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USE OF PETHIDINE FOR PAIN MANAGEMENT IN THE EMERGENCY DEPARTMENT

A Position Statement of the NSW Therapeutic Advisory Group Inc.

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INTRODUCTION

Pethidine is widely prescribed in hospitals despite lack of research evidence to support its preferential use. It has no proven advantage over other opioid analgesics and there is significant potential for iatrogenic problems with its use. During 2003 NSW TAG conducted a multi-centre drug usage evaluation project looking at the use of analgesics in emergency departments. A number of questions were raised during the course of the project regarding appropriate doses of analgesics other than pethidine.

This statement will examine the adverse effects that may be associated with the use of pethidine and common conditions for which pethidine has been prescribed in emergency departments. Alternative treatment options will be discussed. While there may be a limited role for the use of pethidine in some pain management scenarios, its use in the management of acute pain in the emergency setting in particular, is extremely limited. Numerous other opiate analgesics with better side effect profiles and lesser abuse potential are available for use in this setting.

1. COMMON PRESENTATIONS TO THE ED- evidence for use of pethidine, other opioids and alternative drugs

1.1 BILIARY COLIC

Various studies provide evidence that equianalgesic doses of pethidine cause similar effects on the sphincter of Oddi and the biliary tract to other opioids. All opioids have been found to increase biliary tract pressure¹, which may result in spasm of the sphincter of Oddi, leading to epigastric distress and biliary colic.²

Resting intrabiliary pressure, perfusion pain level and pressure changes have been measured post-operatively utilising T-tube drainage of the bile duct in the presence of pethidine 100 mg IM, codeine 60 mg SC and morphine 10 mg SC.³ Codeine caused the least spasm of the sphincter of Oddi, followed by pethidine and then morphine. Other studies directly measuring intrabiliary pressure have shown that parenteral pethidine and morphine produce a similar degree of increase in biliary pressure.^{1 4 5} The clinical relevance of these observations is unclear, as these studies did not address the effect of these agents on the control of pain in acute cholecystitis or biliary colic pain in the emergency setting. It is unlikely that there is any significant difference in the clinical effects of these drugs in these situations when used in equianalgesic doses.

The effect of ketorolac on biliary tract pressure has been compared with that of morphine and placebo.⁶ Intraoperatively, thirty-one anaesthetised patients received either ketorolac 30 mg IV (n=16) or morphine 5 mg IV (n=15) after a cholecystectomy or gallstone removal, and intrabiliary tract pressure measured 5 minutes after dosing. There was a significant increase in pressure over baseline with morphine but not with ketorolac.

The analgesic efficacy and tolerability of intravenous ketorolac (30mg) and intravenous pethidine (50mg) were compared in a prospective, randomised, double blind study in 324 patients presenting to the ED with a history and physical examination compatible with biliary colic, enrolled over a 2 year period.⁷ No significant difference in pain control was found between ketorolac and pethidine in either the visual analogue scale (VAS) or verbal rating system (VRS) for any time interval studied. Although no significant difference was found in overall drug tolerability, patients receiving pethidine reported higher incidences of nausea and of dizziness than those receiving ketorolac (p=0.009 and

0.003 respectively). A prospective study of intramuscular ketorolac (60 mg) and pethidine 1.5 mg/kg (maximum dose 100mg) in 30 patients presenting to the ED with acute biliary colic found no significant difference in pain relief achieved by using either ketorolac or pethidine.⁸

Diclofenac has also been found to be effective in relieving the symptoms of biliary colic in a double-blind study of 53 patients, given 75mg intramuscularly.⁹ However no studies comparing diclofenac with any opioid in the treatment of biliary colic could be identified.

In biliary colic

- The preferential use of pethidine over any other opioid is not supported by the evidence.
- NSAIDs are effective.^{7,9}
- If an opioid is required, intravenous morphine, fentanyl or hydromorphone may all be used in place of pethidine.^a
- Smooth- muscle relaxants eg hyoscine-n-butylbromide have previously been suggested, however little evidence could be found in the literature to support this.

