



NSW Therapeutic Assessment Group

Pethidine FAQs

What is the mechanism by which pethidine causes seizures?

Pethidine is metabolised in the liver via 2 separate pathways, hydrolysis to pethidinic acid (inactive metabolite) or demethylation by cytochrome P450 to **norpethidine**, a non opioid active metabolite. After intramuscular administration, the elimination half life of pethidine averaged 3.6 hours¹ however the elimination half life of norpethidine is around 14-21 hours with normal renal function² and 35 hours in renal failure³. Norpethidine has half the analgesic potency of pethidine but two to three times the potency as a central nervous system (CNS) excitatory agent^{1 4} and may cause anxiety, hyperreflexia, myoclonus, seizures and moods changes⁵. There is not a clear relationship between neurotoxicity, cumulative dose and serum norpethidine.⁶ Several cases of seizures have been reported, including when pethidine was used for patient controlled analgesia (PCA)⁶. In Australia alone, between 1975 and 1997, ADRAC (Adverse Drug Reactions Advisory Committee) received 35 reports describing convulsions in association with pethidine, in 17 of which pethidine was the only suspected drug. Risk factors include repeated dosing of pethidine, with associated renal insufficiency, sickle-cell anaemia, high doses of pethidine, and the concurrent administration of phenothiazines or drugs that induce hepatic enzymes.

If I use an NSAID such as ketorolac, what dose should be employed and what is the time to onset of action?

The usual starting dose of parenteral ketorolac is 10-30mg for patients less than 65 years and 10-15mg for patients over 65 years⁸. (Alternatively, 10mg may be given orally). Ketorolac is rapidly and completely absorbed with a peak plasma concentration of 0.52 to 1.31 microgram/mL occurring 35 minutes after a single 10 mg tablet. The intramuscular form has a bioavailability of 100% and a mean peak plasma concentration of 2.2 microgram/mL occurs an average of 50 minutes after a single 30 mg dose. Ketorolac is expensive, and its efficacy is no better than that of other orally or rectally administered NSAIDs

If I don't want to prescribe pethidine, what dose of other agents should I use and how often?

All opioids are capable of producing the same degree of analgesia providing equianalgesic doses are given. Dose schedules will vary according to the age of the patient, concomitant disease states, use of other medications and route of administration. In adults, patient age rather than weight has been shown to be a better predictor of opioid requirement (Level III)⁷. Due to incomplete cross tolerance between opioids it may be wise to start at a lower dose than that indicated in the following table and titrate to patient response.

Table 1

Drug	Approximate equi-analgesic dose ¹		Duration of action ² (hours)
	Parenteral	Oral	
pethidine	75-100mg im/sc	300mg	2-3
morphine	10mg im/sc	30mg	2-3
oxycodone		20-30mg	3-4
fentanyl	150-200µg sc/iv	NA	0.5-2 (IV)
hydromorphone	1.5-2mg im/iv	6-7.5mg	2-4
codeine	130mg im	200mg	3-4
tramadol	80-100mg im	100mg	3-6

(Table adapted from Australian Medicines Handbook 2003)

Where fentanyl is an appropriate choice, what dosing schedule should be used?

According to Drugdex, 25-50 micrograms of fentanyl intravenously or 50-100 micrograms intramuscularly may be given every 2 hours.

What is the basis for the perceived benefit of pethidine in biliary and renal colic?

Pethidine was first synthesised in 1939 as an anticholinergic agent; chemically induced spasm of isolated smooth muscle from guinea pig large intestine was relaxed by *direct application* of pethidine solution⁹. However their tests on intact dog intestine and isolated duodenal and ileal strips of cats and rabbits, showed that pethidine increased tonus and peristalsis while decreasing the organ's volume- attributed to smooth muscle spasm.

