



Should New Zealand continue signing up to the Pethidine Protocol?

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Abstract

Pethidine is no longer considered a first-line analgesic. The evidence for this view is critically presented. Clinicians around the World recommend its removal from health-systems or restriction of its use. New Zealand needs to follow these trends.

Pethidine (meperidine) is still widely used in New Zealand by general practitioners, accident and emergency units¹, and surgical and maternity suites.² Ninety-six percent of obstetric facilities in New Zealand have access to intramuscular pethidine.³ Pethidine is often a preferred analgesic by both patients and physicians in the treatment of migraines. In the light of recent evidence, there is a movement globally to replace pethidine with more efficacious and less toxic opioid analgesics.⁴ In New Zealand, is pethidine a second-line agent with first-line prescribing practices?⁵

Analgesic effects

The initial studies demonstrating the analgesic efficacy of pethidine were mostly case reports and not double blind, randomised, controlled trials in specific populations.⁴ Subsequent comparative studies failed to demonstrate any advantages of pethidine over comparable doses of other analgesics.^{1,4} There is no conclusive evidence that pethidine is a superior or safer alternative to morphine.⁶

Postoperative pain

In a meta-analysis of the use of intramuscular pethidine (100 mg) for treating acute postoperative pain, the numbers-needed-to-treat (NNT) to produce at least 50% pain relief was 2.9 (95% confidence interval: 2.3–3.9).⁷ Pethidine is an effective analgesic for treating acute pain. But at this dose (100 mg), pethidine produced significantly more drowsiness and dizziness than placebo, with numbers-needed-to-harm (NNH) of 2.9 (2.2–4.4) and 7.2 (4.8–14), respectively.⁷

Opioids remain the main contributors to acute perioperative pain relief especially in procedures giving rise to moderate or severe pain. The modern use of basic multimodal pharmacological analgesia (local anaesthetics, non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol, alpha-2 adrenergic agonists with opioids) minimises doses of opioids needed and provides optimal acute perioperative pain relief in most patients.

Biliary and renal colic

Pethidine is widely used in the treatment of biliary and renal colic and in pancreatitis. There is an historical belief that morphine causes more biliary spasm than pethidine.⁶ Studies using endoscopic retrograde cholangiopancreatography with direct sphincter of Oddi manometry demonstrated that the sphincter of Oddi is sensitive to all opioids

including pethidine.⁹ Other studies have clearly demonstrated that pethidine is no more efficacious in treating biliary or renal tract spasm than comparative mu opioids.⁴ The sphincter of Oddi is equally sensitive to all opioids, at equianalgesic doses.¹⁰ NSAIDs have been found to have similar efficacy to pethidine in the management of acute biliary colic with a decreased number of adverse effects.^{11,12}

Similar efficacy was found between pethidine and morphine in the management of acute renal colic.¹³ A recent study showed the use of opioids to be associated with a higher incidence of adverse events, particularly vomiting with pethidine.¹⁴ It did not recommend the use of pethidine in the management of acute renal colic.¹⁴ NSAIDs may be used instead, however.¹⁵

Labour pain

Many clinicians use pethidine to help decrease pain during labour. The most important reason for the widespread use of pethidine during dystocia in the active management of the first stage of labour was an increase in uterine contractility found in many observational studies with pethidine.¹⁶ However, recent studies clearly show the absence of such an “oxytocic effect” with pethidine.¹⁶

It is recommended that pethidine should not be used during labour for this specific indication.¹⁶ In addition, there are considerable doubts about the analgesic effectiveness of pethidine and concerns about its potential maternal, foetal, and neonatal adverse effects.¹⁷ In one study, intravenous pethidine provided effective pain relief in only 24% of subjects in the first stage of labour.¹⁸ Repeated maternal administration of pethidine results in significant foetal exposure and neonatal respiratory depression.¹⁹

Maternal administration of pethidine with promethazine has a significant effect on foetal heart rate indices during the active phase of normal labour.²⁰ Pethidine has relatively long-acting behavioural and neurological effects in the newborn due to its slow elimination.²¹ As a result, breastfeeding is delayed and the mother-infant interaction is disturbed. There is concern about the routine administration of pethidine in this context.²¹

In obstetric analgesia in labour, increasing use is made of neuraxial combinations of local anaesthetics and opioids (ropivacaine, levobupivacaine, bupivacaine with fentanyl, sufentanil)^{22,23} and the utilisation of patient controlled epidural analgesia.²⁴ Remifentanyl has been suggested as an ideal opioid for patient-controlled analgesia (PCA) in labour, but its safety profile has not been established.^{25,26}

Repeated administration of pethidine, in contrast to morphine, affects the suckling infant negatively. Safer alternatives to pethidine should be considered in lactating mothers.²⁵ The use of morphine should be preferred.²⁷ It has been suggested that the course of behavioural maturation during certain periods of infancy is influenced by pethidine administration at birth.²⁸

