CLINICAL PRACTICE

Pethidine — does familiarity or evidence perpetuate its use?

Tamara Kredo, Rudy Onia

A review of the current literature shows pethidine (meperidine) use to be less favourable than commonly thought. When first synthesised in the 1930s, it was prematurely lauded as a substitute for morphine, and marketed as a drug lacking many of the adverse effects such as respiratory depression, urinary retention, constipation and chemical dependency typical of opioids such as morphine. None of these claims has been substantiated[1] by clinical evidence; in fact pethidine carries additional risks that ensure its declining use internationally.[1,2] These risks, and the evidence questioning its analgesic efficacy, make it necessary to review its continued popular use in South Africa.

Pethidine is typically used for management of moderate to severe pain.[2] At best, dose for dose, it may be as good as morphine. Studies have been conducted in a variety of settings, most commonly postoperatively or intrapartum, or they have investigated patient-controlled analgesia, but there remains no conclusive evidence that pethidine is a better or safer alternative to morphine in any setting.[1,3-6]

Pethidine is metabolised by the liver into a variety of metabolites, most important of which is the active metabolite, norpethidine. Norpethidine is neurotoxic with epileptogenic potential. Pethidine has a plasma half-life of 2.5 - 4 hours, with a similar duration of analgesic effect. Norpethidine on the other hand has a considerably longer plasma half-life of between 14 and 21 hours — which is further prolonged in patients with renal or hepatic dysfunction.[2,6,7] Norpethidine has approximately half the analgesic effect of pethidine,[2] and this, coupled with pethidine's short plasma half-life, results in repeated doses of pethidine being required to manage pain. This multiple dosing leads to accumulation of the harmful metabolite, norpethidine, increasing the potential for a neurological adverse event.

The neurotoxicity of norpethidine results in a range of symptoms, from irritability, restlessness and agitation (potentially mistaken as pain) to tremors, gross jerking, confusion and seizures. The mechanism of this neurological action is related to its ability to increase serotonin and noradrenalin in the central nervous system.[1]

Pethidine has the potential to cause the serotonin syndrome when used concomitantly with other serotonergic agents. The selective serotonin re-uptake inhibitors and tramadol must be used with great caution when pethidine is also part of management, and it is an absolute contraindication to co-administer pethidine with the monoamine-oxidase inhibitors (MAOIs); several fatal reactions have been reported. Pethidine should never be prescribed within a 14-day period of stopping an MAOI.[1,2]

Also of note is that commonly used drugs such as theophylline, tricyclic antidepressants and the fluoroquinolones may potentiate pethidine's seizure potential.[6]

Pethidine has a vagolytic action, which may lead to tachycardias or arrhythmias, particularly in patients post myocardial infarction and in those with supraventricular tachycardia.[2,8] This action of pethidine makes morphine preferable in the setting of the acute coronary syndrome.

Pethidine is generally used in preference to other opioids in the treatment of biliary colic or pancreatitis, based on the historical presumption that morphine causes more biliary spasm than pethidine.[9] Review of the published data revealed that equivalent doses of pethidine were not used (i.e. 100 mg : 10 mg) in those studies. Relatively lower doses of pethidine were used, thereby showing it to be less spasmogenic than morphine. Of note, the sphincter of Oddi is equally sensitive to all opioids, at equi-analgesic doses.[10]

Globally there has been a move away from the use of pethidine.[2] Growing awareness of its adverse effects is ensuring its rational use in updated pain management protocols.[1] One example is the recommendation of the Agency for Health Care Policy and Research, which states categorically that pethidine is contraindicated for the treatment of chronic pain. It adds that pethidine 'may be used in acute pain situations for very brief courses in otherwise healthy individuals who have not demonstrated an unusual reaction (i.e. local histamine release at the infusion site) or allergic response to other opioids such as morphine. It is absolutely contraindicated in patients with renal dysfunction'.[9,11] Most recently, in April 2003, the World Health Organization removed pethidine from the model essential drugs list stating that 'morphine is the preferred

Dr Rudy Onia is a registrar in clinical pharmacology at Groote Schuur Hospital. His special interests lie in the fields of addiction and complementary, alternative and traditional medicines.

Dr Tamara Kredo is a registrar in clinical pharmacology at Groote Schuur Hospital. Her interests include rational prescribing and drug safety, ongoing medical education particularly in HIV management, and advancing the development of intergrative health care practice.