1.2 RENAL COLIC

A recent Cochrane review assessed the relative efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids in 1613 patients presenting with a clinical diagnosis of acute renal colic.¹⁰ Relative analgesic effect was examined through 3 outcomes: pain scores at a specified time after study drug administration, proportion of patients who achieved complete pain relief within a fixed time, and the need for rescue analgesia. Both opioids and NSAIDs demonstrated a clinically important analgesic effect, with a marked reduction in pain scores over time. There was no significant difference between NSAIDs and opioids in the proportion of patients who achieved complete pain relief in a short time frame. Patients treated with NSAIDs were significantly less likely to require rescue analgesia (RR 0.75, 95% CI 0.61-0.93; p=0.007) within an hour of study drug administration (9 of 10 trials pooled for this analysis used pethidine as their opioid). Adverse events were generally higher in patients receiving opioids. Vomiting was reported as a specific adverse event in 10 trials (826 patients) with significantly less vomiting in patients treated with NSAIDs (RR 0.35, 95% CI 0.23-0.53, p<0.00001). Subgroup analysis by type of narcotic demonstrated that the risk of vomiting was particularly notable in patients receiving pethidine (RR 0.30, 95% CI 0.18-0.49; p<0.00001)

The authors concluded that single bolus doses of both NSAIDs and opioids provide pain relief to patients with acute renal colic. When a single bolus of analgesia is used, the authors recommended an NSAID rather than an opioid, and if an opioid is to be used (either because of contraindications to NSAIDs or ease of titration) that pethidine should be avoided given the higher rate of associated vomiting.

In renal colic

- rectal NSAIDs are effective¹¹, although onset of action is not as rapid as intravenous NSAIDs.^{12, 13}
- parenteral NSAIDs are as effective as opioids.¹⁰
- The use of hyoscine-n-butyl bromide is not supported in the literature.¹⁴

^a The authors note that some approved product information for morphine lists a contraindication in a variety of acute abdominal conditions, including biliary colic. However the evidence presented in this paper indicates that morphine does not cause any significant problems with spasm any different to other opioids. Clinical experience and expert opinion also suggest that morphine does not cause significant problems in this regard.

1.3 MIGRAINE

A number of randomised controlled trials have concluded that pethidine is no more effective than dihydroergotamine, chlorpromazine, prochlorperazine or an NSAID.¹⁵⁻¹⁹ Pethidine is short acting compared with the duration of migraine and therefore is an inappropriate choice of analgesic.²⁰ Consequently, the Australian Association of Neurologists does not recommend the use of pethidine in treatment of migraine.^{21 22}

1.4 LOW BACK PAIN

Oral opioids may be useful in the short- term management of acute back pain when early mobilisation is the goal of therapy, but there are no randomised controlled trials to support this.²² A single intramuscular dose of an opioid may be beneficial when patients must be transported, and intramuscular injection in hospitalised patients may be necessary in the acute phase if pain is severe.²³ In such cases morphine is the drug of choice.

There are no randomised controlled trials investigating the efficacy of opioids and compound analgesics in acute low back pain.²⁴

There is no place for the general use of injectable opioids such as pethidine in the treatment of chronic low back pain.²²

2. ADVERSE EFFECTS

2.1 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 has been shown to average 3.6 hours²⁵ however the elimination half life of norpethidine is around 14-21 hours with normal renal function²⁶ and 35 hours in renal failure.²⁷ Norpethidine has half the analgesic potency of pethidine but two to three times the potency as a central nervous system (CNS) excitatory agent^{25 28} and may cause anxiety, hyperreflexia, myoclonus, seizures and mood changes.²⁹ There is not a clear relationship between neurotoxicity, cumulative dose and serum norpethidine.³⁰ Several cases of seizures have been reported, including when pethidine was used for patient controlled analgesia (PCA).³⁰ In Australia between 1975 and 1997, ADRAC (Adverse Drug Reactions Advisory Committee) received 35 reports describing convulsions in association with pethidine. In 17 of these, 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.

2.2 DRUG INTERACTIONS

Pethidine inhibits both serotonin and noradrenaline reuptake mechanisms. As a result, the use of pethidine may result in the production of serotonin toxicity in the presence of a second medication with serotonergic activity. Serotonin toxicity (also known as serotonin syndrome) 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 (methylene 3, 4 dioxymethamphetamine -MDMA), inhibiting serotonin reuptake

(selective serotonin reuptake inhibitors-SSRIs), inhibiting serotonin metabolism (monoamine oxidase inhibitors-MAOIs) and directly stimulating serotonin receptors (bromocriptine, lithium). Specific diagnostic criteria for serotonin toxicity have been identified.^{31 32} Clinically, serotonin toxicity may vary 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 discontinued.³³ Severe forms of the syndrome with marked hyperpyrexia, muscle rigidity, myoclonus, rhabdomyolysis and seizures have resulted in death.³⁴

Reuptake of serotonin is inhibited by the SSRI antidepressants such as fluoxetine. Other agents such as the appetite suppressant sibutramine, and the analgesic tramadol also inhibit serotonin reuptake.³⁵ Thus the combination of pethidine with any of these agents may result in accumulation of serotonin and may theoretically lead to serotonin toxicity. St John's wort (*Hypericum perforatum*) also increases CNS serotonin concentrations but to date, serotonin toxicity 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, hypertension and hypotension, flushing, sweating and unconsciousness may occur very rapidly.

