MEPERIDINE: A DRUG PAST ITS PRIME

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Objectives

- To increase awareness of appropriate and inappropriate uses of meperidine.
- To encourage utilization of alternate opiates such as morphine and hydromorphone as 1st-line agents in treating acute or chronic pain.
- To reduce meperidine usage.

Background information

- Meperidne is a frequently used synthetic opioid analgesic.
- Meperdine is associated with significant CNS side effects.
- Known as “ analgesic of choice” for acute pancreatitis, cholecystitis, sickle cell anemia, and migraines.
- AHCPR acute pain guidelines recommends meperidine be reserved for very brief courses in otherwise healthy patients who have demonstrated an unusual reaction to morphine or hydromorphone.
- APS recommends meperidine not be used for > 48hrs or at doses > 600mg/24hrs.

Meperidine Pharmacokinetics

- Bioavailability
  - oral: absorption varies (50-60%)
  - parenteral: well absorbed.
- Half-life: 3-5 hours
  - duration of analgesic activity only 2-4hours
- Distribution:65-80% protein bound.
- Metabolism: PO route:50% metabolized in the 1st pass thru liver
  - normeperidine: active.
- Excretion:
  - breast milk: safe in breastfeeding
  - renal excretion: 0.5-5.2% excreted unchanged in the kidney. Normeperidine:0.6% to 21% excreted unchanged in the urine.

Narcotic analgesic pharmacokinetics

Drug	Onset (min)	Peak (hrs)	Duration (hrs)	t ½ (hrs)	Equi-analgesic dose (mg)
Fentanyl	7-8	no data	1-2	1.5-6	IM: 0.1 to 0.2 TD: 25mcg/hr
Hydro-Morphone	15-30	0.5-1	4-5	2-3	IM,SQ: 1.3 PO: 7.5
Meperidine	10-45	0.5-1	2-4	3-5	IM, SQ: 75 PO: 300
Morphine	15-60	0.5-1	4-6	2-4	IM, SQ: 10 PO: 30-60

Meperidine Drug interactions

- MAOIs (isocarboxazid, phenelzine, tranylcypromine, selegiline)
- Isoniazid, linezolid, procarbazine--hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension.
- Serotonin-receptor agonists, SSRIs, St. John's Wort, lithium, and sibutramine--increased risk of serotonin syndrome.
- Some antiretrovirals (ie: ritonavir)-plasma levels of meperidine reach toxic levels quickly

Meperidine Contraindications

- Hypersensitivity.
- Patients who are receiving MAOIs or Zyvox or those who have received MAOIs or Zyvox in the past 14 days.
  - If given together: symtom cluster (agitation, fever, seizures, coma, or death.)
- Patients with untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy,or urethral stricture.

Meperidine Precautions

- GI obstruction, ileus, UC, pre-existing constipation, pulmonary disease, respiratory depression, hx of substance abuse, glaucoma, hepatic disease, cardiac arrhythmias, urinary retention.
- Pre-existing convulsive disorders.
- Patients receiving drugs known to predispose to seizures (e.g., imipenem)
- Renal failure: use with caution and reduce dose
- Elderly patients (age > 65)-due to decreased renal function and to avoid anticholinergic effects

How should meperidine be used?

- Not as first-line agent and not for chronic pain control
- Management of acute episodes of moderate to severe pain if:
  - Unmanageable adverse reactions to other 1st-line opioids.
  - Treatment failure to other 1st-line opioids given in adequate doses.
- Prevention or treatment of drug-induced or blood product-induced rigors (eg: amphotericin B, muromonab, platelets)
- Treatment of post-anesthesia shivering

How should meperidine be used? (continued)

- Conscious sedation used prior to adult procedures, where rapid onset and short duration may improve patient care.
- Neuraxial analgesia for acute pain management.
- Intraoperative and periprocedure use by anesthesiologists.

Problems with meperidine

- It is often under-dosed and given too infrequently. Its duration of action is only 2-4hours, shorter than that of morphine and hydromorphone.
- It is subject to extensive first pass metabolism after oral administration
  - 300mg (PO) = 10mg parenteral morphine
  - compared with parenteral route, oral route results in higher normeperidine concentration.
- It is metabolized in the liver to toxic metabolite, normeperidine:
  - long t 1/2 (15-30 hrs in normal renal function)
  - accumulates with chronic dosing or diminished kidney function.

Problems with meperidine (continued)

- Normeperidine metabolite:
  - cause adverse neurological effects including tremors, twitches, myoclonus, hallucinations, confusion and seizures.
  - Levels can be increased by CYP 2D6 inducers such as Rifampin, carbamazepine, barbiturates, phenytoin, and ritonavir.
- Naloxone does not reverse the effects of normeperidine and may precipitate seizures.

Benefits of other opioids (morphine, hydromorphone)

- No active metabolites.
- Longer duration of action.
- Less drug-drug interactions.

Common uses of Meperidine

- Acute pancreatitis
- Cholecystitis/cholelithiasis
- Post-operative pain (PCA, IM or IV route)

Meperidine IM in post-operative pain: should it be used?

- Intramuscular opioid administration is often ineffective following surgery.
  - ➢ Erratic absorption
  - ➢ Painful (discourage pts from requesting next pain med)
- PO, IV, SQ administrations of pain medications-preferable to IM.
- Pharmacokinetics, onset,and duration of action of IM medications - similar to PO medications
- Pts with small muscle mass-not candidates for IM injections.
- **IM injections**:
  - ➢ significant risk of infection (eg: deep intramuscular abscess);
  - ➢ persistent soreness at the site of administration if not rotated sites
  - ➢ If not given by a qualified person, the needle used to give an IM injection in the arm can injure the radial nerve.
- Avoid IM injections in pts on anticoagulants (heparin, warfarin), thrombolytics (alteplase, urokinase), glycoprotein 2b/3a inhibitors.
- Conclusion: causing pain to treat pain should be avoided.

