Meperidine (Demerol): A Relic Misfit for Chronic Pain

Therapeutic Value

Meperidine was developed as an atropine analogue initially, but soon gained popularity as a pain medication as its analgesic properties were noticed. A lot of its initial popularity stemmed from assumptions and anecdotal evidence rather than scientific evidence. For instance, it was initially thought to have a lower spasmogenic effect and was preferred for use in acute pancreatitis[1], but later research refuted this idea and found all opioids, including meperidine, to have this effect[2]. Another example is the use of meperidine for headaches[3], which was recommended at one time when this was the only opioid studied in headache patients. However, subsequent research showed meperidine to be less effective for acute headaches than dihydroergotamine (DHE) or anti-emetics, and to be non-superior to an NSAID while carrying more serious risks[4]. At this point in time, there is enough evidence to conclude that meperidine has no advantage to offer over any other opioid.

Table 1. Insufficient Evidence

There is insufficient evidence of the benefit of meperidine over other pharmacologic options for:

- Pain
- Acute pancreatitis
- Headaches

The use of meperidine may post greater risks, particularly in the elderly.

Current Alberta Trends

Since early 2017 there has been almost an 80% drop in the number of meperidine prescribers and patients. In 2020, only 1,000 prescriptions were dispensed for over 300 Albertans[5]. There is an opportunity for clinicians to positively impact their patient's health and help reduce serious harm by working with these patients to explore safer alternatives and switch, and/or taper, depending on the clinical situation.

Pharmacology and Risks

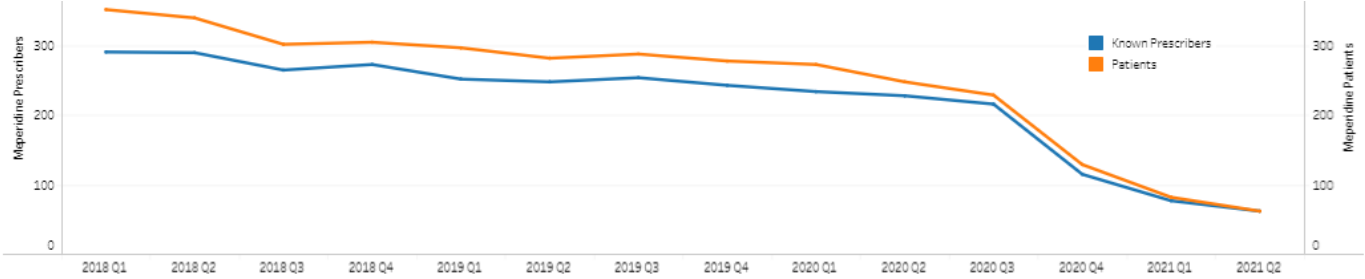
The risks associated with meperidine arise from its unique pharmacological properties, as seen in Table 2[6-12].

Table 2. Pharmacology and Risks

- Meperidine is an anticholinergic and serotonergic opioid which is metabolized through hepatic glucuronidation to normeperidine which is then renally cleared.
- Normeperidine is a non-opioid with limited analgesic potency but has two to three times the neurotoxic potential of meperidine.
- Normeperidine has a half-life of 14-48 hours, which is a problem given the short duration of action for meperidine of only 1-2 hours depending on route of administration. This poses a clinical dilemma: to achieve any meaningful analgesia, the required frequency of meperidine dosing predisposes a patient to dangerous accumulation of the toxic metabolite, even in the context of normal renal function.
- Elderly patients are more likely to have compromised renal function in addition to an increased sensitivity to the neurotoxic effects of normeperidine which puts them at an even greater risk of toxicity, neuroexcitation, seizures, agitation and delirium.
- Naloxone is not effective in reversing the toxic effects of seizures and neuroexcitation unique to meperidine use.
- Meperidine is contraindicated in patients with cirrhosis and renal impairment.
- The elderly may be more sensitive to the neurotoxic and anticholinergic action of the medication.

Meperidine is on the Beer's list of potentially inappropriate medication for use in the elderly.

Patients and prescriber data over the last four years



In addition to Table 2, other pharmacological challenges with meperidine are the poor bioavailability with oral use (around 40-60%) and, of what escapes first pass metabolism, only 40% exists in unbound form available for pharmacological efficacy[13]. It is no surprise then that, in research, oral meperidine has very poor analgesic efficacy (~10 times lower than morphine).

Another concern and contributor of serious overdose is the high oral to parenteral conversion ratio for reasons described. Parenteral use is associated with an even lower duration of action and as such, the frequent injections required can cause dystrophy and increase the risk of infections.

As discussed, the duration of action of meperidine is short. This coupled with the intense central effects, which only last a few minutes and result in a profound euphoria, reinforces use. In comparison to morphine, meperidine has been linked to higher elation, greater work impairment and more dizziness[7].

In addition to the drug interactions which are attributable to opioids as a class, such as CNS and respiratory depression, meperidine has its own set of interactions due to its action at multiple receptor levels. Serotonin syndrome is one such reaction and has been reported with meperidine use in conjunction with other medications and over-the-counter products that affect serotonin levels[10].

Table 3. ISMP Recommendations

1. Removal of oral meperidine from formularies. (Alberta Health Services removed both oral and parenteral forms of meperidine for analgesia from their formulary in 2014. Meperidine is restricted to use for drug- or blood-product induced rigors and select cases of shivering. Therefore, continued use post-hospitalization is not warranted.)

2. Restricting use of parenteral meperidine to short-term pain management in patients with normal renal, hepatic and CNS function where alternative opioids are contraindicated while:

   a) Not exceeding a daily dose of 600mg/ day; and,
   b) Limiting duration of use to 48 hours.

Recommendations

Due to the serious risks with meperidine, the Institute of Safe Medication Practices (ISMP) Canada issued multiple safety warnings[14, 15] advising against the use of meperidine. See Table 3 for ISMP recommendations made in its 2004 bulletin[14].

The 2017 Canadian Guideline for Opioids for Non-Cancer Pain[16] do not recommend initiating a trial of meperidine for patients with chronic non-cancer pain due to limited effectiveness and toxic metabolite accumulation in high doses or in renal insufficiency.

Nor is meperidine recommended for use in the cancer pain population[17] (for the reasons mentioned above).

Clinical situations that meperidine may still be considered for include a true allergy to other opioids. This is very rare in practice so when an allergy is suspected, it should be carefully assessed for confirmation. The histamine release following opioid use may cause a rash and itchiness which may be mistaken as an allergic reaction. In the case of a true hypersensitivity reaction, using a structurally different opioid class or even switching to a semi-synthetic opioid are available alternatives. Another use for meperidine may be for post-operative shivering, although there are other alternatives such as ondansetron[18].

Conclusions

While there are very rare situations where limited and well deliberated use of this medication may be appropriate, in the majority of clinical situations, it is not the best available choice. Continued use of meperidine should be supported by documentation, including the rationale for use of this product in the specific patient. As a clinician, the well-being of the patient must be the primary consideration and patient-centered care may include refusing patient requests for continued prescribing of a dangerous medication. Clinicians should work with their patients to explore alternatives whenever possible and, after an appropriate assessment of the specific patient circumstance, seriously consider de-prescribing meperidine for patients who are chronically using this medication.

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