Chronic pain

Recommendations from the Agency for Health Care Policy and Research (AHCPR), an organisation which has defined standards of care for acute and chronic pain management, contraindicate the use of pethidine in chronic pain.^{5,29} Patients reliant on

regular pethidine for chronic non-malignant pain, require multidisciplinary assessment and management. A quality improvement approach using a traditional plan-do-check-act (PDCA) model can help reduce the inappropriate use of pethidine.³⁰

Tramadol can be an effective and well-tolerated alternative for the management of chronic pain of malignant or non-malignant origin, particularly neuropathic pain. Nausea is the most common adverse effect of tramadol with an incidence of 6.1% for oral administration and 20.7% for patient-controlled analgesia.³¹ To reduce nausea and vomiting, a slow intravenous injection (over 1–3 minutes) and initial low doses followed by gradual dose increases (go low, start slow) are used.³¹ Tramadol produces less constipation and dependence than equianalgesic doses of strong opioids.³²

Neuraxial use

Pethidine has molecular pharmacological features of a local anaesthetic (sodium channel blocker) in addition to its opioid properties.³³ Because of its intermediate lipid solubility, pethidine may have advantages over many other epidural opioids. It is an effective epidural opioid for the treatment of acute pain. Its use has been well described in Australian and New Zealand practice, particularly in the field of obstetric anaesthesia.³⁴ Epidural pethidine is efficacious as an analgesic for post Caesarean section pain control.³⁵ However, the potential for accumulation of norpethidine limits its use to relatively short durations of treatment.

The use of intrathecal opioids, including pethidine, does not significantly affect the natural progression of labour, and no adverse foetal outcomes have been reported.³⁶ Pethidine has been used as the sole intrathecal agent for spinal anaesthesia³⁷ but has no real advantages over lignocaine.³⁸

Shivering

Postoperative shivering consists of muscular tremor and rigidity. Pethidine has been used to decrease the incidence and intensity of shivering associated with general or spinal anaesthesia.^{39,40} Other alternatives include clonidine and tramadol. Intravenous tramadol 1 mg/kg has been found to be more effective for the treatment of postoperative shivering than pethidine 0.5 mg/kg.⁴¹

Pharmacology

Pethidine is a phenyl-piperidinic synthetic drug, used in the management of moderate to severe pain. It has been widely used since its introduction in the 1930s.⁴² In the United Kingdom, pethidine became the most commonly used opioid in hospitals.⁴³ Pethidine was initially synthesised as an anticholinergic agent but was soon discovered to have analgesic properties.⁴ It was introduced as a drug lacking many of the adverse effects of morphine such as respiratory depression, urinary retention, constipation, and chemical dependency. None of these claims have been substantiated.⁶

Pethidine, ethyl-1-methyl-4-phenyl-piperidin-4-carboxylate, is a predominantly mu-receptor agonist.³⁴ It can be administered orally or parenterally. Pethidine has a plasma half-life of 2.5-4 hours with a similar duration of analgesic effect (shorter than

morphine).^{34,44} Reported methods of parenteral delivery include bolus injection, continuous infusion, and patient-controlled epidural analgesia.²

Toxic metabolites

Pethidine has poor oral bioavailability, and is metabolised extensively by the liver.¹ In recent years, the use of pethidine has diminished because of the toxicity of one of its several metabolites. A long-term oral or systemic pethidine administration can give rise to an accumulation of the hepatically formed metabolite, normeperidine. This active metabolite is neurotoxic due to its ability to increase serotonin (and noradrenaline) in the central nervous system.¹⁰

Toxicity usually results from excessive intrasynaptic serotonin.⁴⁵ Such elevations are likely to occur with high doses of pethidine, prolonged administration of pethidine, decreased excretion of normeperidine in patients with impaired renal function, and increased hepatic metabolism of pethidine in patients receiving medications that induce hepatic enzyme systems.⁴⁶

The opioids, tramadol, methadone and dextromethorphan and propoxyphene, appear to be weak serotonin re-uptake inhibitors, and have all been involved in serotonin toxicity reactions (discussed later).⁴⁵

Normeperidine is half as potent an analgesic as pethidine, but is two to three times more potent as a convulsant.^{47,48} The intensity of the central nervous system excitation is highly correlated with the plasma concentration of normeperidine.⁴⁷ Symptoms range from irritability, restlessness and agitation, to myoclonias, tremors, jerking, confusion, and convulsions.⁴⁹ Due to normeperidine's extended half-life (14–21 hours), accumulation of normeperidine can occur in any patient receiving repeated doses of pethidine.¹⁰ The presence of active metabolite norpethidine with its increased elimination half-life in patients with poor renal or hepatic function makes the routine use of pethidine ill advised in these patients.⁵⁰

Another impurity may be present in pethidine. It is *N*-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP), a synthetic substance derived from the hydrolytic degradation of an ester group.² MPTP is a very toxic compound, implicated as the cause of severe and irreversible Parkinsonian symptoms. This impurity causes the destruction of nigrostriatal dopamine neurones, leading to symptoms that closely resemble those present in human idiopathic Parkinson's disease.² Despite extensive purification of pethidine, the drug may still contain traces of MPTP.