Repeated findings provide evidence that equianalgesic doses of pethidine cause similar effects on the sphincter of Oddi and the biliary tract to other opioids. Gaensler et al¹⁰ studied resting intrabiliary pressure, perfusion pain level and pressure changes resulting from drugs, and found that pethidine caused spasm of the sphincter muscle of the common bile duct and that it also increased rather than relieved natural spasm. Although pethidine produced slightly less spasm than morphine when compared to codeine, it was still significant. Economou and Ward-McQuaid demonstrated that both pethidine and morphine produced a marked increase in biliary pressure¹¹. Equianalgesic doses of intravenous morphine (0.125 mg/kg) and pethidine (1.25mg/kg) caused a prolonged spasm of the human biliary sphincter¹². Radnay et al showed that 1mg/kg of pethidine increased biliary pressure by 52.7% whereas 0.125mg/kg of morphine increased the biliary pressure by 61.3%¹³.

Practice Points

In renal colic

- rectal NSAIDs are as effective as parenteral NSAIDs, and parenteral NSAIDs are better than opioids
- metoclopramide and hyoscine-n-butylbromide may also be effective

In biliary colic

- the preferential use of pethidine over any other opioid is not supported by the evidence.
- NSAIDs are effective
- consider smooth muscle relaxants eg hyoscine-n-butylbromide
- If opioid required, use morphine IV

Which drug interactions with pethidine are clinically significant?

Pethidine inhibits both serotonin and noradrenaline reuptake mechanisms. As a result, the use of pethidine may result in the production of serotonin syndrome in the presence of a second medication with serotonergic activity. Serotonin syndrome (SS) is caused by excess serotonin in the central nervous system (CNS). Pharmacological mechanisms which increase serotonin levels in the CNS include augmenting serotonin synthesis (L-tryptophan), increasing serotonin release (MDMA), inhibiting serotonin reuptake (SSRIs), inhibiting serotonin metabolism (MAOIs) and directly stimulating serotonin receptors (bromocryptine, lithium). Specific diagnostic criteria for serotonin syndrome include the presence of three or more of the following signs: mental status changes, confusion, hypomania, agitation, incoordination, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhoea, or fever¹⁵ Clinically, serotonin syndrome may range in severity and is usually self limiting when appropriate supportive care has been instituted. Symptoms commonly resolve over 12 to 24 hours when the offending drugs are discontinued¹⁶ – Severe forms of the syndrome with marked hyperpyrexia, muscle rigidity, myoclonus, rhabdomyolysis and seizures have resulted in death¹⁷.

Reuptake of serotonin is inhibited by the serotonin selective reuptake inhibitors (SSRIs) such as fluoxetine. Agents such as sibutramine also inhibit serotonin reuptake. Tramadol enhances the concentration of extraneural serotonin by interacting with the serotonin transporter¹⁸ resulting in inhibition of monoamine uptake mechanisms¹⁹. Thus the combination of pethidine with any of these agents may result in accumulation of serotonin and may theoretically lead to serotonin syndrome. St John's wort (*hypericum perforatum*) also increases CNS serotonin concentrations but to date, serotonin syndrome has not been reported with this agent. Notably, the concurrent use of pethidine and irreversible MAOIs (eg; phenelzine, tranylcypromine) has resulted in serious and life threatening serotonergic reactions. Marked muscle rigidity, hyperpyrexia, myoclonus, seizures, hyper- and hypotension, flushing, sweating and unconsciousness may occur very rapidly.

There is a theoretical risk of drugs which induce cytochrome P450 enzymes eg phenytoin increasing hepatic metabolism of pethidine, and thus increasing production of norpethidine. Data are derived from one pharmacokinetic study in which 4 normal subjects received pethidine (50mg IV and 100mg orally) before and after phenytoin 1g followed by 300mg daily for 9 days²⁰. The area under the blood concentration-time curve for norpethidine was considerably increased in the presence of phenytoin. However, the degree to which phenytoin and other enzyme inducers reduces the analgesic effect of pethidine or increases toxicity because of increased norpethidine concentrations is not known.

My patient has a history of 'morphine allergy'. Should pethidine be used in this situation?

Hypersensitivity or allergic reaction is the result of an immune response of the organism leading to formation of specific IgE antibodies, sensitised lymphocytes or both.²¹ Opiates are able to release histamine from tissue mast cells through triggering mechanisms which are independent from those acted upon by IgE receptors²¹.

