg/kg) in divided doses demonstrated a dose-dependent increase in frequency of contractions from 2.4 to 7.9 per minute. Meperidine (100 mcg/kg), also in divided doses, produced a dose-dependent decrease in the frequency of contractions from 1.5 to 0.8 per minute. Despite this different effect on the frequency of contractions, the authors found that there were no significant changes in basal sphincter pressure, contraction amplitude, or wave propagation direction. Others have also deduced that “preference of meperidine over morphine is the medical equivalent of an urban legend” in patients with cholecystitis and pancreatitis.⁶⁷ Clinically, the preferential use of meperidine over any other opioid cannot be supported using scientific findings. Meperidine has as much effect on smooth muscle as do other opioids when dosed in equianalgesic amounts. When the neurotoxic side effects are taken into pharmacotherapeutic consideration, other drugs must become the preferred treatment. Dog bladders show a small increase in tone after meperidine, rather than relaxation. 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 fewer breakthrough medications were needed with hydromorphone (31% versus 68%), fewer intravenous pyelograms (28% versus 54%), fewer hospital admissions (25% versus 49%), and improved analgesia with the hydromorphone. Clinically, patient outcomes were significantly better with hydromorphone, and using hydromorphone rather than meperidine provided more cost effective treatment.

- Renal dysfunction

- Meperidine and propoxyphene are metabolized to active compounds that are excreted primarily by the kidneys
- Morphine's active metabolite M6G (glucuronide) accumulates in renal failure. It is 3.7 more potent than morphine and has a duration of action twice that of morphine. It has been studied as an analgesic. A second and primary metabolite, morphine 3 glucuronide, may antagonize the effect of morphine and M6G and accumulates in ESRD. Both metabolites cross the blood brain barrier.
- Meperidine is metabolized to normeperidine, which is renally excreted. Meperidine excretion is 25% in acid urine, normeperidine excretion is 30% in acid urine, and both dramatically decreased in alkaline urine. Renal clearance of normeperidine is equivalent to creatinine clearance. Renal impairment increases the risk of seizures and agitation secondary to normeperidine but is found in only 50% of patients developing ADE. Seizures have occurred after one day of meperidine therapy and are associated with various modes of administration (IM, IV and PCA). The incidence of central nervous system toxicity associated with IV PCA was 2% in Use of Meperidine in Patient-Controlled Analgesia and the Development of a Normeperidine Toxic Reaction, Simopoulos TT. Arch Surg. 2002;137:84-88. A double blind study (Plummer JL Anesth Analg 1997;84:794-9) showed a much higher rate of central nervous system toxicity with meperidine (24%) versus 9.6% with morphine.

Morphine PCA Is Superior to Meperidine Patient-Controlled Analgesia for Postoperative Pain Plummer JL Anesth Analg 1997;84:794-9		
	Meperidine N=50	Morphine N=52
Confusion	12% (6/50)	3.8% (2/52)
Hallucinations	12% (6/50)	3.8% (2/52)
Myoclonic Jerks	2% (1/50)	1.9% (1/52)

- Meperidine Neurotoxicity

- Signs of normeperidine neurotoxicity include:
 - Anxiety, hallucinations, illusions, restlessness, seizure, shakiness, nervousness, confusion, fluctuations in awareness levels, agitation, disorientation, bizarre feelings, diaphoresis, myoclonic jerks, tremors, and seizures.
 - Naloxone should not be used as it does not reverse the effects of normeperidine, and may actually precipitate seizure activity.
- Factors associated with neurotoxicity:

- renal failure causing accumulation of normeperidine
- alkaline urine, decreases excretion of normeperidine
- hepatic enzyme-inducing agents increase conversion to normeperidine
- coadministration of phenothiazines lower the seizure threshold
- Elevated normeperidine to meperidine ratio

Literature findings:

Meperidine Toxicity

Ann Pharmacother 2003 Apr;37(4):534-7Related Articles, Links
Meperidine misuse in a patient with sphincter of oddi dysfunction.
Hubbard GP, Wolfe KR.

Garrick P Hubbard MD, Internal Medicine Chief Resident, Medical Education Department, Ball Memorial Hospital, Muncie, IN.