Drugs that induce cytochrome P450 enzymes (eg phenytoin) may increase the hepatic metabolism of pethidine, and thus increase production of norpethidine.³⁶ However, the degree to which phenytoin and other enzyme inducers reduce the analgesic effect of pethidine or increase toxicity because of increased norpethidine concentrations in the clinical setting is unknown.

2.3 HISTAMINE RELEASE

Hypersensitivity or allergic reaction is the result of an immune response leading to formation of specific IgE antibodies, sensitised lymphocytes or both.³⁷ Opioids are able to release histamine from tissue mast cells through triggering mechanisms that are independent from those relying upon IgE receptors.³⁷

The first report of elevated histamine levels in humans after the intravenous administration of *1mg/kg* morphine^b was published in 1982.³⁸ A randomised 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 responses.³⁹ Morphine stimulated significant histamine release, correlating with a decrease in blood pressure and systemic vascular resistance. Prior administration of diphenhydramine (1 mg/kg) and cimetidine (4 mg/kg) provide greater protection from those haemodynamic responses than either agent alone. When morphine is used in higher (anaesthetic) doses, marked cardiovascular changes are associated with histamine release. At subanaesthetic or analgesic doses, however, the relationship between histamine release and side effects has been less well documented.

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 anaesthesia.⁴⁰ Increased plasma histamine concentrations occurred in 5 of 16 patients given a mean dose of pethidine of 4.3 mg/kg^c and were accompanied by hypotension, tachycardia, erythema and increased plasma adrenaline concentrations. Only 1 in 10 patients given morphine (mean dose 0.6mg/kg ie 42mg for 70 kg patient) and none receiving fentanyl (mean dose 7 µg/kg ie 490 micrograms for 70

^b note that this is an anaesthetic dose; a 10mg dose in a 70kg patient is equivalent to 0.14 mg/kg.

^c For 70kg patient this represents approx 300mg

kg patient) or sufentanil (mean dose 1.3 µg/kg) showed evidence of histamine release. However, in a study of morphine alone⁴¹ (0.3 mg/kg intravenously ie 21 mg for 70 kg patient) 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 concentrations.³⁸ However in-vitro studies of histamine release in human skin mast cells induced by morphine, fentanyl and oxymorphone found that this did not parallel analgesic potency.

Morphine is metabolised mainly to morphine-3 glucuronide (M3G) and morphine- 6 glucuronide (M6G). The latter is implicated in most cases of pruritis or nausea.⁴²

2.4 ANAPHYLAXIS AND CROSS ALLERGENICITY

Anaphylactic and true allergic reactions to opioid analgesics are rare.⁴³ A literature review covering the years 1975-1987⁴³ carried single case reports of anaphylactic reactions to pethidine⁴⁴, pentazocine⁴⁵, morphine^{46,47} and fentanyl.^{48,49} None of these reports documented cross-sensitivity with other opioid analgesics. Reviews of studies involving several thousands of patients receiving pethidine or morphine revealed no cases of cross-sensitivity.⁵⁰

Opioid analgesics have been categorised using at least 3 different schemes, which to some extent, address the potential for cross-sensitivity.⁴³ The first categorisation involves naturally occurring vs semi-synthetic vs synthetic compounds, the second is based on the presence or absence of a 6-hydroxyl group on the basic morphine structure and the third is a separation based on basic chemical structure. (See following Table 1). Thus if hypersensitivity occurs with a drug from one class, it may be useful to try a product from a different class.