Corresponding author: *T Kredo (tkredo@uctgsh1.uct.ac.za)*

potent opioid'.[12]

Pethidine also carries a high potential for abuse. A recent report published in this *Journal* on substance-abusing doctors indicates that the drug is highly abused.[13] Twenty-five per cent of all cases of abuse reported to the Medical and Dental Professions Board involved pethidine. Pethidine addiction by medical personnel appears to be an occupational hazard. Easy availability and access to the drug, and long and stressful working hours are major contributing factors and when combined with individual emotional or mental susceptibility, can lead to addiction.[14] Although it is known to occur, there is much less evidence of pethidine abuse in the general population. Other opiate abuse, such as that involving heroin or codeine, is more prevalent.[15]

In conclusion, popular use of the opioid analgesic pethidine is perpetuated by familiarity rather than by evidence of its effectiveness. It has a shorter duration of analgesic action than morphine; it produces a neurotoxic metabolite norpethidine that accumulates due to its longer half-life; it interacts dangerously with several drugs; it has vagolytic potential; and most importantly, its analgesic efficacy is not superior to that of other opioids.

Morphine, therefore, remains the drug of choice in the setting of moderate to severe pain management.

1. Latta K, Ginsberg B, Barkin R. Meperidine: a critical review. *American Journal of Therapeutics* 2002; **9:** 53-68.
2. McEvoy G. *American Hospital Formulary Service Drug Information*. Bethesda: American Society of Hospital-System Pharmacists, 2004: 2044-2046.
3. Molloy A. Chronic and cancer pain program. *Australian Prescriber* 2002; **25:** 12-13.
4. Clark R, Wei E, Anderson P. Meperidine: Therapeutic use and toxicity. *J Emerg Med* 1995; **13:** 797-802.
5. Pryle BJ, Grech H, Stoddart PA, Carson R, O'Mahoney T, Reynolds F. Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; **304:** 1478-1479.
6. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol* 2001; **96:** 1266-1272.
7. Hardman JG, Limbird LE, Molinoff PB, Rudden RW, Gilman AG. *Goodmann &, Gilman's The Pharmacological Basis of Therapeutics.*10th ed. New York: McGraw Hill, 2001: 582-595.
8. Sanofi-Synthelabo. Prescribing information. Demerol (meperidine hydrochloride), September 1999. **www.sanofi-synthelabo.us/products/pi_demerol/pi_demerol.html** (last accessed 15 Sep 2004).
9. Carr D, Jacox A, Chapaman C. Acute Pain Management Guideline Panel. *Clinical Practice Guideline for Acute Pain Management: Operative or Medical Procedures and Trauma*. (Agency for Health Care Policy and Research Publication No. 92-0032). Rockville: US Public Health Service, 1992.
10. Hubbard G, Wolfe K. Meperidine misuse in a patient with sphincter of Oddi dysfunction. *Ann Pharmacother* 2003; **37:** 534-537.
11. American Pain Society Quality of Care Committee. Quality improvement guidelines for the treatment of acute pain and cancer pain. *JAMA* 1995; **274:** 1881-1882.
12. World Health Organisation Essential Medicines Library. Medicines withdrawn from the 13th model list, April 2003. **http://mednet3.who.int/eml/withdrawnMedicinesList.asp** (last assessed 15 Sep 2004).
13. Bateman C. The drug-addicted doctor — who dares to care? *S Afr Med J* 2004; **94:** 726-727.
14. Parry C, Plüddemann A, Bhana A, Harker N, Potgieter H, Gerber W. May 2004 South African Community Epidemiology Network on Drugs Use. **http://www.sahealthinfo.org/admodule/sacendumay2004.pdf** (update accessed 22 Sep 2004).
15. Green RC jun. Carroll GJ, Buxton WD. Drug addiction among physicians. The Virginia experience. *JAMA* 1976; **236:** 1372-1375.

IN BRIEF

Gas and other fume-emitting heaters may cause asthma in children

Asthma is one of the most prevalent chronic diseases in childhood, and is globally a major public health problem. Various exposures have been suggested as causative or exacerbating factors. These include environmental tobacco smoke, air pollution and combustion products from fume-emitting appliances as well as indoor and outdoor allergens. Several studies have shown adverse effects of gas cookers and heaters on respiratory health. The long-term effects of early life exposure to these appliances is not known. A study was conducted to investigate the effect of exposure to fume-emitting heaters, currently and during the first year of life, on the risk of asthma outcomes (*Thorax* 2004; **59:** 741-745). A cross-sectional study of schoolchildren aged 8 - 11 years was conducted in Australia. Information on symptoms and heating types was collected by parent-completed questionnaire. It emerged from the survey that there was no association between asthma and current use of fume-emitting heaters. However, having been exposed to fume-emitting heaters during the first year of life was associated with an increased risk of airway hyper-responsiveness and recent wheeze in later years of childhood. If confirmed in other settings, this finding would indicate a review of the range of types of heaters appropriate for use where young children live.