OBJECTIVE: To report a seizure occurring secondary to meperidine treatment despite normal renal and central nervous system (CNS) function, and to provide a review of meperidine's role in pain management, including its use in pancreatitis and sphincter of Oddi dysfunction. **CASE SUMMARY:** A 55-year-old white woman with a history of sphincter of Oddi dysfunction presented to the emergency department with severe abdominal pain. On admission to the hospital, the serum creatinine level was 0.6 mg/dL with slightly elevated aspartate aminotransferase of 56 U/L (normal range 0-31) and alanine aminotransferase of 34 U/L (0-31). The patient received repeated and escalating doses of intravenous meperidine, resulting in a generalized seizure on day 4 of hospitalization. The accumulated meperidine dose was 2125 mg. Buprenorphine was substituted in place of meperidine, and the patient had no further reported complications. She was then transferred to a tertiary-care facility for sphincter of Oddi reevaluation. An objective causality assessment revealed the adverse drug event as probable. **DISCUSSION:** Despite alternative opioids, meperidine continues to be used in pain management. Meperidine is different from other opioids because its active metabolite, normeperidine, is neurotoxic. Patients with renal insufficiency, liver failure, or CNS dysfunction are at increased risk for adverse drug reactions related to normeperidine accumulation. Due to normeperidine's extended half-life, however, accumulation of normeperidine can occur in any patient receiving repeated doses of meperidine. **CONCLUSIONS:** This case demonstrates the potential hazards that exist when using meperidine in any patient. Meperidine's inherent risks of both undertreating pain and causing adverse drug reactions should prompt clinicians and health organizations to restrict its use in pain management. This restriction should not make exceptions to meperidine's traditional use in pancreatitis or sphincter of Oddi dysfunction.

Arch Surg 2002 Jan;137(1):84-8Related Articles, Links

Use of meperidine in patient-controlled analgesia and the development of a normeperidine toxic reaction.

Simopoulos TT, Smith HS, Peeters-Asdourian C, Stevens DS. Department of Anesthesiology and Critical Care, Postoperative Pain Services, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, USA. tsimopou@caregroup.harvard.edu

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.

Reducing delirium after hip fracture: a randomized trial.

Marcantonio ER, Flacker JM, Wright RJ, Resnick NM.

Division of General Medicine and the Department of Orthopedic Surgery, Brigham and Women's Hospital, Boston, Massachusetts, USA.

OBJECTIVES: Delirium (or acute confusional state) affects 35% to 65% of patients after hip-fracture repair, and has been independently associated with poor functional recovery. We performed a randomized trial in an orthopedic surgery service at an academic hospital to determine whether proactive geriatrics consultation can reduce delirium after hip fracture. **DESIGN:** Prospective, randomized, blinded. **SETTING:** Inpatient academic tertiary medical center. **PARTICIPANTS:** 126 consenting patients 65 and older (mean age 79.8 years, 79% women) admitted emergently for surgical repair of hip fracture. **MEASUREMENTS:** Detailed assessment through interviews with patients and designated proxies and review of medical records was performed at enrollment to ascertain prefracture status. Subjects were then randomized to proactive geriatrics consultation, which began preoperatively or within 24 hours of surgery, or "usual care." A geriatrician made daily visits for the duration of the hospitalization and made targeted recommendations based on a structured protocol. To ascertain study outcomes, all subjects underwent daily, blinded interviews for the duration of their hospitalization, including the Mini-Mental State Examination (MMSE), the Delirium Symptom Interview (DSI), and the Memorial Delirium Assessment Scale (MDAS). Delirium was diagnosed using the Confusion Assessment Method (CAM) algorithm. **RESULTS:** The 62 patients randomized to geriatrics consultation were not significantly different ($P > .1$) from the 64 usual-care patients in terms of age, gender, prefracture dementia, comorbidity, type of hip fracture, or type of surgical repair. Sixty-one percent of geriatrics consultation patients were seen preoperatively and all were seen within 24 hours postoperatively. A mean of 10 recommendations were made throughout the duration of the hospitalization, with 77% adherence by the orthopedics team. Delirium occurred in 20 / 62 (32%) intervention patients, versus 32 / 64 (50%) usual-care patients ($P = .04$), representing a relative risk of 0.64 (95% confidence interval (CI) = 0.37-0.98) for the consultation group. One case of delirium was prevented for every 5.6 patients in the geriatrics consultation group. There was an even greater reduction in cases of severe delirium, occurring in 7 / 60 (12%) of intervention patients and 18 / 62 (29%) of usual-care patients, with a relative risk of 0.40 (95% CI = 0.18-0.89). Despite this reduction in delirium, length of stay did not significantly differ between intervention and usual-care groups (median interquartile range = 5.2 days in both groups), likely because protocols and pathways predetermined length of stay. In subgroup analyses, geriatrics consultation was most effective in reducing delirium in patients without prefracture dementia or activities of daily living (ADL) functional impairment. **CONCLUSIONS:** Proactive geriatrics consultation was successfully implemented with good adherence after hip-fracture repair. Geriatrics consultation reduced delirium by over one-third, and reduced severe delirium by over one-half. Our trial provides strong preliminary evidence that proactive geriatrics consultation may play an important role in the acute hospital management of hip-fracture patients. **Note:** Protocol calls for elimination of meperidine use.