Adverse effects

The most frequently reported adverse effects with pethidine are drowsiness, somnolence, dizziness, lightheadedness, nausea, and vomiting.⁷ In a recent evaluation, the usage patterns and frequency of adverse drug reactions with pethidine—central nervous system effects (confusion, anxiety, nervousness, hallucinations, twitching, and seizure)—were documented in approximately 14% of patients.⁵¹

Patients using patient-controlled (PCA) pethidine were at particularly high risk of experiencing adverse drug reactions based on cumulative doses and duration of treatment.⁵¹ There is a significant association between pethidine (odds ratio 2.5, $p < 0.01$), and delirium in elderly hip-fractured patients.⁵² Thus, pethidine should not be

used in this group of patients. In addition, hypotension, tachycardia, and erythema may occur with pethidine due to release of histamine from mast cells.⁴⁹

Pethidine has vagolytic (atropine-like) effects on heart rate⁵³ giving rise to tachycardias and arrhythmias in patients after myocardial infarction or with supraventricular tachycardias.⁶ The use of morphine would be preferable in the acute coronary syndrome. For premedication in children, profound anticholinergic effects follow the intravenous administration of pethidine with atropine or glycopyrrolate.⁵⁴ Such combinations are not suitable for clinical purposes.

Drug interactions

The serotonin syndrome is caused by excess serotonin (5-hydroxytryptamine; 5-HT) availability in the central nervous system at the 5-HT_{1A}-receptor.⁵⁵ It is characterised by a constellation of symptoms (confusion, fever, shivering, diaphoresis, ataxia, hyperreflexia, myoclonus, or diarrhoea).⁵⁵ Pethidine has the potential to induce a serotonin syndrome when used together with other agents. The syndrome may result from coadministration of pethidine with dextromethorphan, pentazocine, tramadol, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs).⁵³ Even the combined use of moclobemide with pethidine should be avoided.⁵⁶

Several fatal reactions have been reported with the coadministration of pethidine with the MAOIs.⁶ Pethidine should not be used within a 14-day period of stopping a MAOI.⁶ Furthermore, commonly used drugs (such as theophylline, tricyclic antidepressants, and the fluoroquinolones) can potentiate the seizure potential of pethidine.⁹

Abuse potential

Pethidine possesses a high potential for abuse. Pethidine, similar to other opioids produces euphoria in some patients, providing the motivation for abuse, which can be detrimental even with occasional use.⁵⁷ Treatment of acute migraine headaches with pethidine is potentially ineffective and may lead to abuse.⁵⁸

Pethidine addiction by medical personnel, however, seems to be an occupational hazard.^{6,59} In New South Wales, from 1985 to 1994, 79 doctors had their drug authorities withdrawn for opioid addiction.⁵⁵ Pethidine was the main drug used (66 doctors or 84%).⁶⁰ Other opioids (morphine, fentanyl, sufentanil) can also give rise to substance-use disorders amongst physicians.⁶¹

Fentanyl and sufentanil are the opioids of choice for anaesthetists.⁶² In all of these cases, toxicological investigations are difficult as half-lives of the compounds are short, and the circulating concentrations weak.⁶²

Conclusion

Pethidine is a widely used opioid by virtue of its familiarity and low cost.⁶³ But it lacks potency, has a short duration of action (half life 3–4 hours), and a narrow therapeutic index.⁴³

Equianalgesic doses of pethidine when compared to morphine are as follows:
pethidine 100 mg intramuscularly/intravenously (or 400 mg orally) is equianalgesic to

morphine 10 mg intramuscularly/intravenously (or 30 mg orally).⁶⁴ In controlled trials, its analgesic efficacy has rarely proven superior to alternative opioids.¹ In addition, clinical evidence shows that pethidine has no advantages over other opioids for the treatment of biliary or renal colic or of pancreatitis.⁴²

The metabolism of pethidine gives rise to a neurotoxic metabolite norpethidine that accumulates due to its longer half-life.⁶ Therefore, pethidine should only be used for short intervals to treat acute pain (24–48 hours).⁶⁵ It should not be used with renal dysfunction. Another disadvantage is that it is vagolytic. The use of pethidine is complicated by dangerous drug interactions that include serotonergic crises. It is not indicated in the management of chronic pain.

Pethidine is no longer considered a first-line analgesic. It has no unique clinical advantages over other stronger opioids (morphine, oxycodone).⁴ Its poor efficacy, toxicity, and multiple drug interactions have resulted in many clinicians around the World recommending that pethidine be removed from health-systems or that its use be restricted.⁴² Surely, it is time for clinicians in New Zealand to re-evaluate its widespread use?

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