Morphine PCA superior to Meperidine PCA for post-operative pain

- 102 patients scheduled for major abdominal surgery, randomly assigned to receive PCA with Morphine or Meperidine for pain control (52-morphine, 50-meperidine)
- Results:
  - Pain on sitting (p=0.037) but not pain at rest (p=0.8) was significantly less in pts receiving morphine.
  - Meperidine use was associated with poorer performance in the ability to concentrate and a greater incidence of dry mouth at 24hrs (96% vs 79%, p =0.015)
  - Severity of nausea, mood and incidence of unusual dreams did not differ significantly between drugs
- Conclusion: Morphine has greater efficacy for post-op pain than Meperidine. Meperidine use should be reserved for patients when Morphine use is inappropriate.

Anesth Analg 1997; 84: 794-9

Hydromorphone vs Meperidine for ureteral colic

- Prospective, double-blind, randomized clinical trial over 6 months at a tertiary referral center with 93,000 annual ED visits.
- 73 pts completed the study: 36 pts received hydromorphone 1mg IV. 37 pts received meperidine 50mg IV. Pain intensity was determined using a 10-cm visual analog scale at t=0, 15, 30, 60 and 120 minutes.
- A second dose could be given between t =15 and t =120 minutes when the clinician believed the initial dose ineffective.
- Results:
  - Initial pain intensities, age distributions, sex distributions, and side effects were comparable.
  - Pain relief better ($p < 0.05$) with hydromorphone at t =15,30,60, 120 min.
  - Hydromorphone group required rescue analgesia less often (31% vs 68%, $P < 0.01$), had fewer IV pyelographies (28% vs 54%, $p < 0.05$) and had a lower proportion of hospital admissions (25% vs 49%, $p = 0.08$)
- Conclusion: Pts receiving hydromorphone achieved more pain relief, less rescue medication, fewer IVPs, avoided hospital admission more frequently. Acad Emerg Med 1994; 1 (6): 539-543

Ketorolac vs Meperidine in acute biliary colic

- Randomized, prospective, double blind study of pts presenting to ED with a diagnosis of acute biliary colic.
- 30 pts: 16 in ketorolac group (60mg IM) and 14 in meperidine group (1.5mg/kg with a maximum dose of 100mg IM).
- Results:
  - Average pain score at time 0 was 7.6 for ketorolac group and 7.3 for meperidine group.
  - Pain relief at time 30min was 3.8 in ketorolac group and 3.9 in meperidine group (not statistically different)
  - Mean global pain score and need for an emergency cholecystectomy were similar.
  - Rescue medication for additional analgesia at 30min was need in 4 pts in meperidine group and 2 pts in ketorolac group (28.6% vs 12.5%, NS)
- Conclusion: there was no significant difference in the pain relief achieved by using either ketorolac or meperidine.

J Emerg Med 2001; 20 (2): 121-4

Misconception between Morphine vs Merperidine

- Myth: morphine induces “spasm” in the sphincter of Oddi (SO) and should not be used in acute pancreatitis. Meperidine is the analgesic of choice because it does not elevate SO pressure.
- Clinical evidence does not link morphine with increased risk over other opioids in relation to causing or aggravating pancreatitis or cholecystitis.
- No studies or evidence exist to indicate that morphine is contraindicated for use in acute pancreatitis.
- No studies directly compare the effects of meperidine or morphine on SO manometry or in acute pancreatitis.

Narcotic analgesic effects on the Sphincter of Oddi

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Summary of effects on Biliary Pressure

- Initial studies measure biliary Pr after narcotic administration in animals, post-op and intraop cholecystectomy patients
  - All narcotics increased biliary Pressure.
  - morphine increased contractions of SO to a greater extent than meperidine in one small study.
- Later studies using ERCP with direct SO manometry:
  - SO sensitive to all narcotics including meperidine.
  - A small increase in biliary sphincter pressure seen with higher doses of morphine.
  - All narcotics increase SO phasic wave frequency and interferes with SO peristalsis.

Summary of effects on Biliary Pressure - continued

- In the majority of studies there was no statistically significant change in the mean basal SO pressure with meperidine or morphine.
- The belief that meperidine should be used in place of morphine in the treatment of pancreatitis because of spasms of the SO is not supported by literature.
- Morphine may compromise bile duct emptying, but how this affects pancreatic duct emptying or the course of acute pancreatitis is not known.
- No study has compared the outcomes of patients with acute pancreatitis treated with meperidine, morphine or other narcotics.

Summary

- Meperidine is a frequently used opioid analgesic often inappropriately dosed and associated with significant adverse effects.
- Meperidine should be used with caution in patients with impaired renal function, seizure disorders, elderly patients, patients needing high or prolonged doses, or patients with drug-seeking behavior, etc.
- Morphine might be used safely to decrease the possible side effects of large doses of meperidine, which include euphoria, seizures, and drug interactions
- Morphine has the benefit of a longer duration of action--reducing the frequency of drug administration, less toxicity and associated drug interactions.

Recommendations

- Educational efforts should be implemented to increase awareness, knowledge and understanding of complications and risks associated with Merperidine therapy.
- Meperidine. should not be used as first-line therapy, except for patients who demonstrate intolerance to morphine or other first-line agents.
- Guidelines should be developed encouraging utilization of alternative agents such as Morphine and Hydromorphone.

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