South Med J 1997 May;90(5):556-8Related Articles, Links

Meperidine-induced generalized seizures with normal renal function.

Marinella MA.

Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, USA.

Meperidine is a widely prescribed opioid analgesic used in a variety of clinical situations. The parent compound has central nervous system depressant effects. However, the sole active metabolite, normeperidine, is a central nervous system excitatory agent and has the ability to cause seizures, especially in patients with renal failure. Patients with normal renal function rarely manifest seizure activity when given meperidine, but if the drug is used in large doses at frequent dosing intervals, seizures may occur. Reported here is the case of a man with normal renal function who had a tonic-clonic seizure due to meperidine that was administered for the pain of underlying chronic pancreatitis.

Clin Pharmacokinet 1996 Dec;31(6):410-22 Related Articles, Links
Pharmacokinetics of opioids in renal dysfunction.

Davies G, Kingswood C, Street M. University of Brighton, England.

Patients with renal insufficiency commonly require the administration of an opioid analgesic to provide adequate pain relief. The handling of morphine, pethidine (meperidine) and dextropropoxyphene in patients with renal insufficiency is complicated by the potential accumulation of metabolites. While morphine itself remains largely unaffected by renal failure, accumulation, as denoted by an increase in both mean peak concentrations and the area under the concentration-time curve, of both the active metabolite (morphine-6-glucuronide) and the principal metabolite (morphine-3-glucuronide, thought to possess opiate antagonist properties) have been reported. The increased elimination half-lives of the toxic metabolites norpethidine and norpropoxyphene in patients with poor renal function administered pethidine and dextropropoxyphene, respectively, makes their routine use ill advised. Case reports of prolonged narcosis associated with the use of both codeine and dihydrocodeine in patients with renal insufficiency call for care to be used when prescribing these agents under such conditions. Although the pharmacokinetics of buprenorphine, alfentanil, sufentanil and remifentanil change little in patients with renal failure, the continuous administration of fentanyl can lead to prolonged sedation.

J Fla Med Assoc 1996 May;83(5):315-9 Related Articles, Links

Meperidine associated mental status changes in a patient with chronic renal failure.

Stock SL, Catalano G, Catalano MC.

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Meperidine is widely used for pain control in the hospital setting. It is also known for its propensity to cause mental status changes in renally and hepatically impaired patients. A case is reported of a 37-year-old man with chronic renal failure maintained on peritoneal dialysis in whom delirium developed when he was treated with meperidine not only on one occasion but also on two subsequent admissions. The pharmacology of meperidine is reviewed and the implications of using the medication in patients with renal impairment are discussed.

Drug Intell Clin Pharm 1987 Oct;21(10):773-83 Related Articles, Links

Effects of renal insufficiency on the pharmacokinetics and pharmacodynamics of opioid analgesics.

Chan GL, Matzke GR.

College of Pharmacy, University of Minnesota, Minneapolis.

The disposition and pharmacologic activities of morphine, meperidine, methadone, propoxyphene, dihydrocodeine, and codeine are reviewed. Dose-related toxicities of these opioid analgesics include mental obtundation, respiratory depression, and hypotension. Furthermore, convulsions have been associated with normeperidine and cardiac toxicities with norpropoxyphene. Hepatic metabolism is the primary route of elimination, except for methadone, for which there is also significant renal excretion. Although the pharmacokinetics of morphine are unchanged in renal insufficiency, accumulation of active metabolites may lead to narcosis. Similar accumulation of normeperidine and norpropoxyphene, metabolites of meperidine and propoxyphene, respectively, as well as propoxyphene itself, and dihydrocodeine and codeine may explain reports of adverse reactions in patients with impaired renal function. A high index of suspicion of opioid-induced toxicities should be maintained in patients who have renal dysfunction and receive opioids.