Table 1⁴³

Opioid analgesic	Source of opioid	Morphine-related structure with 6 hydroxyl group	Related structural group
Alfentanil	Synthetic		Pethidine
Buprenorphine	Synthetic	No	Morphine
Codeine	Natural	Yes	Morphine
Dihydrocodeine	Semi-synthetic	Yes	Morphine
Fentanyl	Synthetic		Pethidine
Hydromorphone	Semi-synthetic	No	Morphine
Pethidine	Synthetic		Pethidine
Methadone	Synthetic		Unique
Morphine	Natural	Yes	Morphine
Oxycodone	Semi-synthetic	No	Morphine
Propoxyphene	Synthetic		Morphine

3. PLACE IN THERAPY

- Pethidine has a shorter duration of action than morphine with no additional analgesic benefit. It has similar side effects to morphine, including increased biliary pressure.
- Pethidine is metabolised to norpethidine, which has potential toxic effects (eg convulsions) especially in patients with renal dysfunction.
- Pethidine can cause seizures and has the potential for significant drug interactions, thus a full medication history should be obtained before prescribing it.

For these reasons, and because less toxic, equianalgesic alternatives exist, pethidine should not be considered a first line agent for treatment of severe pain.

4. RECOMMENDED ALTERNATIVES TO PETHIDINE

4.1 OPIOIDS

All opioids are capable of producing the same degree of analgesia providing equianalgesic doses are given. There is no evidence to suggest that pethidine provides any better analgesia than other opioids for any type of pain.² Dose schedules for opioids 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 (with increasing age decreasing doses are required) has been shown to be a better predictor of ongoing opioid requirement.⁵¹

Intermittent intravenous doses permit a predictable and readily observable response, and allow titration of dose to response. This method of dosing is useful in the emergency department situation, for obtaining initial and rapid pain relief. Rapid control of severe acute pain may be obtained by giving small intravenous bolus doses of opioid until pain relief is achieved. The total dose for this 'titration' is a guide to subsequent dose requirements.²¹

Table 2 Equianalgesic opioid doses

Drug	Approximate equi-analgesic dose ^d		Duration of action ^e (hours)
	Parenteral (IM/SC)	Oral	
morphine	10mg	30mg	2-3
oxycodone	NA ^f	20-30mg	3-4
fentanyl	100µg sc ^g	NA	0.5-2 (IV)
hydromorphone	1.5-2mg	6-7.5mg	2-4

^d Published tables vary in the suggested doses that are equianalgesic to morphine, thus titration to clinical response is necessary (Information for this table derived from Australian Medicines Handbook 2004 and NHMRC: Acute Pain Management- Scientific evidence 1999). These doses are equianalgesic to pethidine 100mg.

^e depends on dose and route of administration. Duration does not include controlled release preparations.

^f A suppository form of oxycodone 30mg is available in Australia.

^g Fentanyl is not recommended for intermittent IM use. Lower doses, repeated as required, should be used for IV use. A suggested initial dose is 0.5-1 mcg/kg up to 100 mcg, and then give titrated analgesia every 3-5 minutes depending on response to pain and haemodynamic state.

A clearly documented history of previous drug reactions is important in patient management. True allergy to opioids is rare.

i. **Morphine**

Morphine remains the major drug for the treatment of moderate to severe pain.² In addition morphine lacks many of the potential drug interactions of pethidine.

ii. **Fentanyl**

Fentanyl is a synthetic analogue of pethidine **and thus if true allergy to morphine exists, fentanyl may be prescribed**. Fentanyl has a shorter duration of action than morphine. See Table 1 for dosage.

iii. **Hydromorphone**

Hydromorphone is structurally similar to morphine but considerably more potent. By the intravenous route hydromorphone has a rapid onset (within 5 minutes), a short time to peak effect (10-20 minutes) and a relatively short duration (3-4 hours). Because the metabolite morphine 6- glucuronide is implicated in most case of pruritis or nausea with morphine administration, hydromorphone, which has no 6- glucuronide metabolite, may alleviate these problems.⁴² Hydromorphone is presented as a concentrated solution (10mg/ml), and thus care should thus be taken with dosage calculations to avoid overdosage. It is an option in patients with morphine allergy.

4.2 TRAMADOL

There is a very limited role for tramadol in the emergency department. This may include chronic pain patients who have had it prescribed by their pain specialist. Adverse effects are common and sometimes serious. Seizures have been reported with normal doses. The potential for serious drug-drug interactions with tramadol should not be underestimated. In particular, there is a risk of serotonin toxicity when administered with other serotonergic agents such as SSRI antidepressants.

4.3 KETOROLAC

The usual starting dose of parenteral ketorolac is 10-30mg for patients less than 65 years and 10-15mg for patients over 65 years.²¹ Alternatively, 10mg may be given orally, as ketorolac is rapidly and completely absorbed after oral administration. The efficacy of parenteral ketorolac is no better than other orally and rectally administered NSAIDs.

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