The first report of elevated histamine levels in humans after the intravenous administration of 1mg/kg morphine was published in 1982²². When used in higher doses, marked cardiovascular changes are associated with histamine release, however, at subanaesthetic or analgesic doses, the relationship between histamine release and side effects has been less well documented. A randomized double blind study in 40 patients examined the quantitative effects of intravenous morphine 1mg/kg on plasma histamine and the ability of prior administration of H₁ and H₂ blockers to attenuate haemodynamic responses²³. Morphine stimulated significant histamine release, correlating with a decrease in blood pressure and systemic vascular resistance. Prior administration of diphenhydramine (1mg/kg) and cimetidine (4mg/kg) provide greater protection from those haemodynamic responses than either agent alone.

A double blind study found that histamine release was more frequent after pethidine than after morphine, fentanyl or sufentanil administered intravenously for the induction of anaesthesia²⁴. Increased plasma histamine concentrations occurred in 5 of 16 patients given a mean dose of pethidine of 4.3mg/kg and were accompanied by hypotension, tachycardia, erythema and increased plasma adrenaline concentrations. Only 1 in 10 given morphine (mean dose 0.6mg/kg) and none receiving fentanyl(mean dose 7µg/kg) or sufentanil(mean dose 1.3µg/kg) showed evidence of histamine release. However, in a study of morphine alone²⁵ (0.3mg/kg intravenously) serum histamine concentrations rose in all 10 patients and all subjects exhibited to varying degrees clinical manifestations of histamine release including flushing of face, neck chest and extremities and a generalised sensation of warmth. Six patients complained of facial itching.

It has been postulated that the amount of histamine released relates primarily to the concentration of drug achieved at mast cell membranes, and thus will be least with extremely potent drugs such as fentanyl, since clinically useful effects occur at extremely low concentrations²². However, this is disputed by Hermens²⁶ et al who compared in- vitro histamine release in human skin mast cells induced by morphine, fentanyl and oxymorphone and found that it did not parallel analgesic potency and was not a non-specific effect of high drug concentration.

- **Practice Points - Previous reactions to morphine**
- true allergy is rare
- to prevent morphine- induced vomiting , patient may be pretreated with metoclopramide
- use fentanyl or give morphine slow IV and monitor

Is tramadol a good substitute for pethidine?

Tramadol appears to have reasonable dose related efficacy in comparison with other opioid analgesics, with a relative lack of respiratory depression, major organ toxicity or abuse potential. However, it may induce convulsions, especially when the dose exceeds the recommended upper daily dose limit. Tramadol may therefore have a limited role in the small number of patients who are intolerant of conventional opioid and other non-opioid analgesics, those who have pre-existing cardiopulmonary disease, such as the elderly or obese, and those in whom codeine use is inappropriate. In the ongoing management of acute and post-operative pain, tramadol may have a place in multi-modal analgesia, where opioid and non-opioid drugs are given in combination to achieve analgesia, with a reduction in the incidence and severity of side effects. Similarly, in chronic pain conditions, tramadol should be considered (as a single agent or in combination) where non-opioid analgesics have proven ineffective or where multimodal therapy might be advantageous in order to limit side-effects (eg where a reduction in NSAID dosage is desirable). Potential for serious drug-drug interactions with tramadol should not be underestimated. In particular, the potential for the development of serotonin syndrome when administered with other serotonergic agents such as SSRIs antidepressants needs to be remembered.

How should I respond when the patient says ‘nothing else works’?

Practice Points

- an accurate pain history is vital
- consider parenteral NSAIDs, morphine, fentanyl, and/or adjuvants (depending on circumstances)
- use effective dose of alternative analgesics.

References:

1. Mather, L.E. and P.J. Meffin, *Clinical Pharmacokinetics pethidine*. Clin Pharmacokinet, 1978. **3**: p. 352-368.
2. Verbeeck, R.K., R.A. Branch, and G.R. Wilkinson, *Meperidine disposition in man: Influence of urinary pH and route of administration*. Clin Pharmacol Ther, 1981. **30**: p. 619-28.
3. Clarke, R.F., E.M. Wei, and P.O. Anderson, *Meperidine therapeutic use and toxicity*. J Emerg Med, 1995. **13**: p. 797-802.
4. Jiraki, K., *Lethal effects of normeperidine*. Am J Forensic med Pathol, 1992. **13**: p. 42-43.
5. Kaiko, R.F., et al., *Central nervous system excitatory effects of meperidine in cancer patients*. Ann Neurol, 1983. **13**(2): p. 180-5.
6. Stone, P.A., P.E. Macintyre, and D.A. Jarvis, *Norpethidine toxicity and patient controlled analgesia*. Br J Anaesthesia, 1973. **71**: p. 738-40.
7. Macintyre, P.E. and D.A. Jarvis, *Age is the best predictor of postoperative morphine requirements*. Pain, 1995. **64**: p. 357-64.
8. National Health and Medical Research Council, *Acute pain management: scientific evidence*. 1999, Commonwealth of Australia: Canberra.
9. von Eisleb, O. and O. Schaumann, *Dolantin, ein neuartiges spasmolytickum und analgetikum*. Dtsch med Wochenschr, 1939. **55**: p. 967-968.
10. Gaensler, E.A., J.M. McGown, and F.F. Henderson, *A comparative study of the action of Demerol and opium alkaloids in relation to biliary passage pressure*. Surgery, 1947. **22**: p. 211-220.
11. Economidou, G. and J.N. Ward-McQuaid, *A cross-over comparison of the effect of morphine, pethidine, pentazocine and phenazocine on biliary pressure*. Gut, 1971. **12**: p. 218-221.
12. Joehl, R.J., K.L. Koch, and D.L. Nahrwold, *Opioid drugs cause bile duct obstruction during hepatobiliary scans*. Am J Surgery, 1984. **147**: p. 134-138.
13. Radnay, P.A., et al., *The effect of equianalgesic doses of fentanyl, morphine, meperidine, butorphanol and naloxone*. Anesth Analg, 1984. **63**: p. 441-444.
14. Weiner, A.L., *Meperidine as a potential cause of serotonin syndrome in the emergency department*. Acad Emerg Med, 1999. **6**: p. 156-158.
15. Sternbach, H., *The serotonin syndrome*. Am J Psychiatry, 1991. **148**: p. 705-13.
16. Bodner, R., et al., *Serotonin syndrome*. Neurology, 1995. **45**: p. 219-23.
17. Hernandez, A.F. and e. al, *Fatal moclobemide overdose or death caused by serotonin syndrome?* J Forensic Sci, 1995. **40**: p. 128-30.
18. Driessen, B. and W. Reimann, *Interaction of the central analgesic tramadol with the uptake and release of 5-hydroxytryptamine in the rat brain in vivo*. British Journal of Pharmacology, 1992. **105**: p. 147-151.
19. Raffa, R.B., et al., *Opioid and non opioid components independently contribute to the mechanism of action of tramadol, an atypical opioid analgesic*. Journal of Pharmacology and Experimental Therapeutics, 1992. **260**: p. 275-285.
20. Pond, S.M. and K.M. Kretschmar, *Effect of phenytoin on meperidine clearance and normeperidine formation*. Clin Pharmacol Ther, 1981. **30**: p. 680-686.
21. de Weck, A.L., *Immunopathological mechanisms and clinical aspects of allergic reactions*, in *Allergic Reactions to Drugs*, A.L. de Weck and H. Bundgaard, Editors. 1983, Springer-Verlag: Berlin.
22. Rosow, C.E., et al., *Histamine Release during Morphine and Fentanyl Anesthesia*. Anesthesiology, 1982. **56**(2): p. 93-96.
23. Philbin, D.M., et al., *The Use of H1 and H2 Histamine Antagonists with Morphine Anesthesia: A Double-blind Study*. Anesthesiology, 1981. **55**(3): p. 292-296.
24. Flacke, J.W. and e. al, *Histamine release by four narcotics: a double blind study in humans*. Anesth Analg, 1987. **66**: p. 723-30.
25. Fahmy, N.R., N. Sunder, and N. Soter, *Role of histamine in the hemodynamic and plasma catecholamine responses to morphine*. Clin Pharmacol Ther, 1983. **33**(5): p. 615-620.
26. Hermens, J.M., et al., *Comparison of Histamine Release in Human Skin Mast Cells Induced by Morphine, fentanyl and Oxymorphone*. Anesthesiology, 1985. **62**(2): p. 124-129.