J Clin Pharmacol 1987 Jul;27(7):516-22 Related Articles, Links

Pharmacokinetics of low-dose intravenous pethidine in patients with renal dysfunction.

Chan K, Tse J, Jennings F, Orme ML.

Department of Pharmacology, Faculty of Medicine, Chinese University of Hong Kong.

The kinetics and elimination of pethidine (meperidine) after intravenous administration (150 micrograms/kg) to ten healthy volunteer subjects were compared with those obtained from 18 patients who suffered from varying degrees of renal dysfunction. In both groups of subjects, pethidine was eliminated triexponentially from plasma. However, plasma concentrations in the patients (who were subdivided into patients with severe dysfunction, moderate dysfunction, and mild dysfunction) were consistently higher. The mean +/- SEM elimination half-life (t1/2) of pethidine was significantly longer in the three groups of renal patients: 7.9 +/- 1.1, 20.2 +/- 13.6, 16.6 +/- 5.4, and 14.3 +/- 3.1 hr, respectively, for healthy volunteers, patients with severe, moderate, and mild dysfunction; their mean +/- SEM creatinine clearances were 97.3 +/- 7.5, less than 9.5, 30.0 (3.7), and 63.3 +/- 8.5 mL/min respectively. The mean plasma clearance of the drug was higher in healthy subjects (342.7 +/- 62.5 mL/min) than various groups of renal patients (99.9 +/- 11.6, 120.9 +/- 45.8, and 123.8 +/- 34.1, respectively, for patients with severe, moderate, and mild dysfunction). Impairment of renal function also reduced total plasma protein binding: 58.2 +/- 5.0% in healthy subjects and 31.8 +/- 3.9%, 44.5 +/- 5.0%, and 42.5 +/- 5.6%, respectively, for the three renal patient groups. The percentage of pethidine recovered in the urine was significantly lower in the severe dysfunction group while norpethidine recovery was significantly lower in all three groups of renal patients. (ABSTRACT TRUNCATED AT 250 WORDS)

Ann Neurol 1983 Feb;13(2):180-5 Related Articles, Links

Central nervous system excitatory effects of meperidine in cancer patients.

Kaiko RF, Foley KM, Grabinski PY, Heidrich G, Rogers AG, Inturrisi CE, Reidenberg MM.

The analgesic meperidine has been reported to produce signs of central nervous system excitation in human beings. To determine the relationship between signs and symptoms of central nervous system excitation and plasma levels of meperidine and normeperidine, we studied 67 patients receiving meperidine for the relief of postoperative or chronic pain. In 48 patients, excitatory effects ranging from mild nervousness to tremors, twitches, multifocal myoclonus, and seizures were directly correlated with accumulation of normeperidine in plasma. Evidence of compromised renal function occurred in only 14 of the 48 symptomatic patients, suggesting that renal dysfunction may contribute to but is not the sole factor in the accumulation of normeperidine or its relation to adverse neurological signs. In a second study we surveyed mood alterations in 47 patients receiving meperidine and 29 receiving other narcotic analgesics for postoperative pain. The repeated administration of meperidine was associated with adverse alterations in various elements of mood (e.g., apprehension, sadness, restlessness).

	Number of Patients	Days of Meperidine	Mg/day	Normeperidine Ng/ml	Normeperidine/Meperidine Ratio
Asymptomatic	28% (19/67)	1.2 (1-2)	170	56	0.2
Shaky feelings	30% (20/67)	8 (1-22)	350	422	1.3
Tremors/twitches	27% (18/67)	6.7 (1-30)	370	463	2.2
Myoclonus/grand Mal	15% [(18+2)/67]	6.9 (3-10)	420	814	3

JAMA 1994 Nov 16;272(19):1518-22 Related Articles, Links

Comment in: ACP J Club. 1995 May-Jun;122(3):80

The relationship of postoperative delirium with psychoactive medications.

Marcantonio ER, Juarez G, Goldman L, Mangione CM, Ludwig LE, Lind L, Katz N, Cook EF, Orav EJ, Lee TH.

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OBJECTIVE--To examine the role of medications with known psychoactive properties in the development of postoperative delirium. **DESIGN**--Nested case-control study within a prospective cohort study. **SETTING**--General surgery, orthopedic surgery, and gynecology services at Brigham and Women's Hospital, Boston, Mass. **PATIENTS**--Cases (n = 91) were patients enrolled in a prospective cohort study who developed delirium during postoperative days 2 through 5. One or two controls (n = 154) were matched to each case by the calculated preoperative risk for delirium using a predictive model developed and validated in the prospective cohort study. **MAIN OUTCOME MEASURES**--Medication exposures were ascertained from the medical record by a reviewer blinded to the study hypothesis. Exposures to narcotics, benzodiazepines, and anticholinergics were recorded for the 24-hour period before delirium developed in the 91 cases and for the same 24-hour postoperative period for the 154 matched controls. **RESULTS**--Delirium was significantly associated with postoperative exposure to meperidine (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.3 to 5.5) and to benzodiazepines (OR, 3.0; 95% CI, 1.3 to 6.8). Meperidine had similar associations with delirium whether administered via epidural or patient-controlled routes, although only the epidural route reached significance (OR, 2.4; 95% CI, 1.3 to 4.4; OR, 2.1; 95% CI, 0.4 to 10.7, respectively). For benzodiazepines, long-acting agents had a trend toward stronger association with delirium than did short-acting agents (OR, 5.4; 95% CI, 1.0 to 29.2; vs 2.6; 1.1 to 6.5), and high-dose exposures had a trend toward slightly stronger association than low-dose exposures (OR, 3.3; 95% CI, 1.0 to 11.0; vs 2.6; 0.8 to 9.1). Neither narcotics (OR, 1.4; 95% CI, 0.5 to 4.3) nor anticholinergic drugs (OR, 1.5; 95% CI, 0.6 to 3.4) were significantly associated with delirium as a class, although statistical power was limited because of the high use of narcotics and the low use of anticholinergics in the study population. **CONCLUSIONS**--Clinicians caring for patients at risk for delirium should carefully evaluate the need for meperidine and benzodiazepines in the postoperative period and consider alternative therapies whenever possible.

Surg Today 2002;32(4):310-4Related Articles, Links

A novel approach to the prevention of postoperative delirium in the elderly after gastrointestinal surgery.

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PURPOSE: Postoperative delirium (POD) is known to be one of the most critical complications of major operative procedures in elderly patients. Since disorders of the sleep-wake cycle have been reported to be one of the key factors in POD, we attempted to clarify the effectiveness of improving sleep-wake cycle disorders with medication after surgery to prevent POD, by conducting a prospective randomized study of 42 elderly patients who underwent resection of either gastric or colon cancer through an open laparotomy. **METHODS**: The delirium-free protocol (DFP) group was given an intramuscular injection of diazepam at 20:00 h each night, as well as a continuous intravenous infusion of flunitrazepam and pethidine administered over 8 h, for the first three nights postoperatively. Two patients were excluded because of failure to complete the DFP. **RESULTS**: The incidence of POD was 7/20 (35.0%) in the non-DFP group and 1/20 (5.0%) in the DFP group, this difference being significant (P = 0.023). Morning lethargy produced by the DFP was observed in 40% of the DFP group; however, no other side effects were seen. **CONCLUSIONS**: These findings indicate that DFP treatment is effective for controlling POD in elderly patients after general surgery and does not appear to be associated with severe complications or side effects. To our knowledge, this is the first report proposing artificial control of the sleep-awake rhythm by medication as a means of preventing POD in elderly patients.

J Am Geriatr Soc 2001 May;49(5):523-32Related Articles, Links Comment in: J Am Geriatr Soc. 2001 May;49(5):680-1. J Am Geriatr Soc. 2002 Mar;50(3):589.

A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients.

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OBJECTIVES: To develop and test the effect of a nurse-led interdisciplinary intervention program for delirium on the incidence and course (severity and duration) of delirium, cognitive functioning, functional rehabilitation, mortality, and length of stay in older hip-fracture patients. **DESIGN**: Longitudinal prospective before/after design (sequential design). **SETTING**: The emergency room and two traumatological units of an academic medical center located in an urban area in Belgium. **PARTICIPANTS**: 60 patients in an intervention cohort (81.7% females, median age = 82, interquartile range (IQR) = 13) and another 60 patients in a usual care/nonintervention cohort (80% females, median age = 80, IQR = 12). **INTERVENTION**: (1) Education of nursing staff, (2) systematic cognitive screening, (3) consultative services by a delirium resource nurse, a geriatric nurse specialist, or a psychogeriatrician, and (4) use of a scheduled pain protocol. **MEASUREMENTS**: All patients were monitored for signs of delirium, as measured by the Confusion Assessment Method (CAM). Severity of delirium was assessed using a variant of the CAM. Cognitive and functional status were measured by the Mini-Mental State Examination (MMSE) (including subscales of memory, linguistic ability, concentration, and psychomotor executive skills) and the Katz Index of activities of daily living (ADLs), respectively. **RESULTS**: Although there was no significant effect on the incidence of delirium (23.3% in the control vs 20.0% in the intervention cohort; P = .82), duration of delirium was shorter (P = .03) and severity of delirium was less (P = .0049) in the intervention cohort. Further, clinically higher cognitive functioning was observed for the delirious patients in the intervention cohort compared with the nonintervention cohort. Additionally, a trend toward decreased length of stay postoperatively was noted for the delirious patients in the intervention cohort. Despite these positive intervention effects, no effect on ADL rehabilitation was found. Results for risk of mortality were inconclusive. **CONCLUSIONS**: This study demonstrated the beneficial effects of an intervention program focusing on early recognition and treatment of delirium in older hip-fracture patients and confirms the reversibility of the syndrome in view of the delirium's duration and severity.

J Am Geriatr Soc 2001 May;49(5):516-22Related Articles, Links Comment in: J Am Geriatr Soc. 2001 May;49(5):678-9. J Am Geriatr Soc. 2002 Mar;50(3):589.

Reducing delirium after hip fracture: a randomized trial.

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OBJECTIVES: Delirium (or acute confusional state) affects 35% to 65% of patients after hip-fracture repair, and has been independently associated with poor functional recovery. We performed a randomized trial in an orthopedic surgery service at an academic hospital to determine whether proactive geriatrics consultation can reduce delirium after hip fracture. **DESIGN**: Prospective, randomized, blinded. **SETTING**: Inpatient academic tertiary medical center. **PARTICIPANTS**: 126 consenting patients 65 and older (mean age 79 +/- 8 years, 79% women) admitted emergently for surgical repair of hip fracture. **MEASUREMENTS**: Detailed assessment through interviews with patients and designated proxies and review of medical records was performed at enrollment to ascertain prefracture status. Subjects were then randomized to proactive geriatrics consultation, which began preoperatively or within 24 hours of surgery, or "usual care." A geriatrician made daily visits for the duration of the hospitalization and made targeted recommendations based on a structured protocol. To ascertain study outcomes, all subjects underwent daily, blinded interviews for the duration of their hospitalization, including the Mini-Mental State Examination (MMSE), the Delirium Symptom Interview (DSI), and the Memorial Delirium Assessment Scale (MDAS). Delirium was diagnosed using the Confusion Assessment Method (CAM) algorithm. **RESULTS**: The 62 patients randomized to geriatrics consultation were not significantly different (P > .1) from the 64 usual-care patients in terms of age, gender, prefracture dementia, comorbidity, type of hip fracture, or type of surgical repair. Sixty-one percent of geriatrics consultation patients were seen preoperatively and all were seen within 24 hours postoperatively. A mean of 10 recommendations were made throughout the duration of the hospitalization, with 77% adherence by the orthopedics team. Delirium occurred in 20 / 62 (32%) intervention patients, versus 32 / 64 (50%) usual-care patients (P = .04), representing a relative risk of 0.64 (95% confidence interval (CI) = 0.37-0.98) for the consultation group. One case of delirium was prevented for every 5.6 patients in the geriatrics consultation group. There was an even greater reduction in cases of severe delirium, occurring in 7 / 60 (12%) of intervention patients and 18 / 62 (29%) of usual-care patients, with a relative risk of 0.40 (95% CI = 0.18-0.89). Despite this reduction in delirium, length of stay did not significantly differ between intervention and usual-care groups (median +/- interquartile range = 5 +/- 2 days in both groups), likely because protocols and pathways predetermined length of stay. In subgroup analyses, geriatrics consultation was most effective in reducing delirium in patients without prefracture dementia or activities of daily living (ADL) functional impairment. **CONCLUSIONS**: Proactive geriatrics consultation was successfully implemented with good adherence after hip-fracture repair. Geriatrics consultation reduced delirium by over one-third, and reduced severe delirium by over one-half. Our trial provides strong preliminary evidence that proactive geriatrics consultation may play an important role in the acute hospital management of hip-fracture patients.

Anesthesiology 2000 Feb;92(2):433-41 Related Articles, Links

Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery.

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BACKGROUND: Patient-controlled analgesia (PCA) with intravenous morphine and patient-controlled epidural analgesia (PCEA), using an opioid either alone or in combination with a local anesthetic, are two major advances in the management of pain after major surgery. However, these techniques have been evaluated poorly in elderly people. This prospective, randomized study compared the effectiveness on postoperative pain and safety of PCEA and PCA after major abdominal surgery in the elderly patient. **METHODS:** Seventy patients older than 70 yr of age and undergoing major abdominal surgery were assigned randomly to receive either combined epidural analgesia and general anesthesia followed by postoperative PCEA, using a mixture of 0.125% bupivacaine and sufentanil (PCEA group), or general anesthesia followed by PCA with intravenous morphine (PCA group). Pain intensity was tested three times daily using a visual analog scale. Postoperative evaluation included mental status, cardiorespiratory and gastrointestinal functions, and patient satisfaction scores. **RESULTS:** Pain relief was better at rest ($P = 0.001$) and after coughing ($P = 0.002$) in the PCEA group during the 5 postoperative days. Satisfaction scores were better in the PCEA group. Although incidence of delirium was comparable in the PCA and PCEA groups (24% vs. 26%, respectively), mental status was improved on the fourth and fifth postoperative days in the PCEA group. The PCEA group recovered bowel function more quickly than did the PCA group. Cardiopulmonary complications were similar in the two groups. **CONCLUSION:** After major abdominal surgery in the elderly patient, patient-controlled analgesia, regardless of the route (epidural or parenteral), is effective. The epidural route using local anesthetics and an opioid provides better pain relief and improves mental status and bowel activity.

J Am Geriatr Soc 1992 Aug;40(8):759-67 Related Articles, Links Comment in: J Am Geriatr Soc. 1992 Aug;40(8):848-9.

Post-operative delirium: predictors and prognosis in elderly orthopedic patients.

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OBJECTIVE: To compare the effect of post-operative analgesia using epidural versus intravenous infusions on the incidence of delirium after bilateral knee replacement surgery in elderly patients. Additional risk factors and impact on post-operative recovery were also assessed. **DESIGN:** Prospective randomized controlled trial. **SETTING:** Urban referral hospital specializing in elective orthopedic surgery. **PATIENTS:** 60 consecutive patients undergoing bilateral knee replacement surgery with epidural anesthesia were approached; 51 patients were eligible and consented. The mean age was 68, 55% were women, and there was a high prevalence of comorbid medical disease. No patient was demented pre-operatively. **INTERVENTION:** Random allocation to either continuous epidural infusion of bupivacaine and fentanyl or continuous intravenous infusion of fentanyl. Infusions were initiated at the first complaint of pain and continued through the 36- to 48-hour stay in the recovery room. **MAIN OUTCOME MEASURE:** Acute post-operative delirium defined using an algorithm based on DSM III criteria. **RESULTS:** The overall incidence of acute delirium was 41%, with no difference between types of post-operative analgesia. Predictors of delirium were age, gender, and pre-operative alcohol use. All cases resolved within 1 week, and length of stay and achievement of physical therapy goals were the same for delirious and non-delirious patients. **CONCLUSIONS:** There is a high incidence of post-operative delirium in elderly non-demented patients following bilateral knee replacement, regardless of whether post-operative analgesia is administered by the epidural or intravenous route.

Ann Pharmacother. 1993 Jan;27(1):29-32. Related Articles, Links

Meperidine-related seizures associated with patient-controlled analgesia pumps.

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OBJECTIVE: To report three cases of meperidine-related seizures when meperidine was administered via patient-controlled analgesia pump (PCAP) and to review literature related to meperidine-associated seizures. **DATA SOURCES:** Case reports and review articles identified by a computerized search (MEDLINE) and manual search (Index Medicus). **DATA SYNTHESIS:** PCAPs are being used frequently to relieve the pain of sickle cell crisis as well as pain from many other etiologies. We report three cases of meperidine-related seizures associated with its administration via PCAP. Each of the patients received either relatively high doses, long-term therapy, or both. Meperidine has been associated with seizure activity when administered via traditional routes. Previously identified risk factors for the development of meperidine-related seizures include renal failure, high meperidine dosages, and coadministration of hepatic enzyme-inducing medications or phenothiazines. **CONCLUSIONS:** Meperidine administered via PCAP may be associated with seizures. Optimally, an alternative analgesic should be administered when this route is used.